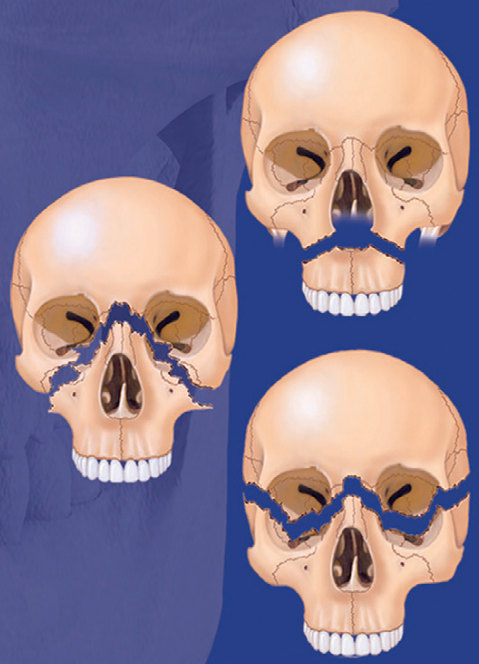
Fonseca

ORAL AND MAXILLOFACIAL SURGERY

third edition



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Trauma
Surgical Pathology
Temporomandibular Disorders

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VOLUME 2

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I recognize Dr. Robert E. Marx, Dr. Edward T. Lally, and the late Dr. Joseph Ashman, the three teachers who taught me oral/head and neck tumor surgery, pathology, and anatomy. My career has been most gratifying due to the education provided to me by these exemplary individuals.

Eric R. Carlson

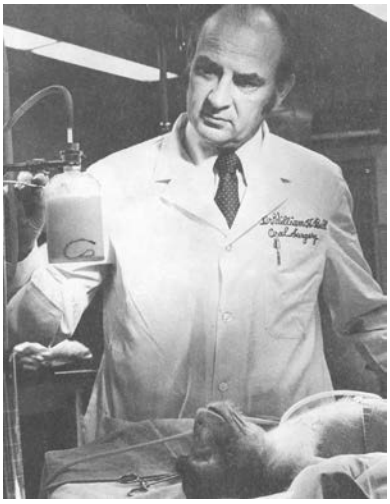
To Chester, Lady, Cheerio, Moxie, Domino, Sasha, Tuxedo, Chairman Meow, Zoey, Apollo, Ayla, Annabelle, and Atticus for enriching our lives.

Raymond J. Fonseca

As a resident I trained under Jerry Goldberg, whose practice was filled with patients suffering from TMJ disorders that few others welcomed. He would come back from early meetings of the American Society of Temporomandibular Joint Surgeons and tell tales of raucous debates over the cutting-edge knowledge, which he then passed on to us. I decided then that I wanted in on this field. When I interviewed for an academic job with Larry Peterson, he asked if I would be comfortable teaching residents to do TMJ surgery. I gave a qualified yes, and he said, "Then you will be our TMJ surgeon." And so it began. Nothing I have accomplished would have happened without the teaching, confidence, and support from these two great mentors, so I dedicate this work to Dr. Goldberg and to the memory of "Pete" Peterson.

Gregory M. Ness

In Memoriam



William H. Bell, DDS

We respectfully dedicate this edition of *Oral and Maxillofacial Surgery* to the memory of Dr. William "Bill" Harrison Bell. Matchless among his peers, Dr. Bell was an inimitable leader in surgery and medicine throughout his career.

In the early 1970s, Dr. Bell revolutionized oral and maxillofacial surgery through his landmark research on the biologic basis and clinical rationale for the Le Fort I osteotomy. In subsequent decades, he guided the hands of generations of surgeons, whether in academic medical centers across the world or through his meticulously detailed textbooks. It is a testament to Dr. Bell's always-passionate and always-persistent pursuit of excellence that his textbooks still remain contemporary decades after their publication.

While Dr. Bell was a revolutionary in our field, it is not simply in this spirit that we dedicate this book. Dr. Bell also served as an inspiration and mentor to us throughout our careers and lives, showing us always a readiness to inspire and a passion to change lives however he could. We are, quite simply, not alone in this feeling. It was this passion that compelled him to devote his life to improving patient care. It was this passion that affected so many others in our field. And it was this passion that also characterized so many areas of his vibrant and rich life—a life very well-lived.

It was an honor to learn from and know Bill. He was unwavering and uncompromising, and his love was unconditional. We know that the passion that burned in him to help others will continue to ignite the spirits of generations of surgeons to come. It will guide our hands and our actions as well.

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Preface

We are excited to present the third edition of *Oral and Maxillofacial Surgery*. This three-volume text is the result of the collaboration of multiple contributors. The first edition, published in 2000, and the second edition, published in 2009, were very well-received. However, with all the advances in our profession, we felt it was time for a new edition. The section editors have done an excellent job recruiting the most knowledgeable individuals in their specific areas of expertise. The authors have submitted chapters that reflect the state of the art in their areas of responsibility.

This text is a comprehensive resource on oral and maxillofacial surgery. Every area in our specialty has been addressed. It defines the scope of the specialty. Every surgical procedure performed by an oral surgeon is covered in this text. This multi-volume text provides coverage of a wide range of issues related to surgical care, such as anesthesia, diagnostic imaging treatment planning, rehabilitation, physical therapy, and psychological considerations.

After an analysis of the changing field of oral and maxillofacial surgery, we strove to present a comprehensive, current book that covers the complete scope of our specialty. We hope that the reader appreciates and agrees with our efforts. We stated in the preface of the first edition that we hoped that our future attempts will present an even broader scope of oral and maxillofacial surgery. The fact that this edition has succeeded in that regard is a testament to the individuals who are constantly expanding the envelope.

Acknowledgments

The third edition of *Oral and Maxillofacial Surgery* is a team approach. The section editors—Eric R. Carlson and Gregory M. Ness (and myself)—were invaluable contributors to the success of this effort. They diligently pestered authors so that deadlines were almost met. This edition, like the last two, attempts to define the scope of oral and maxillofacial surgery and could not have come to fruition without these contributors.

Residents are the lifeblood of our specialty. Many have helped to contribute portions of chapters in this book. They have also provided us with friendship, dedication, intellectual stimulation, and humility, without which this book would not have been written.

Last, I would like to thank all the staff who helped to prepare these manuscripts and the editorial staff at Elsevier, who were so patient with our procrastination and meticulous in their development and editing of this book. Additionally, I would like to thank my staff—Laynee Adams, Sally Brown, Heather Early, Patty Martin, Sarah Merrill, Josie Ray, and Ashley Wood—who collectively and individually make my life so enjoyable.

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Initial and Postoperative Management of the Craniomaxillofacial Trauma Patient

ALISON Y. YEUNG

Introduction

Trauma is the leading cause of mortality globally, and in the United States more than 3 million facial injuries occur each year, resulting in a large percentage of hospital admissions. Because more than 50% of patients with maxillofacial trauma have multisystem injuries as well, a thorough and efficient management strategy is crucial to optimize the care of the patient.

The goal in the management of the facial trauma patient is to restore function and esthetics while minimizing adverse events. The initial evaluation and management of the patient ensures that the appropriate treatment is rendered, whereas the focus in the postoperative setting is on an expeditious recovery with minimal complications. This chapter outlines some of the important principles in the care of the facial trauma patient in the perioperative setting. The subsequent chapters of this text will explore many of these principles in greater detail.

Initial Assessment

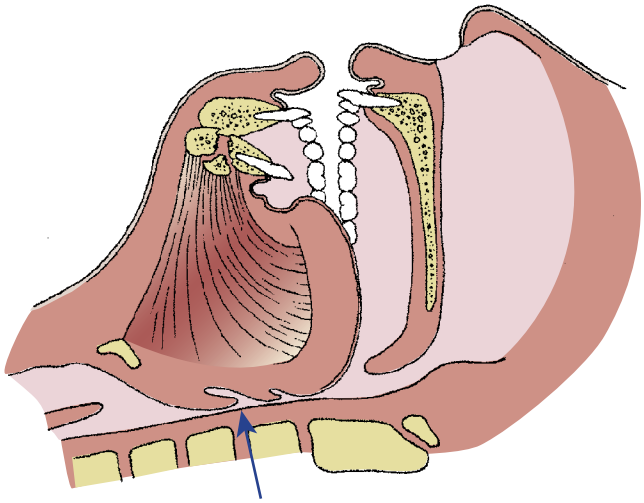
The creation of the Advanced Trauma Life Support (ATLS) course in 1978 provided a systematic approach to addressing the initial needs of the trauma patient. The principles outlined by ATLS (Box 1-1) should be applied to all trauma patients in the emergent setting, to quickly identify and treat any life-threatening injuries. However, it is rare for the oral and maxillofacial surgeon (OMS) to be the sole primary practitioner evaluating a trauma patient who presents to the hospital. A multidisciplinary approach to the management of the trauma patient has been adopted. In most situations, the trauma patient has been evaluated in the emergency room setting and the OMS is brought in as a consultant. This does not negate the need for a thorough understanding of the principles behind trauma care, as it allows the practitioner to be in sync with the efficient and effective methods of optimizing patient care in the hospital setting. In the case that the patient has been referred to you in the outpatient setting, it is important to ensure that all other systems have been evaluated and other systemic injuries have been addressed. If you are concerned that other injuries have not been thoroughly evaluated, a referral to the emergency room is warranted.

A thorough examination of the craniomaxillofacial region is typically achieved as a component of the secondary survey. However, the evaluation of head and neck injuries is tantamount to the management of a patent airway. As airway management is the first step of the primary survey in the ATLS process, it is imperative that the facial structures have stability to support patency. Hemorrhage should be controlled via compressive dressings or ligation of visible vessels. Care should be taken when packing materials or balloon catheters are placed to tamponade bleeding in the case of severe panfacial injuries involving the midface and naso-ethmoidal-orbital regions, as the cranial base can be entered and injury to the brain or orbital contents can occur. Dental prostheses, debris, and avulsed teeth should be removed to prevent aspiration or airway obstruction. Comminuted or severely displaced fractures of the mandible may result in an upper airway obstruction via the posterior displacement of the mandible and tongue base, especially when the patient is in the supine position. When integrity of the mandible is lost, increased laxity of the supporting musculature of the tongue and submental regions can obstruct the posterior oropharynx (Figure 1-1). Manual repositioning of the mandible and tongue can be helpful in relieving the obstruction, until a patent airway can be achieved by placement of

• Box 1-1 Principles of Advanced Trauma Life Support (ATLS)

1. Primary survey
   - Airway management with cervical spine protection
   - Breathing/Ventilation/Oxygenation
   - Circulation with hemorrhage control
   - Disability: Neurologic status
   - Exposure/Environmental control
2. Resuscitation and immediate intervention for life-threatening injuries
   - Normalization of vital functions
   - Imaging: AP CXR/pelvis, abdominal ultrasonography, C-spine
3. Secondary survey
   - Includes a full history and physical examination
   - Reassessment of vital signs
   - Indicated imaging obtained
   - Special procedures
4. Definitive care

AP, Anteroposterior; *CXR,* chest x-ray.



• Figure 1-1 Posterior displacement of tongue and occlusion of upper airway resulting from bilateral mandibular fractures. The *arrow* is indicating the occlusion of the posterior airway space as a result of posterior displacement of the tongue base, in association with bilateral mandible fractures. (From Hupp J, Tucker M, Ellis E: *Contemporary oral and maxillofacial surgery*, ed 6, St Louis, 2014, Mosby.)

an oral airway appliance or endotracheal intubation. The use of bridle wires to stabilize widely displaced mandibular fractures may be beneficial not only to assist in the management of a patent airway, but also to help decrease medullary bleeding as well as provide some pain relief to the patient.

The patient interview should identify the time and by what mechanism the trauma occurred. It should be ascertained whether or not the patient lost consciousness, as this can give an indication as to the degree of head trauma involved and the force sustained to create such injuries.

Mechanism of Injury

When managing trauma patients, having an understanding of the injuries sustained via various mechanisms can guide the evaluation of the patient and the rapid assessment of specific injuries. All wounds should be assessed for degree of contamination, and steps should be taken for appropriate antibacterial therapy.

Penetrating injuries result in a localized focused path of entry and exit of a sharp object. Penetrating wounds to the head and neck require a careful evaluation of the upper airway and vasculature, as direct injury to these structures can occur, in conjunction with facial bone fractures and expected soft tissue lacerations. Appropriate diagnostic studies, such as angiography or computed tomography (CT), should be completed to evaluate these anatomic structures.

Blunt trauma to the head and neck typically results in contusions and shearing forces that result in soft tissue lacerations as a result of tearing or avulsive injury. Wound margins may have extensive ecchymosis and, because of the nature of the injury, may require debridement and refining of the tissue edges to allow for improved adaptation of the margins and healing by primary intention. Facial fractures that occur as a result of blunt injury can be heavily comminuted.

Wounds resulting from gunshots follow a specific trajectory and damage pattern depending on the type of bullet and velocity. Wounds should be inspected for bullet fragments and debris that may have been fragmented and pulled into the wound. Surrounding tissue damage caused by burn injury and coagulative necrosis can have a delayed effect. Repeat evaluations should be performed to assess for progressive tissue damage.

Considerations Regarding the Medical History

A thorough understanding of the patient's preexisting medical conditions dictates the management of the patient in the perioperative period, but also allows the practitioner to better prevent postoperative medical complications, which can lead to prolonged hospital stays and increased resource utilization. Other known risk factors that tend to be commonly associated with the trauma patient can contribute to the complexity of managing craniofacial trauma.

A thorough review of the medical history, known drug allergies, and tetanus immunization should be performed, to anticipate any risks for intraoperative or postoperative complications. If the OMS becomes the primary admitting service, appropriate consultations should be considered to

ture has identified certain chronic medical conditions that have an increased risk for complications and mortality in the inpatient setting. A systematic review of data from the National Trauma Data Bank from 2002 to 2006 showed that preexisting chronic hepatic failure (cirrhosis), dialysis (end-stage renal disease), and anticoagulative therapies were risk factors for both complications and mortality. HIV/AIDS was a risk factor for the development of complications during the hospital stay. However, all other medical conditions require attention in the perioperative period to ensure patient safety. Table 1-1 outlines some common

TABLE 1-1 Common Systemic Medical Conditions and the Considerations that Should Be Made in the Management of Patients with These Conditions, in the Perioperative Setting

Medical Condition	Preoperative Considerations	Postoperative Considerations
Known cardiovascular disease (hypertension, angina/ACS, dysrhythmias, CAD, CHF, valvulopathy, etc.)	Cardiac risk assessment, plan for blood product replacement in the setting of expected high volume blood loss (maintain hemoglobin 7-8 g/dL), antiplatelet/anticoagulant reversal as needed	Consider continuous cardiac monitoring, maintain hemoglobin 7-8 g/dL
Diabetes mellitus	Cardiac and renal function should be evaluated, tight glycemic control, glycated hemoglobin value (glucose between 140 and 200 mg/dL)	Tight glycemic control, compromised immune function requiring considerations for antibacterial therapy, delayed healing, optimize nutrition
Renal failure	Be cautious in the setting of contrast use for imaging studies, renal adjustment for medication administration, evaluate for coagulopathy, consider consultation with renal service to manage the need for dialysis, evaluate nutritional status	Fluid status maintenance, renal adjustment for medication administration, be cautious with the use of nonsteroidal anti-inflammatory medications
Liver failure	Adjustment for medication administration, evaluate for coagulopathy and/or thrombocytopenia, OR positioning in the setting of ascites, evaluate nutritional status, consider consultation with medicine services for management assistance	Optimize nutrition, adjustment for medication administration as needed
Chronic obstructive pulmonary disease (COPD)	Optimize airways for the OR	Avoid prolonged ventilator assistance, aggressive chest physical therapy
Acquired/congenital coagulopathy or antiplatelet activity	Reversal/correction of coagulopathy or platelet dysfunction	Quick resumption of anticoagulant or antiplatelet therapy balanced with the concern for postoperative hemorrhage
Stroke	Antiplatelet or anticoagulant therapy reversal as needed, adjustment to OR positioning,	Aggressive chest physical therapy, consider consultation with neurology/neurosurgery services regarding the timeliness of resuming anticoagulant or antiplatelet therapy
Adrenal insufficiency	Supplemental steroid administration to prevent acute adrenal crisis, evaluate for electrolyte abnormalities	Tight glucose control in the setting of exogenous steroid administration
Immunodeficiency (HIV/AIDS), immune suppression (post-transplant)	Evaluate nutritional status, compromised immune function requiring antibacterial therapy, evaluate for thrombocytopenia, need for supplemental steroid therapy in the post-transplant patient	Delayed healing, tight glucose control in the setting of exogenous steroid administration
Dementia	Concerns in obtaining proper informed consent, evaluate nutritional status	Concerns for compliance
Substance abuse (alcohol/opiate), tobacco	Specific nutritional supplementation (thiamine, folate, multivitamin) for the alcohol dependent patient, consider prophylaxis to prevent acute substance withdrawal, administer nicotine patches as needed	Continue to monitor for withdrawal symptoms, delayed healing, optimize for early discharge, concerns for compliance
Psychiatric illness	Continue all psychiatric medications as previously prescribed	Concerns for compliance
Seizure disorder	Continue all antiepileptic medications, relative contraindication to maxillomandibular fixation	
Pregnancy	Positioning in the OR, OB/GYN consultation for continuous fetal heart monitoring	Avoid nonsteroidal anti-inflammatory medications, avoid medications with known teratogenic effects
Eating disorders	Assess for electrolyte abnormalities, dysrhythmias, evaluate nutritional status	Consider nutrition consultation

ACS, Acute coronary syndrome; *AIDS,* acquired immunodeficiency syndrome; *CAD,* coronary artery disease; *CHF,* congestive heart failure; *HIV,* human immunodeficiency virus; *OB/GYN,* obstetrics and gynecology; *OR,* operating room.

systemic illnesses and considerations that should be made in the management of the patient. All preexisting medications should be continued throughout the hospital stay. In some cases administration parameters should be delineated in the setting of medications that may affect cardiovascular stability.

Patients with chronic medical conditions have a tendency to be undernourished, which can affect healing in the postoperative period. Laboratory studies such as albumin and pre-albumin levels can help to assess nutritional status, and nutrition should be supplemented to optimize healing. Consultations with the nutrition services can be helpful in these settings.

Trauma can be a reoccurring disease process, and certain risk factors are associated with the repeat trauma patient. Alcohol and drug use have been estimated to be involved in as many as 50% to 70% of all trauma patients. The potential for acute substance withdrawal should be assessed based on quantity and frequency of use, and appropriate prophylactic measures should be taken to reduce the risk of the development of withdrawal. Alcohol has been found to affect platelet aggregation and can promote increased intraoperative bleeding. Although typically this bleeding is not profound, in the case of expected high-volume blood loss it could be a major factor.

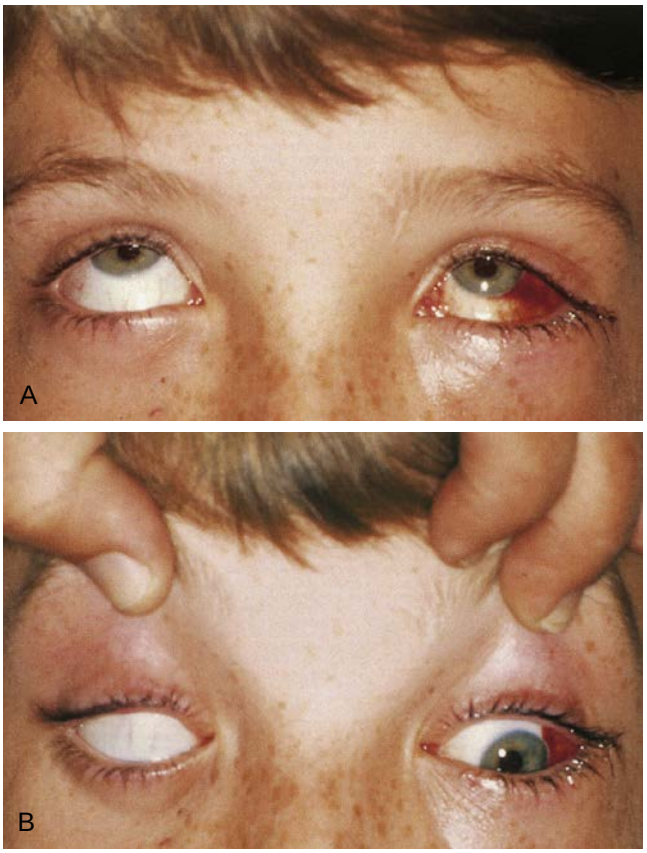
Clinical Examination

The clinical examination of the craniomaxillofacial trauma patient should be performed in a thorough and efficient manner. Every practitioner should develop an algorithm that allows adequate and consistent evaluation of facial and oral structures. The clinical exam should dictate the need for any additional diagnostic studies, which should confirm or refute the clinical suspicion of fracture.

The scalp and soft tissue structures should be directly visualized for any lacerations or abrasions. In the case of patients placed in cervical spine precautions, the assistance of others should be solicited to roll the patient while maintaining proper spinal alignment so the back of the scalp can be examined thoroughly. The OMS should be mindful of the location of lacerations in relation to underlying fractures, as decisions regarding immediate versus delayed repair of the laceration may aid in definitive fracture repair.

If lacerations to ears are extensive or there are suspected fractures to the temporomandibular joints, the tympanic membranes should be evaluated via the use of an otoscope.

The eyes should be examined for lacerations to the eyelids and any penetrating injury to the globe. If lacerations involve the lid margin, an immediate ophthalmologic consultation should be obtained to evaluate the integrity of the canalicular structures. If any fat herniation is present, a globe injury should be suspected, and again an ophthalmologic consultation should be obtained. Pupillary abnormalities should be assessed, and documentation needs to be made if dilatory medications are used to aid the fundoscopic examination. Extraocular muscular function should be examined via range-of-motion and visual-field assessment to rule out the potential for muscle entrapment involving orbital wall defects (Figure 1-2). Measurements should be made of the interpupillary and intercanthal distances, to guide repairs in the setting of naso-orbito-ethmoid complex fractures (Figure 1-3).

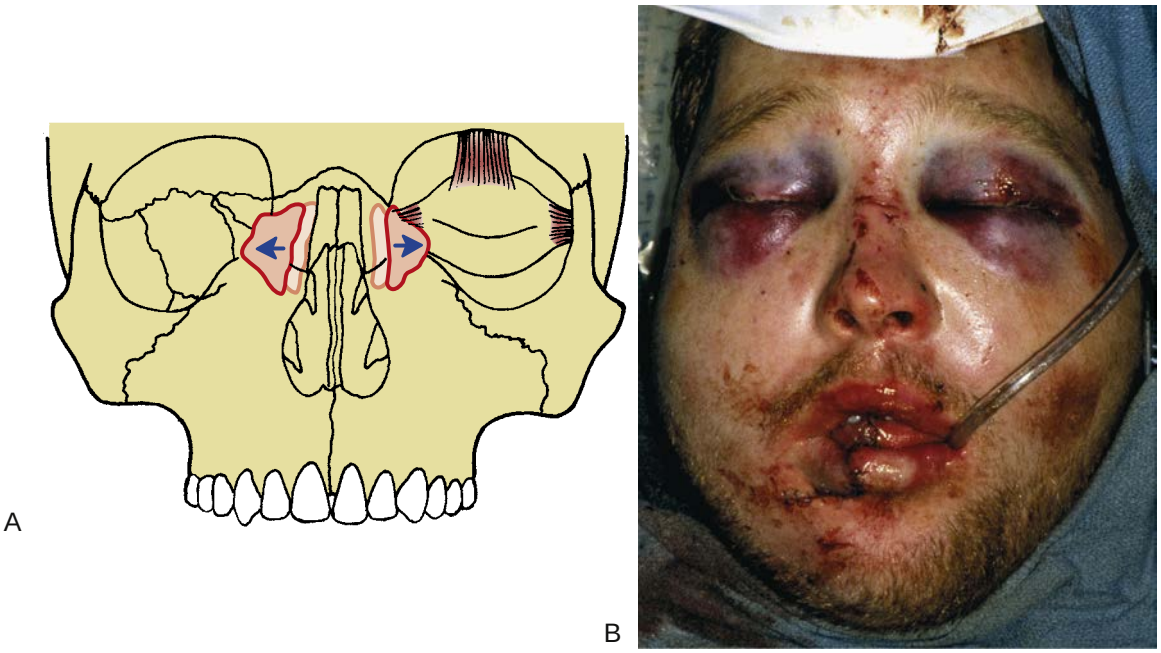


• **Figure 1-2** **A,** A 14-year-old patient with a left orbital floor fracture in upward gaze. **B,** Entrapment of inferior rectus muscle is the result of impingement in area of linear orbital floor fracture. In the down gaze, the patient is unable to rotate the left eye inferiorly, whereas the right eye is fully rotated inferiorly. (From Hupp J, Tucker M, Ellis E: *Contemporary oral and maxillofacial surgery*, ed 6, St Louis, 2014, Mosby.)

All facial structures should be palpated and manipulated for crepitus, mobility, or disruption of normal anatomic structures suggestive of bony fractures. Again, all suspected fractures should be confirmed against radiographic imaging.

The nasal bones should be directly palpated and the patency of the nasal airways should be evaluated. The nasal septum should be evaluated for laceration, perforations, and hematoma formation, as this could result in ischemic changes to the cartilaginous septum.

The intraoral examination should assess the dentition for fractured or avulsed teeth. The occlusion should be evaluated for any malocclusion, premature contacts, or disruption of the arch form. A determination should be made, based on discussions with the patient and the examination of occlusal wear patterns, regarding the patient's preexisting



• **Figure 1-3** Injury to naso-orbito-ethmoid (NOE) complex, which resulted in the displacement of medial canthal ligaments and a widening of the intercanthal distance (i.e., traumatic telecanthus). **A,** Diagram of bony fractures and medial canthal ligament displacement. **B,** Clinical photograph. (From Hupp J, Tucker M, Ellis E: *Contemporary oral and maxillofacial surgery*, ed 6, St Louis, 2014, Mosby.)



• **Figure 1-4** Irregularity of plane of occlusion and laceration in gingiva and mucosa between the mandibular central incisors, indicating a likelihood of mandibular fracture in this area. (From Hupp J, Tucker M, Ellis E: *Contemporary oral and maxillofacial surgery*, ed 6, St Louis, 2014, Mosby.)

occlusal scheme. This will provide guidance during any fracture reduction surgery to create a reproducible occlusion. Gingival or mucosal lacerations, ecchymosis of the tissues of the floor of the mouth and vestibule, crepitus while palpating the vestibule, and areas of point tenderness could be suggestive of mandibular fractures (Figure 1-4). Crepitus and ecchymosis of the maxillary vestibule could be suggestive of a maxillary fracture at the Le Fort I level or a zygomaticomaxillary complex fracture. Bimanual palpation and manipulation of the maxilla and mandible should be performed to assess for gross mobility (Figure 1-5).

Diagnostic Studies

The medical history and clinical examination should identify the need for any additional studies. Laboratory values and radiographic imaging should be discussed and ordered in conjunction with those needed by other services. Typically a complete blood count with differential, hemoglobin and hematocrit, complete or basic metabolic panel, and coagulation studies are ordered for diagnostic and preoperative planning. Although plain films can be helpful, CT is considered the standard of care for imaging the facial bones. The exception in this author's opinion is the panoramic image, which provides valuable information when evaluating a mandibular fracture. Other imaging studies such as angiography and magnetic resonance imaging (MRI) may be useful in certain situations when the vessels or other soft tissue structures need to be evaluated.

Planning for Definitive Care

Once the patient has been thoroughly evaluated and the injuries requiring treatment have been identified, a definitive plan of care needs to be devised. In the case of isolated



• **Figure 1-5** Examination of maxilla for mobility. **A,** Firm pressure on the forehead is used to stabilize the patient's head. Pressure is placed on the maxilla in an attempt to elicit mobility. **B,** A stabilizing hand can also evaluate mobility in the area of nasal bones. (From Hupp J, Tucker M, Ellis E: *Contemporary oral and maxillofacial surgery*, ed 6, St Louis, 2014, Mosby.)

facial lacerations, a decision needs to be made if the repair can be effectively achieved in the emergency or inpatient room, or if the patient needs to be taken to the operating room. Patients whose situations require better lighting, aggressive hemostasis control, large volumes of local anesthetic, complex instrumentation, or a setting better suited for the sedated patient should be taken to the operating room.

In the case of multisystem injuries, the trauma patient may make multiple trips to the operating room. Discussions with other surgical services can allow for coordinated care, so that the risks associated with general anesthesia are kept to a minimum. Positioning and sterile draping can be coordinated to allow simultaneous access to the head and neck and other parts of the body. Communication with the anesthesia staff and trauma team should be clear if the patient will remain in maxillomandibular fixation in the postoperative period, as this may play a factor in airway management. Nasoendotracheal or submental intubation techniques or a tracheostomy will be necessary in the patient remaining in maxillomandibular fixation, and length of time of expected postoperative intubation will typically dictate the technique used.

Informed consent must be obtained from the patient when possible; however, in the trauma setting this may not be feasible. In cases that necessitate a power of attorney or other designated persons, adherence to specific hospital protocols is imperative.

Preventative Measures to Optimize Patient Care in the Preoperative Setting

Hospitalized patients are at risk for the development of various adverse events directly or indirectly associated with the condition that brought them to the hospital. Minimizing the potential for these events can reduce the length of the hospital stay as well as limiting resource utilization in all patients, especially those with multisystem traumatic injuries.

The use of H2 antagonists and proton pump inhibitors can decrease gastric acid production and risk for gastrointestinal bleeding. The increased stress on the body as well as varying parenteral nutrition can promote increased gastric acid production and the potential for peptic inflammation and ulceration.

Prevention of thrombosis and a subsequent embolic event in the trauma patient is imperative. While fractures of the long bones can promote fat emboli, the non-ambulatory state of many patients puts them at risk for the development of deep vein thrombi and possible pulmonary emboli. Sequential compression devices should be used in low-risk patients, and prophylactic anticoagulant therapy in those at greater risk.

Tight glycemic control has been found to positively affect outcomes in the hospitalized patient population. Studies have identified maintaining blood glucose levels between 140 and 200 mg/dL at all times can decrease the risk for adverse events.

Postoperative Management

The postoperative management of any patient should focus on expeditious discharge from the hospital. In the case of the craniomaxillofacial trauma patient, excluding recovery from other injuries, this typically revolves around the resolution of symptoms associated with general anesthesia and the reduction of postoperative complications.

Antibiotic therapy should be tailored for each patient, taking into consideration contamination of the surgical wounds and the integrity of the immune system, balanced with the concerns for the promotion of resistant bacteria and the development of *Clostridium difficile* colitis.

Encouraging ambulation postoperatively helps to decrease the risk of thrombosis, promotes voiding of the bladder, and aids in preventing pulmonary complications. Foley catheters used intraoperatively should be discontinued as soon as possible to promote ambulation and decrease the potential for urinary retention, especially in older male patients.

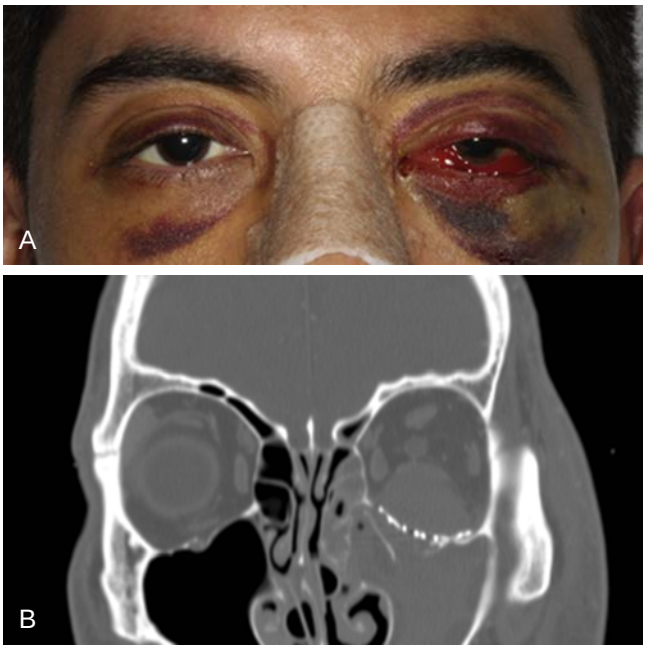
Aggressive incentive spirometry and chest therapy can help in resolving ventilator-associated atelectasis and decrease the risk of nosocomial pneumonia.

Pain in the postoperative period needs to be adequately managed to encourage a quick recovery. However, the use of intravenous medications can delay the discharge process. Transitioning the patient to oral forms of medication is important in discharge planning. Prolonged use of opioid medications has the adverse side effect of promoting constipation. With aggressive Valsalva maneuver while attempting to empty the bowels, there is an initial rise in blood pressure and stroke volume, followed by a decrease in venous return with increased intrathoracic pressure. The initial spike in stroke volume and blood pressure can promote postoperative complications associated with bleeding, such as retrobulbar hematoma formation following orbital floor repairs, or epistaxis following nasal bone reduction or other midface repairs (Figure 1-6). Administering stool softeners and laxatives in conjunction with opioid analgesics can reduce this potential and improve patient comfort.

Proper orders regarding wound care and suture removal should be provided to the nursing staff and to the patient on discharge. Wire cutters should be provided for patients placed in maxillomandibular fixation, to be carried with them at all times in the case of a medical emergency, and clear instructions should be provided on how to release the fixation if necessary.

Dietary restrictions, if any, should be specified for every patient and clearly delineated. All enteral and parenteral feeds should be resumed as soon as possible following surgery.

Instructions for follow-up should be clear and communicated to the patient and all services involved. All inpatient medications should be reviewed and confirmed against preadmission medications and any new medications required as a result of the hospital stay. Medication lists should be adjusted accordingly based on appropriate start and stop times designated by the prescribing service.



• **Figure 1-6** Postoperative hematoma formation in a patient 3 days following left orbital floor repair, who had been taking opioid pain medication for 7 days preoperatively. The patient reported straining and developing immediate sharp pain in the left eye. He reported to the emergency room, at which time evaluation noted a collection of blood in the left orbit. The hematoma was decompressed following release of the sutures used to repair the lateral canthotomy. The patient was evaluated by the ophthalmology service and had no residual visual or cosmetic defects. **A,** Proptosis associated with the left pupil. **B,** Hematoma associated with left orbital floor repair seen on coronal computed tomographic imaging.

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2

Airway and Anesthetic Management for the Traumatized Patient

ELIE M. FERNEINI, JEFFREY D. BENNETT

This chapter focuses on anesthetic and airway considerations in the management of the patient with oral and maxillofacial surgery injuries. This chapter emphasizes the basic principle of management as well as different pre-, intra-, and postoperative anesthetic strategies.

The Importance of the Airway in Maxillofacial Trauma

The maxillofacial trauma patient can present with impending airway compromise. During the initial assessment, the airway should be assessed for patency. Maxillofacial injuries can prevent the trauma surgeon from securing an airway. An airway obstruction can be due to a foreign body, mandibular injury, maxillary injury, tracheal injury, laryngeal injury, or tongue injury, which can be compounded by hemorrhage or edema resulting from injuries to these or associated structures. The trauma surgeon must evaluate the airway using a systematic approach. This will allow the accurate diagnosis of any life-threatening or minor injury.

During this assessment, great care must be taken to avoid excessive movement of the cervical spine. Patients with maxillofacial or head trauma should be presumed to have an unstable cervical spine injury. The patient's neck should not be rotated, hyperflexed, or hyperextended. In order to minimize iatrogenic injury, the patient's neck should be immobilized until a detailed cervical spine examination and complete cervical spine radiographic series are performed and a cervical spine injury has been ruled out.[1] There is no urgency to rule out a cervical spine injury in the newly injured unresponsive patient until the patient becomes fully cognizant and can subjectively respond to the assessment.

A common error in trauma management during the primary survey involves delay in securing the patient's airway. It is important for the trauma surgeon to be comfortable and competent at airway management.[2] Maxillofacial trauma can complicate airway management both in that[3] the injuries can compromise airway integrity, resulting in poor exchange or obstruction, and[4] the soft tissue or skeletal injury may make providing respiratory support difficult.

Initial Airway Assessment

Upon initial evaluation, the airway should be assessed to ascertain patency. Any airway obstruction can prevent securing a definitive airway. The well-established approach to the ABCs (airway, breathing, circulation) is the standard approach. Is the patient able to communicate verbally? Is the patient breathing spontaneously? Does the patient have adequate oxygenation? A negative response to any of these questions will require emergent intervention to secure adequate oxygenation and ventilation. The inability to obtain control of the airway can result in irreversible brain damage due to hypoxia in as little as 4 minutes. Severe head-injury patients with a Glasgow Coma Scale (GCS) score of 8 or less usually require the placement of a definitive airway.

Airway patency does not ensure adequate ventilation. Ventilation requires adequate gas exchange with adequate oxygenation with normal function of the lungs, diaphragm, and chest wall. A rapid assessment of these components is important. Performing a detailed and rapid thoracic lung exam can aid in this assessment. Chest auscultation and percussion can help in assessing the patency of oxygenation; auscultation is the most important technique in assessing air flow through the tracheobronchial tree. Breath sounds may be decreased when air flow is decreased (due to muscular weakness) or when the transmission of sound is poor (due to pleural effusion or pneumothorax). Additionally, the chest wall should be visually inspected to rule out any chest injuries. Conditions such as flail chest or massive hemothorax, as well as tension or open pneumothorax, can compromise ventilation and oxygenation and need immediate attention.

Every trauma patient should receive supplemental oxygen. Maintaining good oxygen saturation and preventing hypercarbia are key factors. A pulse oximeter is essential

in assessing adequate hemoglobin saturation. It is essential to put the pieces together, assessing visual inspection and data obtained from monitors, and integrating that information with the history of the event. This is illustrated by the potential for a false initial assessment for a patient who may have both normalappearing skin tone and oxygen saturation secondary to carbon monoxide exposure. Capnography could be helpful in monitoring the concentration or partial pressure of carbon dioxide (CO_2). It is usually presented as a graph of expiratory CO_2 plotted against time. The capnogram is a direct monitor of the inhaled and exhaled concentration or partial pressure of CO_2 and is actually an indirect monitor of the CO_2 partial pressure in the arterial blood.

Vital signs are an important part of the assessment. Hypotension is usually indicative of hypovolemia. In fact, hemorrhage is the most common cause of shock after injury. Almost all trauma patients have an element of hypovolemia, which is indicative of hemorrhagic shock. Cardiogenic shock due to myocardial dysfunction can occur in trauma patients, especially if they sustain blunt cardiac injury, cardiac tamponade, or myocardial infarction.[5] Skin color could be an important tool in assessing perfusion and oxygenation. Checking capillary refill is a useful tool. This is the rate at which blood refills empty capillaries. Capillary refill is prolonged if it is over 1.5 to 2 seconds. Prolonged capillary refill suggests diminished localized blood flow or dehydration.

History

As appropriate, each trauma patient should have a complete history and medical examination. In many acute trauma patients, history cannot be obtained from the patient. Prehospital personnel and family members may be helpful in providing some of this relevant information. The AMPLE history is a quick mnemonic to use in evaluating the trauma patient:

A: Allergies
M: Medications (currently used)
P: Pregnancy/Past illnesses
L: Last meal
E: Events/Environment related to the injury

Knowing about the past medical history (such as medical problems, medications, and allergies) is a key factor in successfully treating the trauma patient. A patient who is on a beta blocker can have a "normal" heart rate even in hypovolemic shock. Additionally, patients on anticoagulants are prone to severe bleeding and hemorrhage. With many elderly patients on anticoagulants, a neurologic hemorrhage must be ruled out in this patient population. Physiologic changes in the gravid patient present several potential challenges. There is the potential for airway compromise associated with an increased risk of aspiration, decreased functional residual volume, and increased difficulty in intubating the airway. There are hemodynamic changes that impact fluid management, as well as the pharmacokinetics and pharmacodynamics of anesthetic and emergency agents. Many anesthetic and emergency drugs can cross the placenta and have an adverse effect on the fetus.

The mechanism of injury can provide the trauma surgeon with pertinent information about the type of injuries sustained. Blunt injuries usually result from motor vehicle accidents (MVAs), falls, and occupation-related injuries. Important prehospital information to obtain from MVA patients includes seat belt usage, direction and type of impact, steering wheel deformation, and automobile damage. The mechanism of injury can usually predict the injury patterns. For example, rear impact in an MVA will probably result in cervical spine injury and/or soft tissue injury to the neck. Penetrating injuries are usually caused by stabbings and firearms. The extent of injury depends on the region of the body affected, the path of the penetrating object, and the organs in proximity to the injury, as well as the velocity of the missile.

Physical Examination

Airway patency can affect the ability to ventilate and intubate the patient. Part of a detailed trauma examination is to recognize the problem and manage it appropriately. Airway compromise may be partial or complete. Signs such as stridor, dyspnea, tachypnea, and dysphagia may be indicative of airway obstruction. Tachypnea, additionally, could be an early sign of airway or ventilatory compromise. The patient with an altered level of consciousness is at high risk of airway compromise and will require a secure airway.

1. Soft tissue: A detailed soft tissue examination must be performed. Significant tissue avulsions or injuries may result in an ability to secure a mask and provide ventilatory support.
2. Hemorrhage: Hemorrhage can lead to airway irritation, aspiration, and laryngospasm. Pressure packing may be needed to control the bleeding. If the bleeding does not stop, surgical exploration or interventional radiology might be indicated (especially in neck trauma). Hemorrhage can result in an expanding hematoma that can compromise airway integrity. Securing an airway either via intubation or tracheotomy may be required.
3. Skeleton
   (a) Mandibular fractures are common in trauma patients. Bilateral mandibular fractures can lead to a flail mandible. This can lead to an upper airway obstruction due to posterior movement of the tongue. Lying supine can further aggravate the obstruction. Airway adjuncts (e.g., nasopharyngeal airway) may assist in supporting and maintaining airway patency.
   (b) Trauma to the midface can result in injuries to the nasopharynx and oropharynx. These fractures could be associated with hemorrhage, dislodged teeth, or unstable segments (maxilla or midface), any of which could lead to airway compromise. Posterior and downward displacement of a Le Fort fracture can result in an open bite and difficulty with mask ventilation. Displacement of a Le Fort II/III fracture can result in obstruction of the nasopharynx.

(c) Nasal fractures can lead to posterior bleeding and aspiration and thus to nasopharyngeal obstruction. Nasal intubation is relatively contraindicated in midface fractures because of the risk of the endotracheal tube entering either the cranium or the orbit. A hematoma in the oropharynx or nasopharynx can lead to partial or complete airway obstruction. A nasal septal hematoma can lead to nasopharyngeal obstruction. An urgent surgical airway may be needed if endotracheal intubation is not possible.

4. Laryngeal trauma: Hoarseness can be associated with laryngeal trauma. Laryngeal trauma is associated with the triad of hoarseness, subcutaneous emphysema, and a palpable fracture. Patients with arytenoid injury are at higher risk of aspiration. Some of the symptoms of arytenoid injury include hoarseness, dysphagia, sore throat, dyspnea, vocal fatigue, loss of vocal control, and cough.[6] A flexible endoscopically guided intubation may be helpful in laryngeal trauma. Early diagnosis of tooth aspiration in the multi-trauma patient can be difficult because aspiration is rarely considered in the absence of an acute clinical presentation. Accounting for teeth is an important aspect of the maxillofacial exam.

Injuries Affecting the Airway: Cervical Spine Injury

Cervical spine injury must be presumed in any patient with maxillofacial or head trauma. The incidence of cervical injury in the presence of facial fractures has been reported to be 1% to 6%.[7-9] Cervical spine injuries tend to occur in patients between 15 and 45 years of age and are seen more commonly in males (7:3). The most common level of fracture is C2, whereas dislocations occur most commonly at the C5/6 and C6/7 levels.[10]

The exclusion of cervical spine injuries, or "clearance," requires the exclusion of both bony and ligamentous injuries. This usually calls for a combination of clinical assessment and radiologic investigation. Clinical clearance of cervical spine injury is difficult and unreliable in patients who are unconscious or have distracting injuries to other parts of the body.

Examination of the neck includes inspection, palpation, and auscultation. The standard three-view plain film series for a c-spine evaluation includes lateral, anteroposterior, and open-mouth view. The lateral cervical spine film must include the base of the occiput and the top of the first thoracic vertebra. The lateral view alone is inadequate and will miss up to 15% of cervical spine injuries. The lower cervical spine may be difficult to examine, and caudal traction on the arms should be used to improve visualization. If the lower cervical spine is not visualized, a computed tomography (CT) scan of the region is indicated.[11,12] Thin-cut (2-mm) axial CT scanning of specific bone windows, with sagittal and coronal reconstruction, should be used to evaluate abnormal, suspicious, or poorly visualized areas on plain radiology. With technically adequate studies and experienced interpretation, the combination of plain radiology and directed CT scanning provides a false-negative rate of less than 0.1%.[12] Magnetic resonance imaging (MRI) is the gold standard for clearing the cervical spine in a clinically suspicious or unresponsive trauma patient.[13] In most trauma centers, cervical fixation is usually maintained until the patient is awake and can respond to command.

The best method of immobilization is achieved with a combination of a rigid cervical collar, a cervical/head immobilizer, and a backboard.[14] Rigid cervical collars (by themselves) limit rotation and lateral movement only to 50% of normal and flexion and extension only to 30% of normal and do not provide adequate stabilization.

Respiratory complications are common with cervical spine injuries. The severity of respiratory failure depends on the level and severity of the injury. Complete dissection of the spinal cord above C3 will cause apnea and death, unless the patient receives immediate intubation and ventilatory support. For lesions between C3 and C5, the degree of respiratory failure is variable. The vital capacity can be reduced to 15% to 20% of normal. These patients are at risk of increasing diaphragmatic fatigue due to slowly progressive ascending injury resulting from cord swelling and edema. This usually leads to decompensation and retention of secretions on day 3 to 4 post injury. Intubation and ventilation is needed to prevent respiratory failure. Patients with high cervical spine lesions have increased bronchial secretions, possibly due to altered neuronal control of mucous glands. Injuries at C5 or below spare the phrenic nerve and diaphragmatic breathing. However, expiratory reserve may be impaired secondary to accessory muscle paresis.[15]

The decision to intubate depends on several factors, including:[16,17]

- Loss of innervation of the diaphragm (e.g., phrenic nerve injury)
- Fatigue of muscles of respiration
- Failure to clear secretions
- Failure to maintain a patent airway
- History of aspiration
- Presence of other injuries (e.g., head, maxillofacial, and/or chest injuries)
- Premorbid conditions, especially respiratory disease (chronic obstructive pulmonary disease) and/or obesity

Injuries Affecting the Airway: Cervical Airway Injury

Injuries to the cervical airway may result from blunt or penetrating trauma. The incidence is usually rare. Blunt trauma to the airway either from a direct blow to the cervical airway or from severe flexion/extension injuries may result in a thyroid or a cricoid cartilage fracture.[18]

Injuries Affecting the Airway: Thermal and Inhalation Injury

Thermal and/or inhalation injury to the airway must be suspected in any patient presenting with a history

of exposure to fire or smoke. Carbon monoxide (CO) toxicity is a major problem. CO does not cause direct injury to the lungs. Its toxic effect results from a displacement of oxygen from hemoglobin-binding sites, thereby decreasing the oxygen-carrying capacity of the blood. This causes a shift of the oxyhemoglobin dissociation curve to the left. This results in tissue hypoxia because the hemoglobin binds less oxygen for transport to the peripheral tissues and is less able to unload the oxygen to those tissues. CO reacts with myoglobin to further impair oxygen uptake by decreasing facilitated diffusion of oxygen into muscle. This leads to impaired tissue oxygen availability and delivery.[19,20] Cyanide causes tissue asphyxiation through the inhibition of intracellular cytochrome oxidase. It blocks the final step in oxidative phosphorylation and prevents mitochondrial oxygen use. The organs most affected to cellular hypoxia include the central nervous system and the heart.

Inhalation injury can occur with or without evidence of burns. Burns on the face and singed eyebrows and/or facial hair are indicative of smoke inhalation. Patients with respiratory injury present with many symptoms, including minor eye irritation, cough, dyspnea, hyperventilation, tachypnea, rales, wheezing, and facial burns. This can lead to acute respiratory failure. These symptoms usually present within 6 to 24 hours post injury.[19]

Pulse oximetry is an accurate technique to monitor oxygen saturation. However, it is falsely elevated by CO. One must not rely on pulse oximetry until the carboxyhemoglobin level has reached the reference range.

Additionally, arterial oxygen tension (partial pressure arterial oxygen [PaO_2]) does not accurately reflect the degree of CO poisoning or cellular hypoxia. The PaO_2 level reflects the oxygen dissolved in blood that is not altered by the hemoglobin-bound CO. Because dissolved oxygen makes up only a small fraction of arterial oxygen content, a PaO_2 level within the reference range may lead to serious underestimation of the decrement in tissue oxygen delivery and the degree of hypoxia at the cellular level that occurs when CO blocks the delivery of oxygen to the tissues. However, arterial blood gas (ABG) measurements are still useful.

Cyanide levels correlate closely with the level of exposure and toxicity. However, these levels may not be readily available. Many hospitals send out these tests, and results may take several days to a week. Persistent neurologic dysfunction unresponsive to use of supplemental oxygen, cardiac dysfunction, and severe lactic acidosis are usually indicative of cyanide intoxication. In a setting consistent with potential cyanide exposure, empiric therapy should be [19,20]

are

Anesthetic Strategies

The goal of triage is to classify patients into various categories, identifying the urgency of treatment. Traumatized patients are divided into two major categories:

- **Those patients who require airway control as part of the resuscitation.** These patients are usually apneic or have total or near-total airway obstruction. They are identified during the primary survey and will require establishment of a patent airway. Initially, the mouth must be inspected for the presence of any foreign material. Then administration of positive pressure ventilation by mask with 100% oxygen is performed. If ventilation is unsuccessful, placement of an oropharyngeal or nasopharyngeal airway may be used to facilitate mask ventilation. The surgeon must be aware of the potential complications of these airways. The oropharyngeal airway can induce gagging and coughing. This may lead to increased intracranial or intraocular pressure and/or vomiting. The nasopharyngeal airway can lead to epistaxis, and care must be used when using it in a patient with a base-of-lumen airway) may be considered in these cases.
- **Those patients who require semi-elective airway control at some time during hospitalization for surgical management of the maxillofacial injury.** These patients usually require elective intubation or, in selected situations, a tracheostomy. Intubation or a surgical airway in this situation provides a patent airway, protects against aspiration of secretions, allows positive pressure ventilation, decreases anatomic dead space, and provides a potential emergency route for drug administration.

Basic Principles of Management

Prophylaxis Against Aspiration

Trauma patients are always considered to have full stomach. This is due to multiple reasons including:

- Ingestion of food or liquids before injury
- Swallowed blood from oral or nasal injury
- Delayed gastric emptying
- Administration of liquid contrast medium

Various actions are considered to prevent aspiration:

- Administer nonparticulate antacid prior to induction
- Cricoid pressure/Sellick maneuver applied continuously during airway management
- Rapid-sequence induction (RSI)
- Avoidance of ventilation between administration of medication and intubation
- Awake intubation with or without topical or anesthetic blocks to the upper airway

Induction of General Anesthesia

There is no ideal anesthetic drug for trauma patients with hemorrhagic shock. The key to safe anesthetic management

of these patients is to administer small incremental doses of whichever agents are selected. Titration of the general anesthetic is a key factor in preventing complications. Many agents are in our armamentarium for anesthetic planning. Some of the induction agents are propofol, etomidate, ketamine, and dexmedetomidine.

Propofol is an ideal general anesthetic agent used in induction. It has a rapid onset of action as well as fast recovery from its sedative-hypnotic effects. Propofol has antiemetic effects that may be beneficial, especially for a patient who may have maxillomandibular fixation. However, propofol has some unwanted side effects in trauma patients. It may potentiate profound hypotension due to its direct myocardial depression and decrease in systemic vascular resistance. These effects can be potentiated in the elderly or cardiac patient[22] and can be exacerbated in the hypovolemic trauma patient.

Etomidate is widely used in the trauma population because of its cardiovascular stability relative to other induction agents. In fact, etomidate provides advantages for induction of anesthesia in the setting of hemorrhagic shock. In a pig model of hemorrhagic shock, its pharmacodynamics and pharmacokinetics are minimally altered in contrast to other anesthetic drugs. However, etomidate may still produce profound hypotension due to its inhibition of catecholamine release. Additionally, it can cause adrenocortical suppression. Adrenal suppression was found to last 6 to 8 hours in patients following a single induction dose of etomidate, and more than 24 hours following etomidate infusion. However, the impact of single-dose etomidate on outcomes in critically ill patients remains unclear.[23,24]

Ketamine can be used for induction in trauma patients. It is most suitable in children who are hemodynamically unstable or hypovolemic.[25] Similar to propofol, ketamine is also helpful in asthmatic patients because of its bronchodilating properties. It can result in myocardial depression. In normal patients, the effects of catecholamine release usually will mask cardiac depression and result in tachycardia and hypertension. In patients with severe hemorrhagic shock, the cardiac depression may be unmasked. This will lead to cardiovascular collapse.[26,27]

Dexmedetomidine is an agonist of α_2-adrenergic receptors in certain parts of the brain. It is indicated for sedation of critically ill or trauma patients in an intensive care unit setting. Dexmedetomidine may also be used to provide sedation for an awake intubation. Clinically it provides sedation and analgesia. It does so with minimal respiratory compromise. Dexmedetomidine is administered via a slow bolus supplemented with a continuous infusion. It is not administered with incremental boluses because of concerns about peripheral α_2-receptor stimulation, with resulting hypotension and bradycardia. Intravenous infusion is commonly initiated with a 1 mcg/kg loading dose, administered over 10 minutes, followed by a maintenance infusion of 0.2 to 1.0 mcg/kg/hour.[28]

Succinylcholine remains the neuromuscular blocker with the fastest onset (30 seconds) and shortest duration of action. Therefore, it is the agent of choice for RSI. It is especially indicated in trauma patients presenting for an emergency procedure with a potentially full stomach or who have recently eaten.

However, succinylcholine may be contraindicated in selected trauma patients:

- Burn patients: Succinylcholine must be used cautiously in burn victims (after the first 24 hours) because of increased serum potassium. The rise in serum potassium that normally follows succinylcholine administration is markedly exaggerated in burned victims. The levels can reach as high as 13 mEq/L, resulting in ventricular tachycardia, fibrillation, and cardiac arrest.[29,30]
- Crush injury: Succinylcholine must be used cautiously in patients with crush injury. The injury to the muscular tissue secondary to the crush injury results in hyperkalemia, which can be compounded with the administration of succinylcholine.
- Ocular injury: Succinylcholine must be used cautiously in patients with intraocular trauma or ocular injury. It leads to increased intraocular pressure (IOP). The increased IOP occurs within 1 minute after injection, peaks at 2 to 4 minutes, and subsides by 6 minutes.[31]
- Intracranial injury: Succinylcholine results in increased intracranial pressure (ICP). In trauma patients with head injury, succinylcholine must be used cautiously. The risk must be weighed in each individual situation.

Rocuronium can be also used safely during RSI (1 mg/kg), with an onset of relaxation of 60 seconds. Unfortunately, at this dose the duration of action will be 1 to 2 hours.[32] Sugammadex is an agent for reversing the neuromuscular blockade caused by a nondepolarizing agent such as rocuronium. Its main advantage is reversal of neuromuscular blockade without relying on the inhibition of acetylcholinesterase. Its administration is therefore associated with much greater cardiovascular and autonomic stability than the traditional reversal agents. This agent is not yet available on the U.S. market.

Maintenance of anesthesia can be achieved with a combination of inhalation as well as intravenous agents.

Advanced Airway Techniques

The maxillofacial surgeon must be aware of the different available modalities to secure the airway. These include:

1. Two-handed mask ventilation: Bag-mask ventilation is the cornerstone of basic airway management. When a second person is available to provide ventilations by compressing the bag, a two-hand technique can be used. The surgeon creates opposing semicircles with the thumb and index finger of each hand to form a ring around the mask connector and hold the mask on the patient's face. Then, the mandible can be lifted with the remaining digits.[33]
2. Combitube: A Combitube, also known as a double-lumen airway, is a blind insertion airway device (BIAD) used in the prehospital and emergency setting. It is ideal to provide an airway for the trauma patient in respiratory

distress. The simplicity of placement is a major advantage over endotracheal intubation. However, this technique has some serious but rare complications, including aspiration, esophageal perforation, and facial nerve dysfunction.[34]

3. LMA: The laryngeal mask airway (LMA) is an easy way to ventilate a trauma patient (Figure 2-1). It is a supraglottic airway device and is a good alternative to bag-valve-mask ventilation (freeing the hands of the provider with the benefit of less gastric distention).[35] The LMA is actually placed into the back of the mouth following the curve of the tongue (Figure 2-2). The rate of complications is rare (0.15%). These complications include[36,37] aspiration of gastric contents, local irritation, pressure-induced lesions, facial nerve palsies, mild sympathetic response, obstruction, and laryngospasm.
4. The laryngoscope is a useful technique to visualize the

in 1998. Currently, there are several manufacturers of video laryngoscopes. These include the Glidescope, McGrath laryngoscope, Daiken Medical Coopdech C-scope vlp-100, and the Berci DCI laryngoscopes.



• **Figure 2-1** Laryngeal mask airway. (From Nemeth J, Maghraby N, Kazim S: Emergency airway management: the difficult airway, *Emerg Med Clin North Am* 30(2):401-420, 2012.)

6. Retrograde intubation is another alternative to secure an airway in the trauma patient. Under local anesthesia, a cannula is inserted through the cricothyroid membrane into the trachea, and a guide wire is then passed through the needle upward through the vocal cords into the oral cavity. The wire is then used to guide an ET tube through the vocal cords.[39]

Surgical Airways

Emergency airway management in the trauma patient often involves a combination of factors that increase the technical difficulty of intubation and increase patient risk. These factors include:

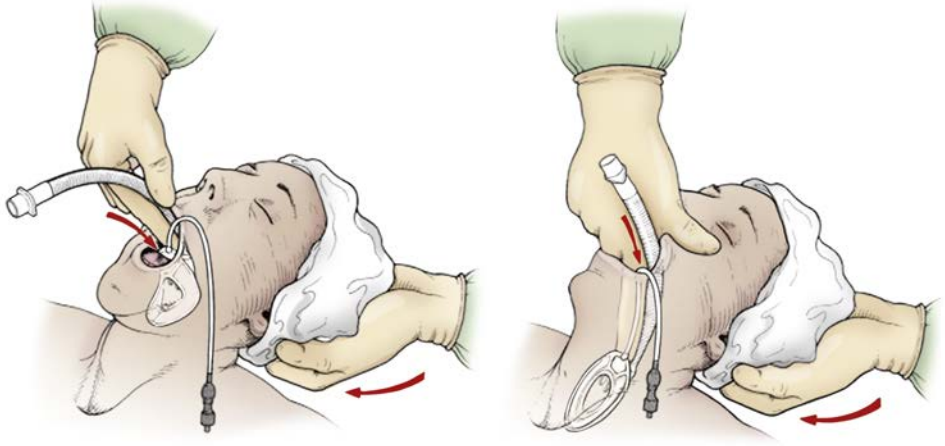
- Dynamically deteriorating clinical situation in the unstable patient
- Respiratory and ventilatory compromise
- Impaired ventilation and oxygenation
- Full stomach (increased risk of regurgitation, vomiting, aspiration)
- Increased secretions, blood, vomitus, and potential for foreign body
- Distorted anatomy

If intubation is not possible, a surgical airway is advised.

Emergency Cricothyrotomy

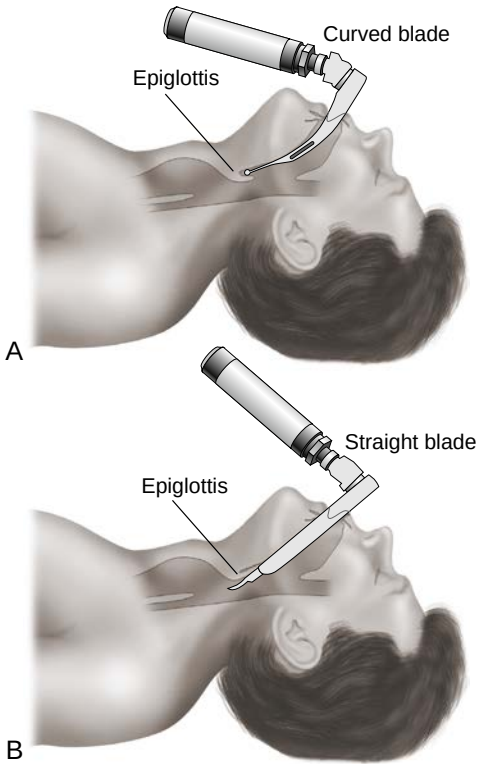
Emergency cricothyrotomy is one of the last-resort and potentially lifesaving procedures for maxillofacial trauma patients who cannot be intubated or ventilated.[40]

Traditionally, a surgical airway has been established by making an incision through the skin and the cricothyroid



• **Figure 2-2** Proper placement of the laryngeal mask airway.

membrane into the tracheal lumen, through which an endotracheal tube is inserted.[41] This method potentially has some serious complications. Several investigators have modified this technique.[42] In recent years, a number of commercial kits that include all of the necessary equipment to establish a surgical airway have reached the market. The surgeon must be familiar with the kit used at his or her trauma center.



• **Figure 2-3** Proper position of the tip of the curved **(A)** and straight **(B)** blades. (From Fonseca RJ: *Oral and maxillofacial trauma*, ed 3, Philadelphia, 2005, Elsevier.)

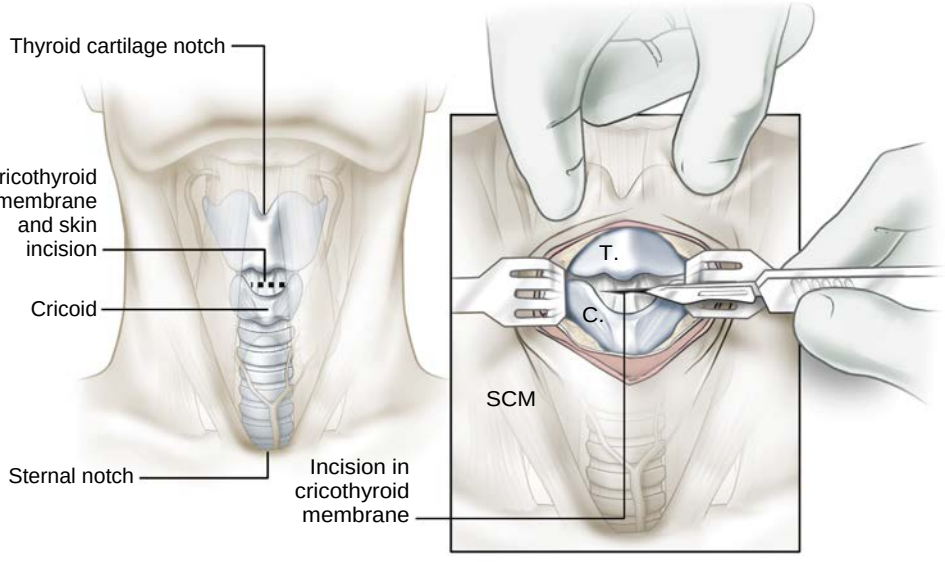
An experienced surgeon with exact knowledge of the anatomy and technique must perform this procedure.

The basic steps to perform a cricothyrotomy include (Figure 2-4):

1. Hyperextend the neck.
2. Identify the groove between the cricoid and thyroid cartilages as well as the cricothyroid membrane.
3. Prep the area (with Betadine) and infiltrate with local anesthetic.
4. Incise through the skin vertically with a 1.5-cm cut. Then use blunt dissection ensuring that you can see the cricothyroid membrane.
5. With a No. 22 or No. 23 scalpel blade, stab through the membrane into the trachea.
6. Rotate the blade 90 degrees, then insert a curved artery forceps alongside the blade. Remove the blade and open the forceps side-to-side. This widens the space between the thyroid and cricoid cartilages.
7. Pass a thin introducer or a nasogastric tube into the trachea (if the access is very small).
8. Run a 4-6 endotracheal tube over the introducer and pass it into the trachea.
9. Remove the introducer, if used.

The tube can stay in place for up to 3 days.

In surgical cricothyrotomy, a scalpel is used to make a horizontal incision over the lower half of the cricothyroid membrane. The only absolute contraindication to surgical cricothyrotomy is age, although the exact age at which a surgical cricothyrotomy can be safely performed is controversial and has not been well defined. Various sources list lower age limits ranging from 5 to 12 years old.[43,44] Our recommendation is to use 12 years as the cutoff age. In patients below this cutoff age, needle cricothyrotomy is indicated because infants and children younger than 12 years usually have a smaller cricothyroid membrane as well as a more funnel-shaped, rostral, and compliant larynx.[45]



• **Figure 2-4** Cricothyroidotomy. (From Cummings C: *Otolaryngology*, ed 4, St Louis, 2005, Mosby.)

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3

Imaging in Maxillofacial Trauma

SRINIVAS SUSARLA, ZACHARY S. PEACOCK

Introduction

Imaging is a critical component of the diagnostic evaluation of a patient with craniomaxillofacial injuries. Although the history and physical examination remain the cornerstones of the initial assessment, two- and three-dimensional imaging techniques are adjuncts for diagnosis, treatment planning, follow-up evaluation, and outcome assessment.[1-11]

The interpretation of radiographic images from the traumatized face can be challenging, even for experienced practitioners. The face and cranium contain numerous critical structures, all confined into a relatively small volume. The superimposition of complex tissue layers over irregularly shaped osseous anatomy complicates the interpretation of plain radiographs. In this regard, the advent of computed tomography (CT) has significantly improved our ability to accurately diagnose, classify, and plan treatment for complex craniomaxillofacial injuries. For most patients with upper facial or midfacial injuries, multi-detector CT scanning (MDCT) is the standard for evaluation.[1,2,12-19] MDCT allows for visualization of the craniofacial skeleton in several planes (coronal, axial, sagittal), three-dimensional reformations, rapid image acquisition with limited requirements for patient positioning, and, more recently, advanced virtual treatment planning. Patients with a clinical examination concerning for mandibular or dental injury without concomitant midfacial or upper facial injury may, in certain circumstances, be adequately imaged by plain film techniques alone.[20-22]

In this chapter, we describe the detailed anatomy of the facial skeleton and predictable patterns of injury based on skeletal support structures, and offer a précis on radiographic identification of regional and complex injury patterns. Although management of specific facial fractures is discussed in detail elsewhere, indications for operative management are often based on a combination of clinical and radiographic findings. As such, this chapter briefly touches on common clinical findings and their correlation to radiographic findings, as well as implications for management.

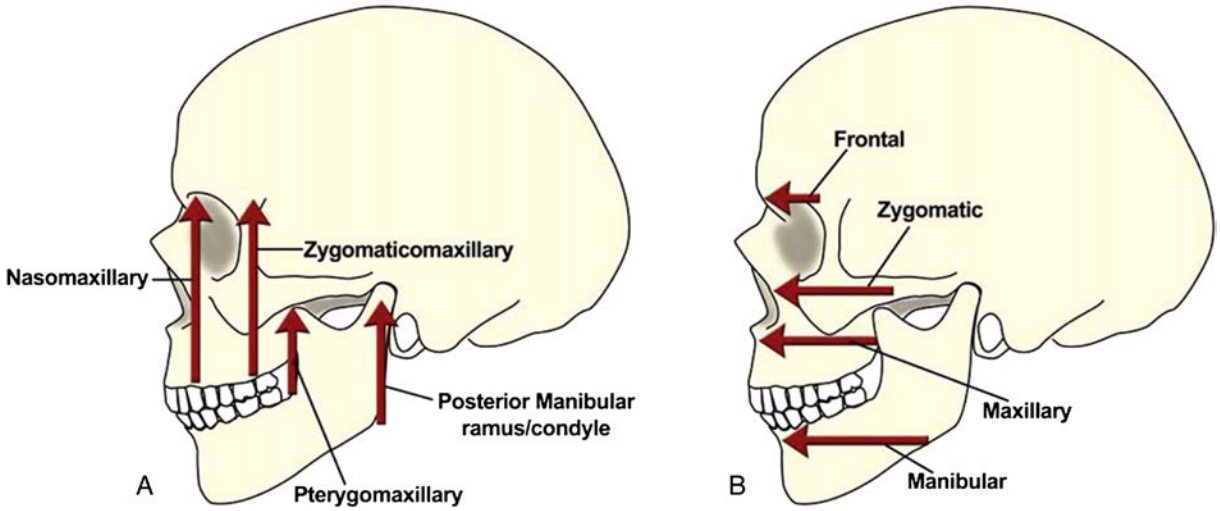
Image Acquisition

Proper diagnosis of fractures of the maxillofacial skeleton requires high-resolution images, ideally formatted in the axial, sagittal, and coronal planes.[1-6] Over the past 15 years, there has been an increased emphasis on the use of three-dimensional reformations for diagnosis and management.[13-18] Standard parameters for scanning should include a narrow slice thickness (e.g., 0.625 mm on a 64-slice scanner), with the field of view extending from the vertex of the skull to the hyoid bone.[1,2] Axial reformations should be performed in both bone and soft tissue windows, with a maximum thickness of 1.25 mm. Coronal and sagittal reformations allow for further elucidation of displacement, angulation, and rotation and should be performed universally. The 0.625-mm source images are necessary for producing high-resolution three-dimensional reformations.[1-4]

In patients with isolated mandibular fractures without clinical suspicion for midfacial or upper facial injuries, two plain film views (e.g., panoramic radiograph with anterior-posterior radiograph) can be adequate. There are classically described plain film imaging techniques for specific mandibular fractures that can be used in the appropriate clinical context (see section on Mandibular Fractures for details).

Image Interpretation

Akin to clinical evaluation of the patient with facial injury, radiographic interpretation can be daunting, particularly for complex injuries. The clinician should take a systematic approach to interpreting the images and proceed in the same fashion with each patient. It is imperative that the clinician recognize that even "simple" injuries may have contre-coup components (e.g., mandibular body and contralateral body/subcondylar fractures). Similarly, one should



• **Figure 3-1** **A**, Vertical buttresses of the facial skeleton include the nasomaxillary, zygomaticomaxillary, pterygomaxillary, and condyle-ramus unit of the mandible. **B**, The frontal bone, zygomatic arch and body, maxilla and mandible make up the horizontal buttresses. (From Fonseca RJ, Barber HD, Powers MP, Frist DE, editors: *Oral and maxillofacial trauma*, ed 4, Philadelphia, 2013, Saunders.)

not be overwhelmed by a seemingly complex injury. A systematic evaluation ensures that no area is overlooked and that a full correlation between the physical findings and imaging occurs, regardless of the mechanism of injury or state of illness of the patient.

One proposed approach for interpreting such images is a "top to bottom" approach. For the purpose of image interpretation, the craniofacial skeleton can be organized into five distinct regions: (1) orbital, (2) nasal, (3) zygomatic, (4) maxillary, and (5) mandibular.[1,23,24] Maxillofacial injuries commonly involve several regions and several contiguous structures within regions. The facial skeleton is composed of several horizontal and vertical buttresses, which act to distribute force away from vital structures, leading to predictable patterns of injury. The horizontal buttresses of the face are the frontal, zygomatic, maxillary, and mandibular buttresses. These areas transmit anterior-posterior forces. The vertical buttresses of the face include the nasomaxillary, zygomaticomaxillary, pterygomaxillary, and mandibular ramus/condyle. Each region of the facial skeleton is supported by a combination of horizontal and vertical buttresses (Figure 3-1).

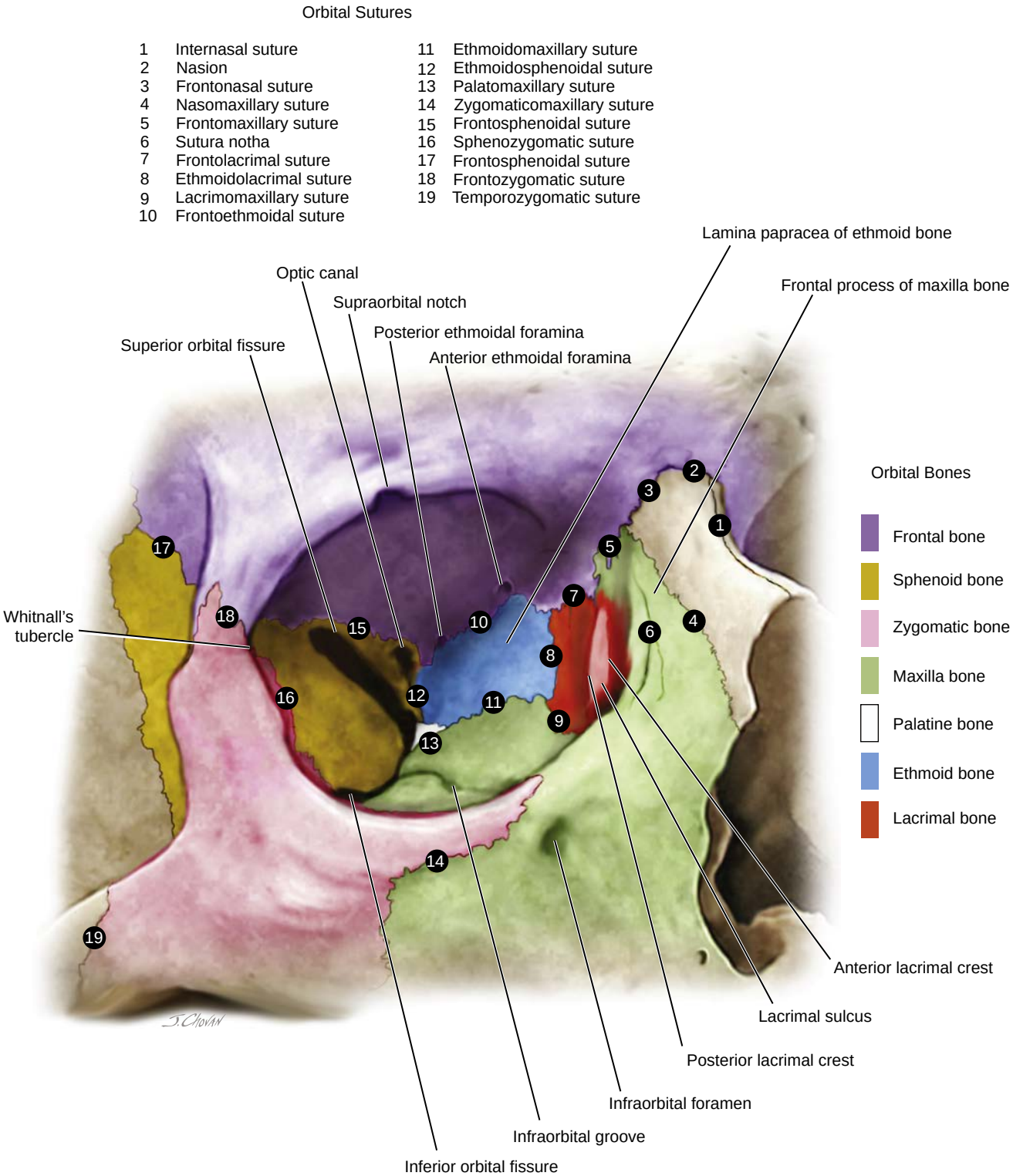
The orbital region includes the conical bony orbit and its contents (extraconal soft tissues, globe, extraocular muscles, nerves, vessels). The bony orbit proper is composed of seven constituent bones: the frontal, zygomatic, ethmoid, palatine, lacrimal, maxillary, and sphenoid (Figure 3-2). The external orbital skeleton (i.e., orbital rim) is primarily and lateral orbital walls. The orbit is horizontally supported by the frontal and zygomatic buttresses, as well as the supra- and infra orbital rims. It is supported vertically by the nasomaxillary and zygomaticomaxillary buttresses. This strong external framework of the external orbit prevents significant displacement of the osseous structures and affords significant protection to the globe and brain. Conversely, significant displacement of the orbital skeleton (e.g., displaced Le Fort III fracture) suggests a high-energy injury and should merit consideration for concomitant intracranial or cervical spine injury.

The nasal region is formed by the paired nasal bones, lacrimal bones, maxilla (frontal processes), nasal septum, and ethmoid sinuses. Horizontal support comes from the zygomatic buttress and the infraorbital rim. Vertical support comes from the nasomaxillary buttress and medial orbital wall.

The midface is primarily composed of the zygomatic and maxillary regions. The zygomatic region serves to connect the temporal, maxillary, and sphenoid bones and has a significant role in midfacial projection. Fractures of the zygoma will disrupt one or more of these connections. The zygomatic region is supported horizontally by the zygomatic arch, infraorbital rim, and zygomatic body. Vertical support is from the frontozygomatic pillar, lateral orbital rim, and zygomaticomaxillary buttress.

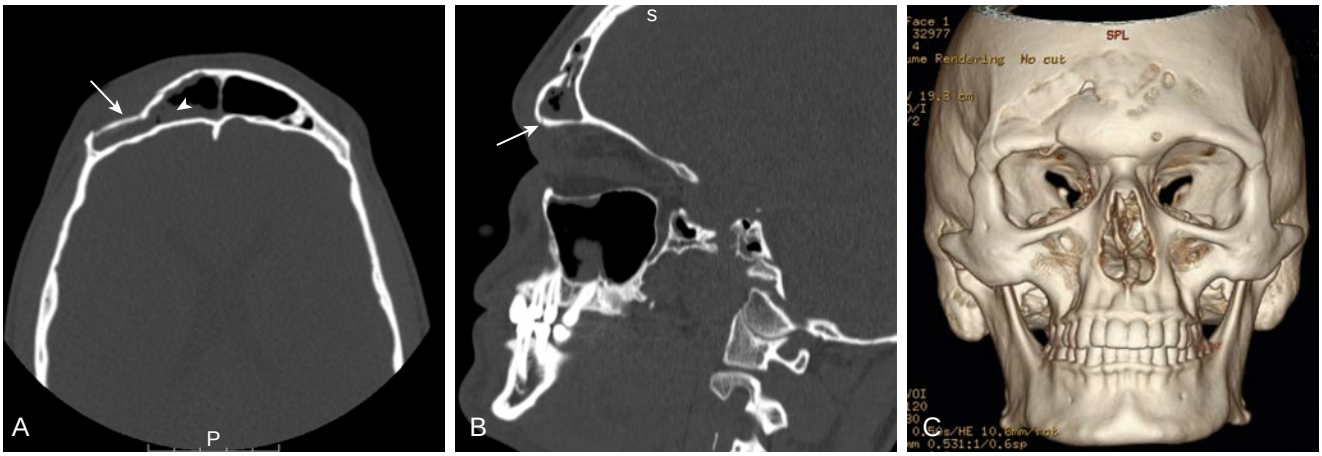
The maxillary region includes the maxilla proper, the maxillary alveolus (including the upper dental arch), and the hard palate (palatine process of the maxilla and the palatine bones). This region is supported horizontally by the maxillary buttress and vertically by the nasomaxillary, zygomaticomaxillary, and pterygomaxillary buttresses. Various patterns of Le Fort injuries will disrupt these buttresses.

The mandibular region is composed of the mandible proper and the mandibular alveolus. The mandible proper includes the temporomandibular joint and the cortical mandible. The mandibular alveolus includes the lower dental arch. The mandible is the only mobile portion of the facial skeleton, articulates with the skull base via the bilateral temporomandibular joints, and has no rigid connection



• **Figure 3-2** Seven bones make up the orbit and periorbital region. The orbital rims are part of the strong

composed of thin bones prone to fracture. Fractures that go through the orbital walls include orbital blow-out fractures, Le Fort II and III, and naso-orbitoethmoid fractures. (From Kademani D, Tiwana P, editors: *Atlas of oral and maxillofacial surgery*, ed 1, Philadelphia, 2015, Saunders.)



• **Figure 3-3** Frontal sinus fracture affecting anterior table only. **A**, Axial image shows depression of the anterior table (*arrow*) on the right side with fluid within the sinus (*arrowhead*). The posterior table is intact. **B**, Sagittal image demonstrates comminution of the anterior table extending to the superior orbital rim (*arrow*). **C**, Three-dimensional reformat shows the depression of the anterior table and extension to the orbital rim.

to the remainder of the craniofacial skeleton. The mandible is a self-contained unit, which has significant implications for injury patterns and management. The mandible is supported by the ramus/condyle unit vertically and the mandibular buttress horizontally.

A systematic approach to reading the maxillofacial CT is to start at the most superior portion of the scan and scroll through the axial slices from superior to inferior on the axial cuts.[1-5] For inexperienced clinicians, it is often helpful to have a pen and paper handy to document the fractures visualized on a particular view. Next, the clinician should scroll through the sagittal (lateral to medial) and coronal (anterior to posterior) views, again documenting the visualized fractures. With experience, one will be able to transpose fractures identified in one plane into the other two, assembling a three-dimensional construct of the injured skeleton. Finally, once the fracture inventory is assessed, the clinician should summarize the findings in terms of patterns of fractures rather than isolated elements of fractured bones. Descriptions in the latter format are cumbersome and unlikely to be helpful for clinical decision making.

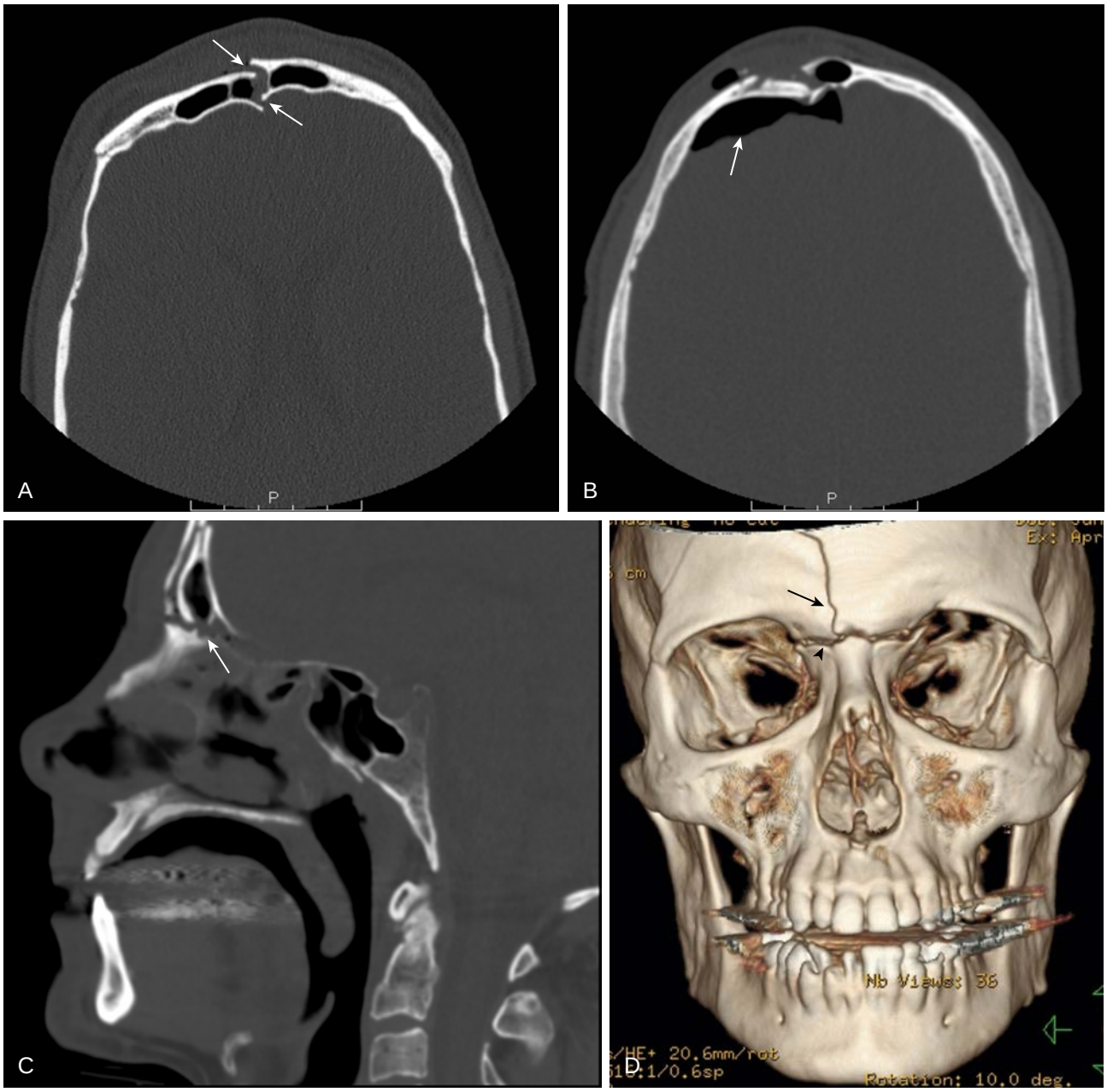
Facial Fracture Patterns

The presence of anatomic buttresses within the facial skeleton not only is useful for segmentalizing the anatomy, but also can serve as a guide for predicting patterns of facial injury, based on the direction of force and magnitude of impact. The need for careful clinical evaluation and meticulous physical examination cannot be overemphasized. Seemingly small soft tissue injuries can often mask significant skeletal injury, due to the dispersal of forces along the facial buttresses. Similarly, massive soft tissue injuries often have significant underlying skeletal injuries that follow predictable patterns to disperse the force of injury away from the brain and spine.

Because facial fractures can and often do involve several contiguous bones or several regions of the facial skeleton, there is little utility in describing fractures on the basis of the bones involved (e.g., fracture of the anterior and posterior walls of the maxillary sinus, zygomatic arch, frontzygomatic suture, and orbital floor). Instead, the clinician should be familiar with patterns of injury and the bones involved (e.g., zygomaticomaxillary complex fracture). Familiarity with the typical pattern and location of facial fractures makes each evaluation more efficient and clinically useful.

Frontal Bone Fractures

Although the frontal bone is not typically considered a primary bone of the facial skeleton, it is often involved in patients sustaining high-energy head injuries and is managed by the specialist treating maxillofacial injuries (Figures 3-3 and 3-4).[25-28] The frontal bone forms the prominence of the forehead and contains the frontal sinus. The frontal sinus divides the frontal bone into an anterior portion (anterior table) and posterior portion (posterior table). The anterior table lies immediately adjacent to the soft tissue of the forehead, and an anterior table injury should be suspected in patients with forehead lacerations. Isolated injuries of the anterior table without deformity, however, are not generally serious and often can be managed non-operatively. On axial views, an air-fluid level within the frontal sinus is suggestive of a frontal sinus injury. Higher energy mechanisms often result in fractures of both the anterior and posterior tables, which are more serious because of potential involvement of the central nervous system. The communication between a nonsterile cavity (frontal sinus) and the intracranial space defines these injuries as compound fractures, requiring, at minimum, antibiotic



• **Figure 3-4** Frontal sinus fracture affecting both anterior and posterior tables. **A**, Axial image shows displacement of anterior and posterior tables (*arrows*) and **B**, pneumocephalus (*arrow*) behind a fractured posterior table. **C**, Sagittal image shows fracture through the anterior and posterior table at the start of the nasofrontal duct. **D**, Three-dimensional image showing displacement of the right frontal bone posteriorly (*arrow*) and the disruption at the inferior aspect of the frontal sinus and nasofrontal suture (*arrowhead*).

TABLE 3-1 Variations of Frontal Sinus Fractures and Clinical Significance

Type	Significance
Isolated anterior table	Displacement > width of anterior table requires open reduction
Posterior table fracture	Considered a compound skull fracture and may result in CSF leak. Antibiotic treatment typically required
Naso-frontal duct involvement	Requires operative intervention to obliterate sinus

treatment. In non-displaced fractures of the frontal sinus, pneumocephalus is a key finding indicative of posterior table involvement. Cerebrospinal fluid rhinorrhea suggests dural disruption, which may occur if the fracture extends along the floor of the anterior cranial fossa, through the cribriform plate. Limitation of extraocular movement, visual acuity changes, or forehead and upper eyelid ecchymosis are physical findings associated with frontal bone fractures involving the orbital roof.

An adequate description of a frontal sinus fracture should include the status of the anterior and posterior tables, as well as the patency of the nasofrontal duct (Table 3-1).[28] Isolated anterior table fractures often require open reduction if there is an aesthetic deformity or if the displacement is greater than the width of the anterior table. Fractures with posterior table involvement generally require neurosurgical consultation. Displaced posterior table fractures require open treatment, which may include cranialization of the frontal sinus. If the nasofrontal duct is obstructed/non-patent, the sinus should be obliterated.

Orbital Fractures

As mentioned previously, the orbit is composed of seven bones of varying size and shape and is rigidly connected to the frontal bone, cranial base, and midface. As such, fractures of the orbital skeleton may occur either in combination with other facial fractures (e.g., frontal sinus, zygomatic, nasal) or in isolation (e.g., orbital floor). Orbital fractures should be suspected

Blow-in fractures are those in which the orbital roof is displaced inferiorly into the orbit, usually from a direct blow to the supraorbital rim or via transmitted forces from a blow to the forehead. Such injuries may propagate posteriorly within the orbit, resulting in involvement of the orbital apex. Several critical cranial nerves (CN II, III, IV, V_1, and VI) travel through the orbital apex, and an orbital apex injury can manifest clinically as visual acuity changes, ophvascular structures. Orbital roof injuries may also involve the anterior cranial fossa, and pneumocephalus may be seen on imaging.[29]

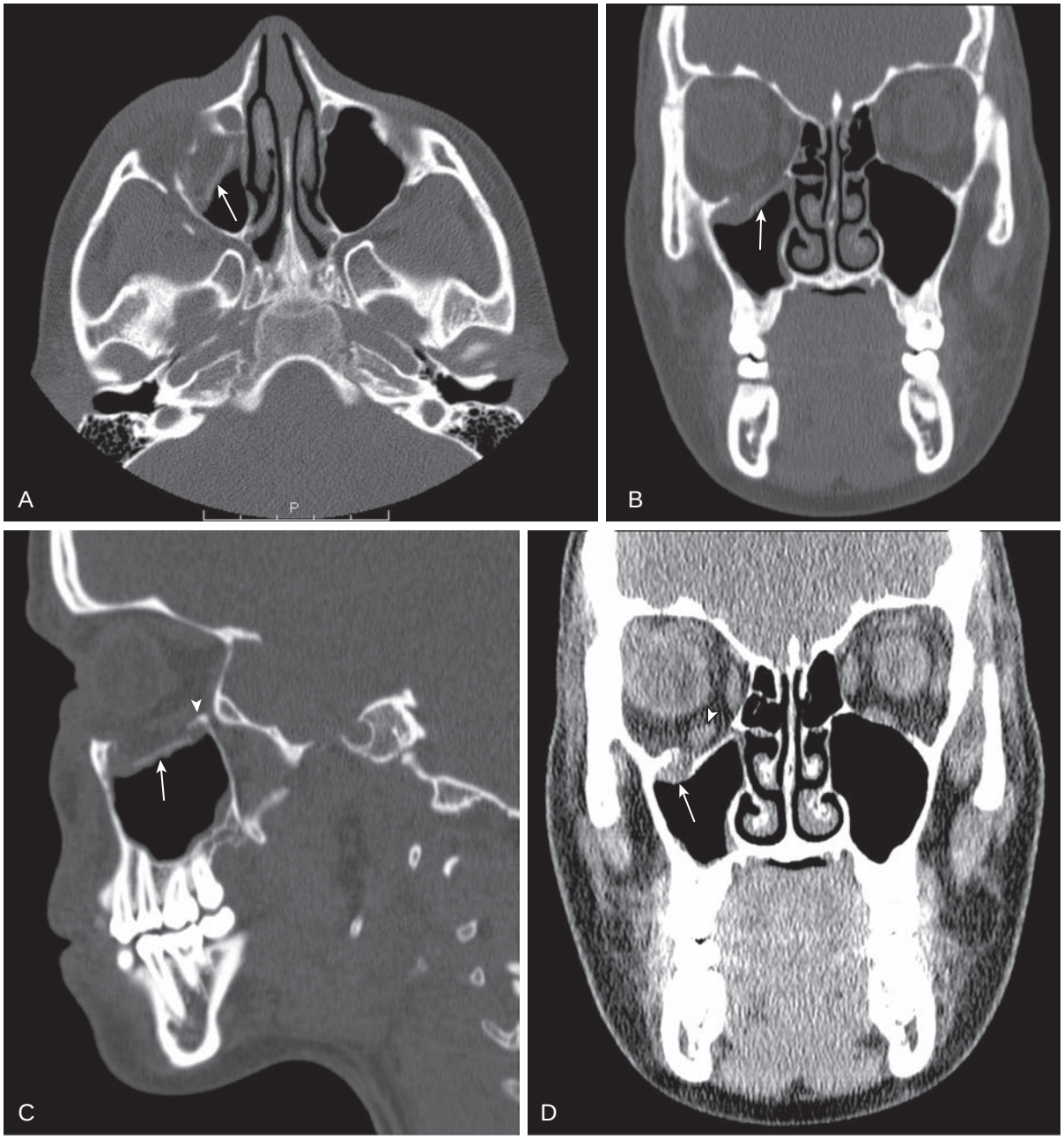
Blow-out fractures are those in which the orbital floor and/or medial wall are fractured and displaced into the surrounding air-filled spaces (i.e., the maxillary and ethmoid sinuses/nasal cavity) (Figure 3-5).[30-32] CT imaging in the axial, sagittal, and coronal planes is essential for accurate diagnosis, as axial cuts may miss orbital floor fractures and sagittal cuts may miss medial wall fractures. The appearance of the orbits should be symmetric, rounded, and smooth, with interruption in the cortex only at the bony articulations. By definition, the infraorbital rim is intact in thin medial wall or orbital floor. The contents of the orbit can herniate into the associated air-filled spaces.

Clinical indications for repair of orbital wall fractures are entrapment or enophthalmos. Herniation of extraocular muscle tissue (i.e., inferior or medial rectus muscles) may result in entrapment and limited extraocular movement (Figure 3-6). This occurs most commonly with small, narrow fractures, where the muscle can become impinged within the fracture.[1,2-31] An abrupt kink in the muscle is sometimes seen with such entrapment. Sagittal reformations are particularly helpful for visualizing entrapment of the inferior rectus in the orbital floor, and coronal reformations are useful for medial rectus entrapment in the medial wall. Larger fractures of the floor and medial wall generally do not result in entrapment but have a higher risk of subsequent enophthalmos.

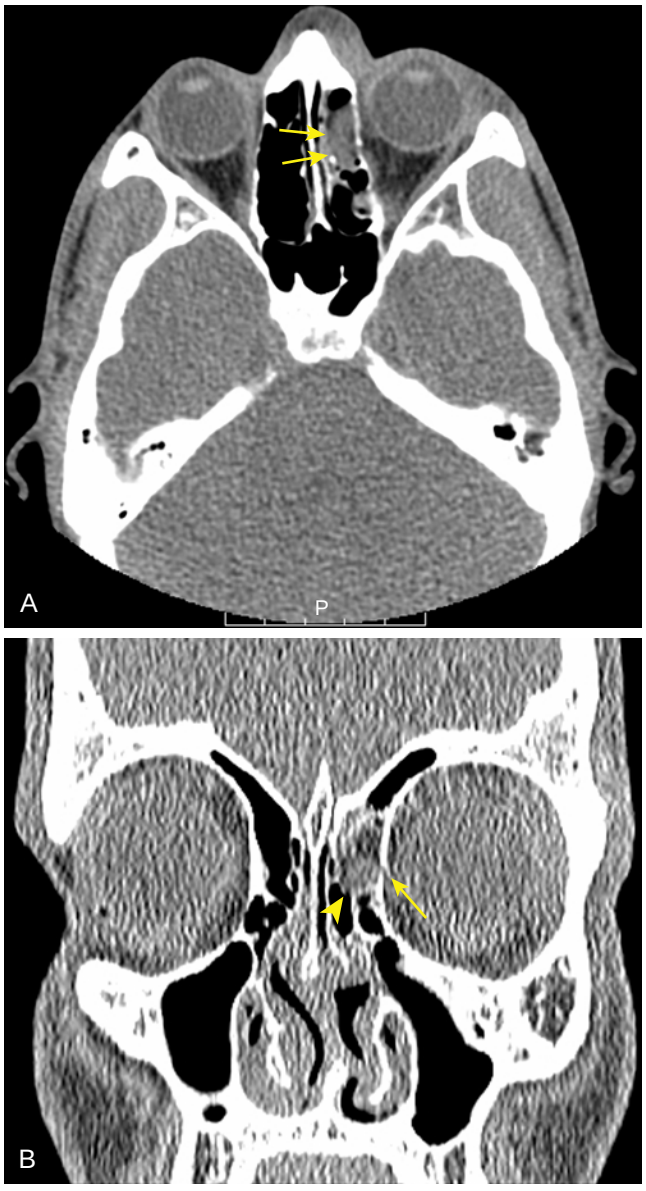
Zygomatic Fractures

Direct blows to the prominence of the cheek or lateral midface can result in injury to the zygoma and its articulations.[33-35] Disruption of the articulations between the zygoma and the temporal, maxillary, and sphenoid bones are generally more common than intra-zygomatic fractures due to the density of the zygomatic body, although high-energy injury injures can lead to comminution of the zygoma (Figures 3-7 and 3-8). These injuries are commonly known as "zygoma," "zygomatic complex," or "zygomaticomaxillary complex" (ZMC) fractures. Diagnosis of ZMC fractures relies on accurate identification of the frontozygomatic, sphenozygomatic, zygomaticomaxillary, and temporozygomatic sutures. Diastasis at any of these articulations should raise suspicion for a ZMC fracture. Coronal and sagittal views afford evaluation of the orbital floor, which is often disrupted at the articulation of the zygoma with the maxilla and sphenoid.

Lateral blows to the face may result in isolated zygomatic arch fractures (Figure 3-9) that may result in a depression of the area anterior to the glenoid fossa. These can be seen on plain films such as the submentovertex or Waters' views, but are best seen on CT scan.



• **Figure 3-5** Orbital blow-out fracture. **A**, Axial views can often be unrevealing, but in this image a fragment of orbital floor is displaced into the sinus (*arrow*) along with orbital tissue. **B**, Coronal image shows downward displacement of the thin orbital floor (*arrow*). **C**, Sagittal image shows inferior displacement of the orbital floor into the maxillary sinus (*arrow*). A posterior shelf has been maintained (*arrowhead*). **D**, Coronal image with soft tissue window shows the displacement of orbital fat (*arrow*), but the inferior rectus remains in the orbit (*arrowhead*).



• **Figure 3-6** Fracture of the medial orbital wall with medial rectus entrapment. No lateral movement was possible with forced duction. **A**, Axial image (soft tissue window) shows entrapment of the medial rectus (*arrows*) through a minimally displace medial wall fracture (trapdoor). **B**, Coronal image (soft tissue window) shows a crack in the medial wall (*arrow*) with the entire medial rectus in the ethmoid sinus (*arrowhead*).

Clinical signs and symptoms of ZMC fractures include loss of cheek prominence, paresthesia in the infraorbital region, trismus with zygomatic arch involvement, and ocular findings if there is significant orbital floor involvement. Aesthetic deformities with displacement, trismus, extraocular muscle entrapment, visual acuity changes, or persistent infraorbital paresthesia secondary to impingement are indicat

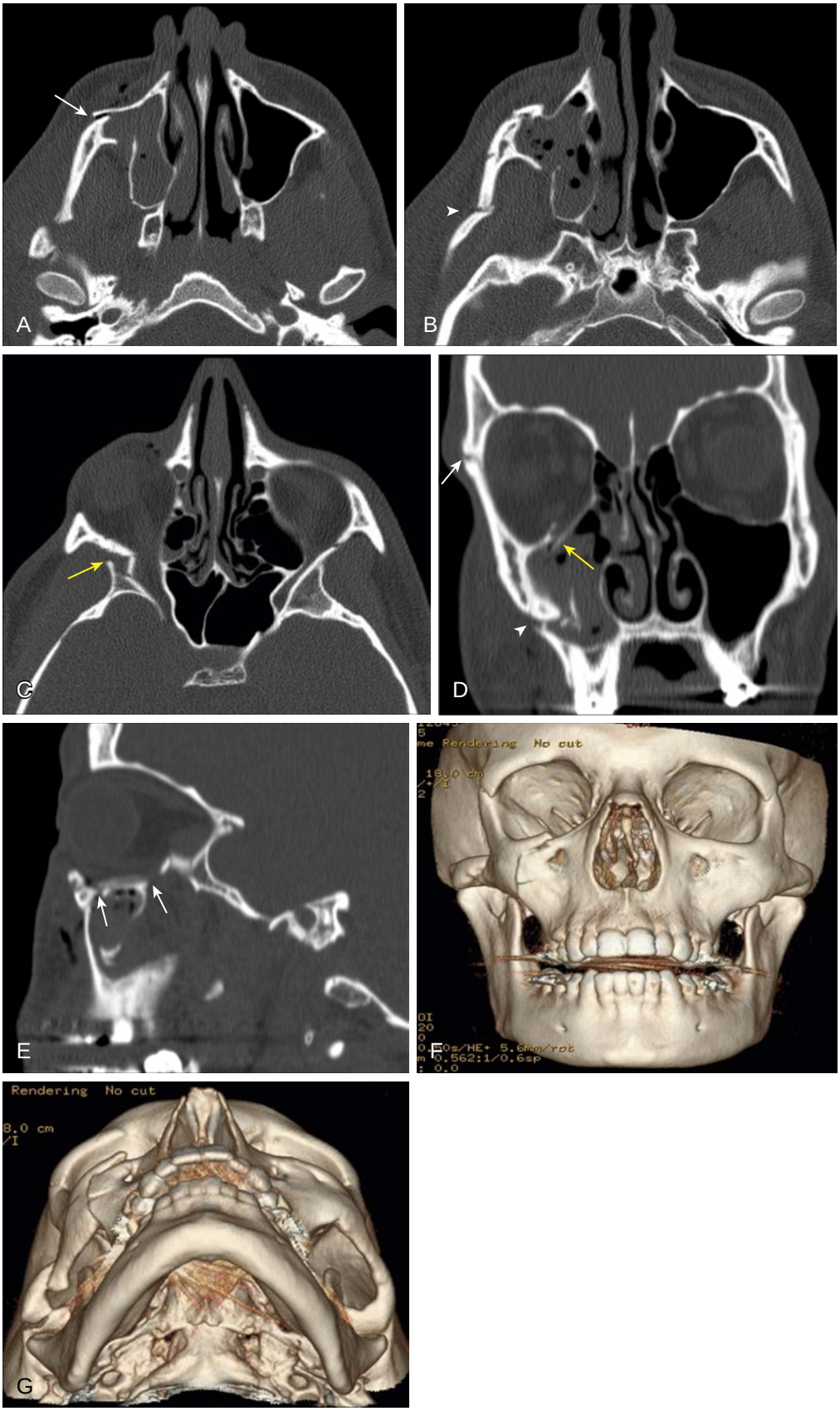
sys
used plain film images to classify ZMC fractures according to the vector of displacement and bony integrity of the zygoma proper. The system hierarchy was based on the stability following closed reduction, with type I fractures (non-displaced) being the most stable, types II and + V generally stable following reduction without fixation, and type III, IV, and VI fractures being the least stable and requiring some form of fixation. It is currently accepted that all displaced ZMC fractures require some form of reduction with or without fixation. More recent classification systems, based on CT imaging, have been useful in establishing the necessity for surgical treatment (see Table 3-2).[33]

Nasal/Naso-orbito-ethmoid Fractures

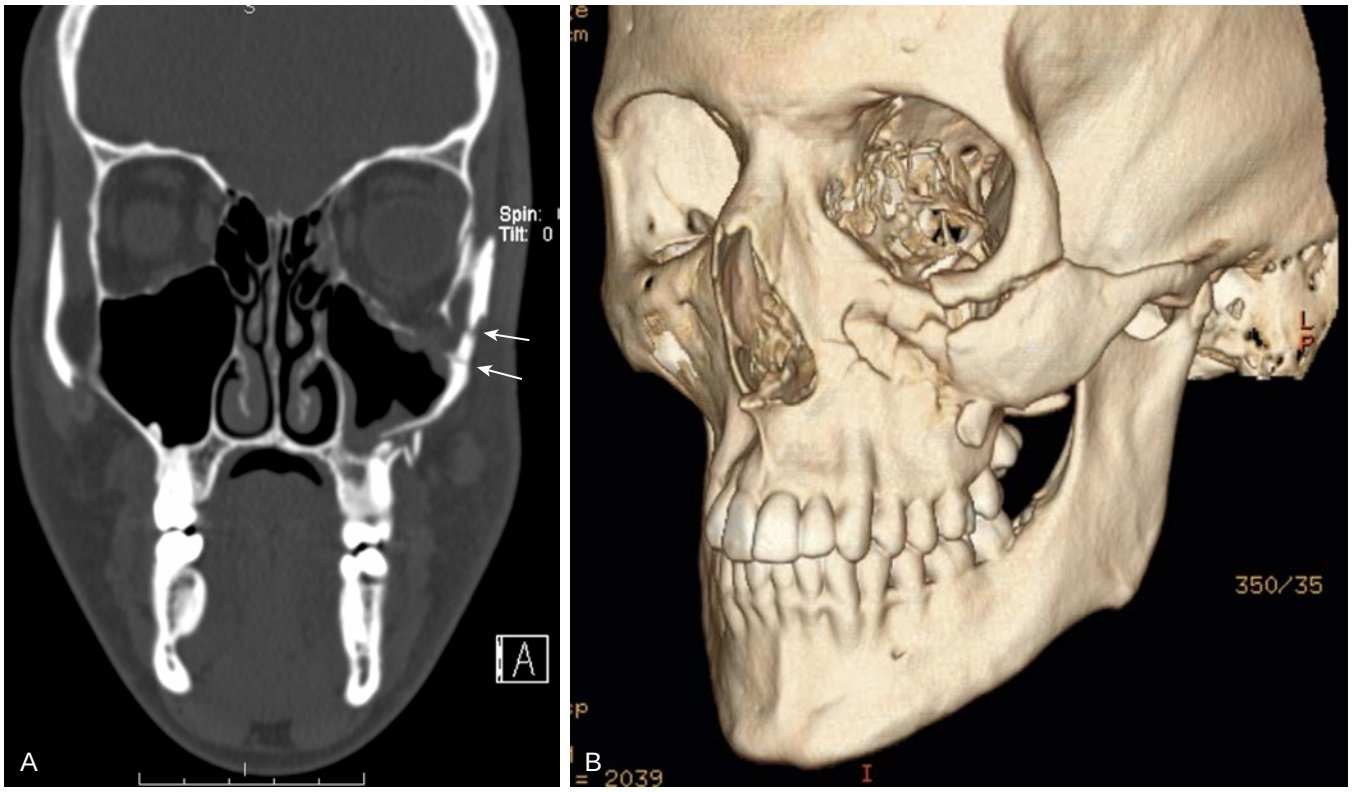
that involve the naso-orbito-ethmoid (NOE) complex. Isolated nasal fractures are relatively common, because of the prominence of the nasal dorsum and its relatively weak bony support (Figure 3-10).[36-38] Patients presenting with isolated nasal fractures will often complain of perinasal swelling and tenderness. Signs include deformity over the nasal dorsum, epistaxis, nasal instability, or crepitus. For low-energy injuries, these features may be transient and there may be a delay in presentation; their absence does not exclude the possibility of nasal injury. As a corollary, old fractures of the nasal bones may appear similar to acute fractures on imaging. The absence of a recent history of trauma or signs of injury (edema, pain, crepitus, etc.) is inconsistent with an acute injury.

The majority of isolated nasal fractures occur as a result of force vectors directed from the lateral aspect.[48] Subsequently, displacement of the nasal bones typically occurs inferiorly and laterally, sometimes with displacement of the nasal septum or fracture of the frontal processes of the maxilla. Disruption of the anterior cartilaginous septum may be associated with fractures of the anterior nasal spine. A stratified classification scheme for nasal fractures has been proposed by Rohrich and Adams and may assist the clinician with management (Table 3-3).[37]

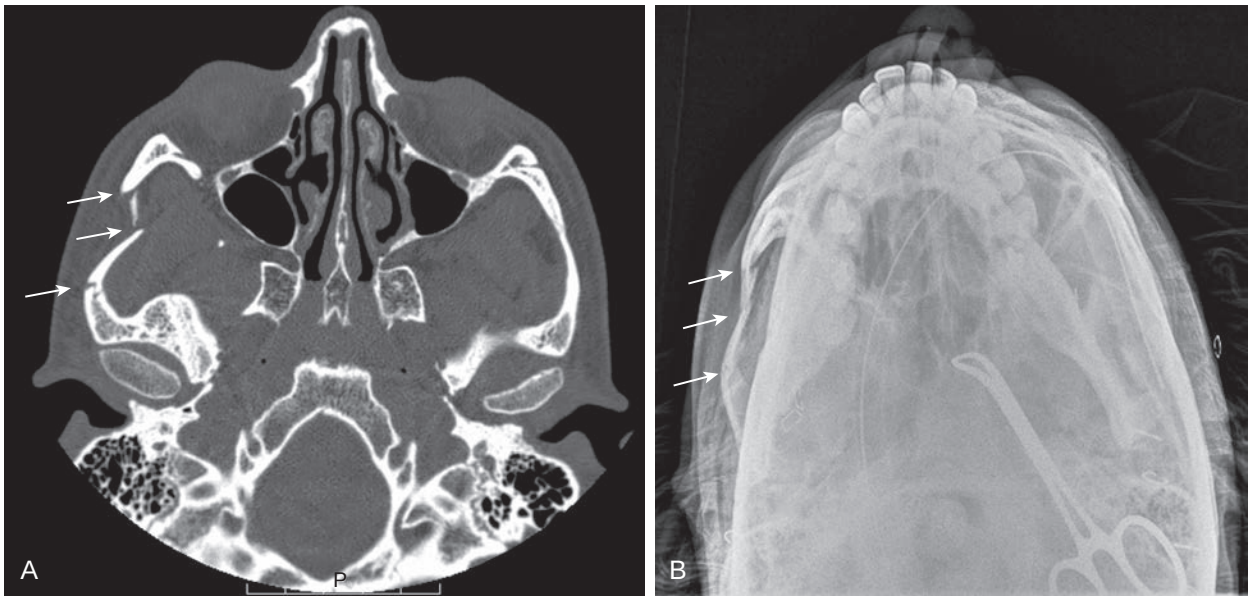
High-energy forces transmitted to the nasal region may result in NOE complex fractures (Figure 3-11). The NOE complex represents the bony union of the nasal and orbital regions and includes the nasal and ethmoid bones as well as the infraorbital rims and orbital floors. The history is typically consistent with a high-velocity or high-energy injury; concomitant intracranial or cervical spine injury should be exonerated. Although the typical clinical presentation is an amalgam of findings that can be seen with either nasal or orbital fractures, there are some specific clinical findings for NOE fractures. Telecanthus, an increase in the distance between the medial canthi, is mechanistically related to NOE fractures in that the medial canthal tendon is a critical anatomical component of the zone of injury. Injury to the medial canthal tendon may also manifest as a positive "bowstring" sign or "traction test." Other signs may include bilateral periorbital ecchymoses ("raccoon eyes," present with associated skull base fracture), epiphora (present with associated nasolacrimal system injury), or cerebrospinal fluid (CSF) rhinorrhea (nasofrontal duct injury).



• **Figure 3-7** Zygomaticomaxillary complex fracture, Type B; Knight and North type IV. **A**-**C**, Axial images show fractures through the articulations of the zygoma: zygomaticomaxillary (*arrow*), zygomaticotemporal (*arrowheads*), and zygomaticosphenoid (*yellow arrow*). **D**, Coronal image shows a minimally displaced fracture through the zygomaticofrontal suture (*arrow*), zygomaticomaxillary buttress (*arrowhead*), and orbital floor (*yellow arrow*). **E**, Sagittal image shows the disruption of the orbital floor at the junction of the zygoma to the maxilla and sphenoid (*arrows*). **F-G**, Three-dimensional reformats highlight the medial rotation of the right zygoma and disruption at all four articulations.



• **Figure 3-8** Comminuted zygomaticomaxillary complex fracture Type C; Knight and North type VI. **A**, Coronal image shows fractures within the body of the zygoma (*arrows*). **B**, Three-dimensional left three-quarter view shows the disruption of the zygomatic body and its articulation with the maxilla.



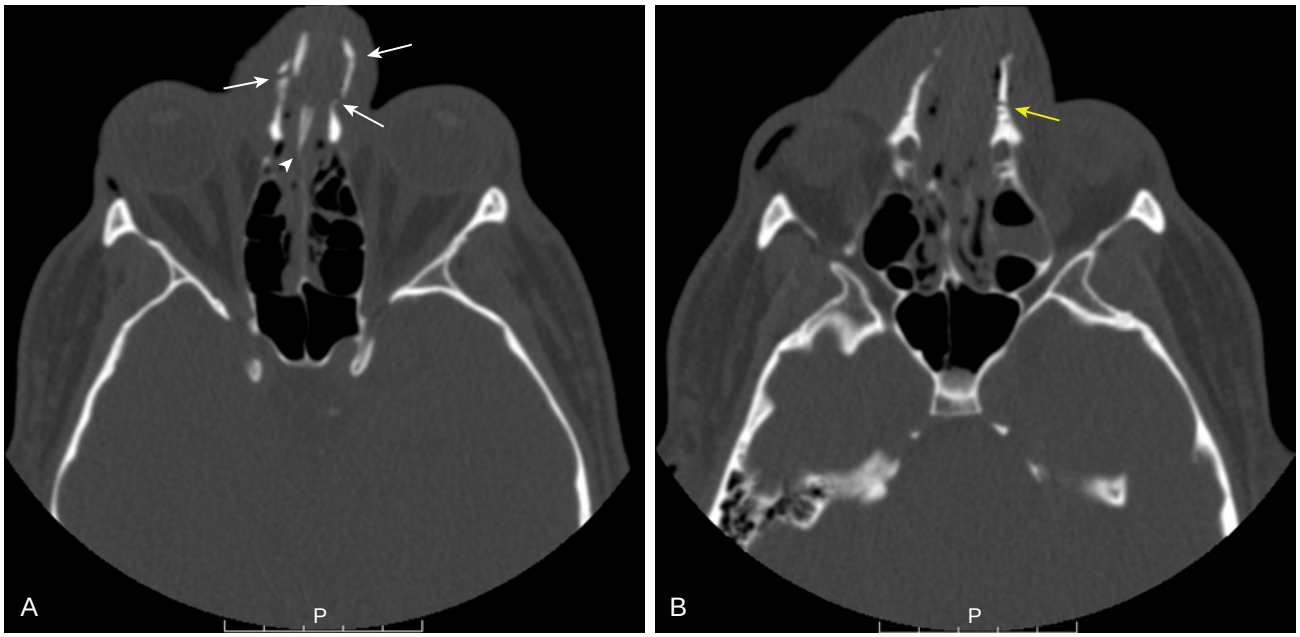
• **Figure 3-9** Zygomatic arch fracture. **A**, Axial image showing the classic three-fracture pattern (*arrows*) forming the letter M. **B**, Submentovertex plain film can also diagnose or determine adequacy of reduction after closed treatment. *Arrows* mark the fracture sites.

TABLE 3-2 Classification of Zygoma Complex Fractures

Type	Characteristics
A	Fracture limited to one zygomatic pillar: zygomatic arch, lateral orbital rim, or infraorbital rim
B	Fracture of all four zygomatic articulations with displacement
C	Multi-fragment fractures including comminution of the zygoma body

Knight and North Classification

Type	Description	Preferred Treatment
I	Non-displaced	Observation
II	Isolated arch	Observation or closed reduction
III	Depressed, non-rotated	Open reduction ± fixation
IV	Medially rotated	Open reduction ± fixation
V	Laterally rotated	Open reduction ± fixation
VI	Complex, comminuted	Open reduction + fixation



• **Figure 3-10** Nasal fractures. **A-B**, Axial images demonstrate comminution and displacement of the bilateral nasal bones (*arrows*) and through the perpendicular plate of the ethmoid (*arrowhead*). The left fracture occurred at the nasomaxillary suture (*yellow arrow*).

Markowitz and colleagues developed the most frequently used classification system for NOE fractures, based on the integrity of the medial canthal tendon (MCT) (Table 3-4, Figure 3-12).[39] Type I fractures involve a large central fragment with preserved attachment of the MCT; type II fractures involve comminuted fragments, but with a preserved MCT; type III fractures are the most severe (and difficult to treat), as they involve a comminuted NOE complex with MCT involvement.

Maxillary Fractures

Fractures of the maxilla are among the most well described injuries to the facial skeleton. Le Fort's seminal work on these injuries remains the foundation for modern diagnosis and management (Figure 3-13).[40] Clinical examination is typically notable for malocclusion and intraoral ecchymosis (commonly along the buccal mucosa or palate). Even non-displaced fractures can be

TABLE 3-3 Nasal Fracture Classification System

Type		Characteristics
I	Simple	Unilateral
II		Bilateral
III	Comminuted	Unilateral
		Bilateral
		Including frontal process of maxilla
IV	Complex	Associated with septal hematoma
		Associated with open nasal laceration
V		Associated with naso-orbito-ethmoid or midface fracture

uncomfortable for patients, and they may report a malocclusion even if an obvious malocclusion is not evident on examination.[23]

The Le Fort I-III level fractures are accepted as standard terminology for fractures of the maxilla alone, with involvement of the nasofrontal complex, or total craniofacial disjunction, respectively. The unifying feature of all levels of Le Fort fractures is fracture of the pterygoid plates.[41] A fracture of the pterygoid plates almost always indicates a fracture at one of the Le Fort levels.[1,41] Maxillary fractures may occur in isolation or with concomitant injury to the nasal, zygomatic, or orbital regions; may be unilateral or bilateral; and may be varied in severity (e.g., left-sided Le Fort I fracture with a right-sided Le Fort III fracture). As such, imaging of such suspected injuries requires careful assessment of the orbital, nasal, frontal, and zygomatic regions and assessment of laterality.

The Le Fort I fracture is a simple maxillary disjunction, separating the maxilla from its connection to the skull base, zygoma, and nasal septum (Figure 3-14). The classical fracture pattern will propagate from the pyriform rim and lateral nasal wall to the pterygomaxillary fissure, extending across the intervening bone by fracturing the anterior and posterior walls of the maxillary sinus. There is often a simultaneous fracture of the nasal septum. Clinically, the maxilla may be mobile, with the hard palate and alveolus mobile relative to the remainder of the midface.

The Le Fort II fracture is also known as a pyramidal fracture because the fracture lines may form a distinct triangular shape when viewed in the coronal plane (Figure 3-15). The Le Fort II pattern extends from the pterygoid plates superiorly and anteriorly, terminating at the nasofrontal suture. The intervening bony segments along the line of fracture are the lateral and anterior walls of the maxillary sinus, the orbital floor, and the medial orbital wall. Clinically, mobilization of the maxilla will result in tactile mobility at the nasofrontal suture.

"Craniofacial disjunction" is a synonym for the Le Fort III fracture. This is the most severe form of maxillary fracture, with a fracture line that propagates from the pterygoid plates superiorly to involve the zygomatic arch, lateral orbit, orbital floor, medial orbital wall, and nasal bones. As a result, the midfacial skeleton becomes separate from the skull base. Clinically, the mobilization of the maxilla will result in simultaneous mobilization of the lateral and inferior orbit.

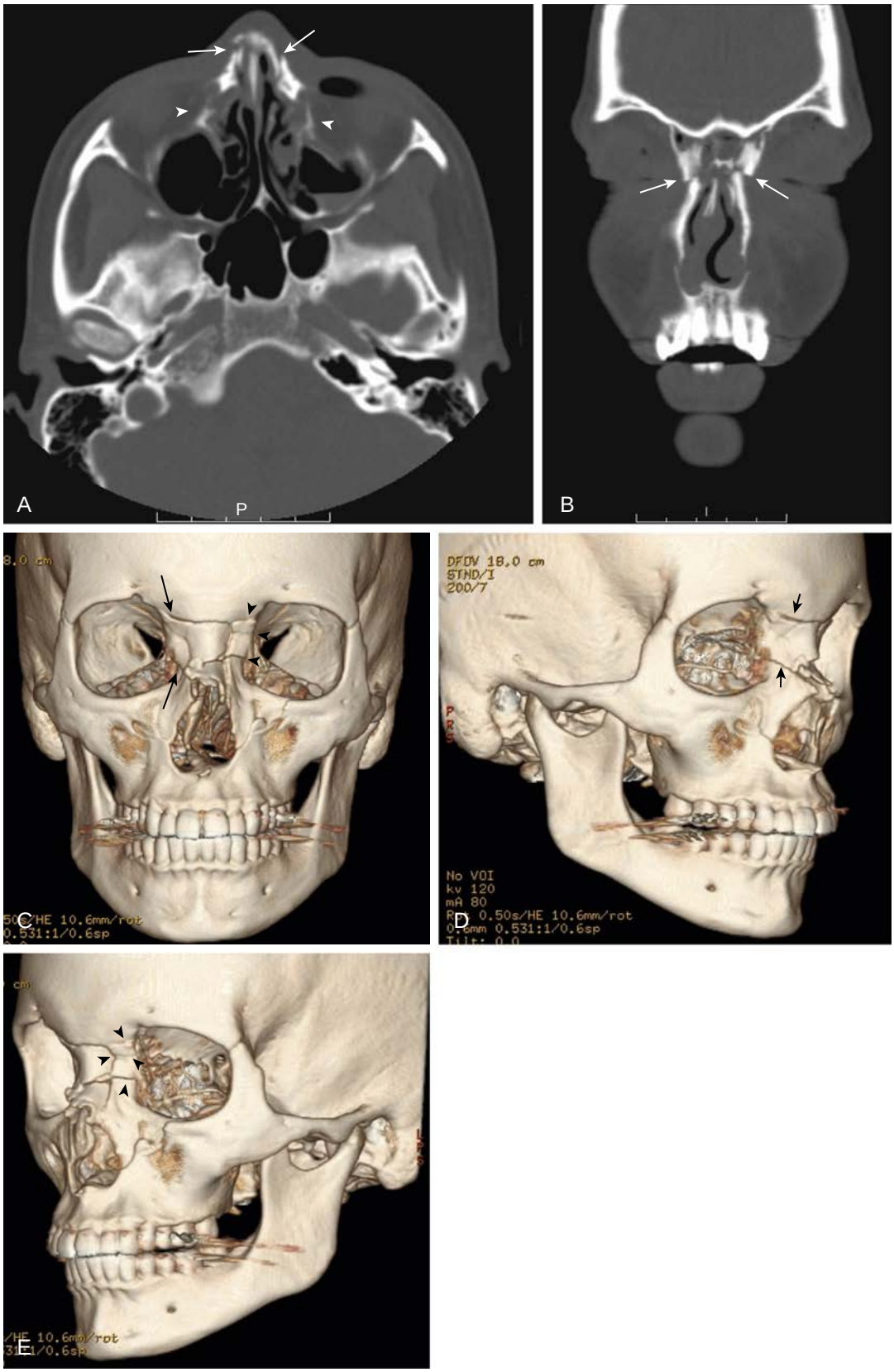
A less common form of maxillary fracture that is independent of the Le Fort schema is the palatal fracture, or sagittal maxillary fracture.[42,43] In this fracture pattern, the fracture propagates along the sagittal or parasagittal planes of the hard palate, separating the maxilla into right and left symmetric segments or greater and lesser asymmetric segments. A malocclusion due to widening of the maxilla is often present. Associated fractures of the alveolar ridge, nasal septum, and maxillary sinus walls are common. Physical examination may be notable for missing or mobile teeth within a mobile alveolus. If there are teeth missing that were not otherwise known to be missing prior to injury and are not identifiable on clinical exam or facial imaging, a plain radiograph of the chest should be performed to exclude tooth aspiration.

Mandibular Fractures

The only mobile bone within the facial skeleton, the mandible is a complex, U-shaped structure with bilateral articulations with the skull base. With its prominent position in the lower face, the mandible is also among the most frequently fractured facial bones.[44-47] Almost half of all patients with maxillofacial injuries have a fracture of the mandible.[47] Given their frequency and the potential complexity of management, any clinician treating patients with maxillofacial injuries should be well-versed in the various radiographic methods for diagnosis of mandibular fractures. Although there is no universally accepted classification scheme for mandibular fractures, an adequate clinical description will include location, pattern, and displacement.

For the purposes of localization of zone of injury, there are six distinct regions of the mandible that are commonly fractured: the condyle/condylar neck, ramus, angle, body, symphysis/parasymphysis, and alveolus (Figure 3-16). The most common location for mandibular fractures is the mandibular body, defined as the region between the distal aspect of the mandibular canine and the distal aspect of the mandibular second molar.[44] The condylar/subcondylar region is the next most frequent, followed by the angle and symphysis/parasymphysis. Isolated injuries to the alveolus and coronoid process are relatively rare, with only the former readily apparent on clinical examination. The most often misdiagnosed or undiagnosed fractures are condylar fractures, particularly intracapsular fractures. This latter finding has important implications for management, as an undiagnosed and untreated intracapsular fracture can result in temporomandibular joint ankylosis.

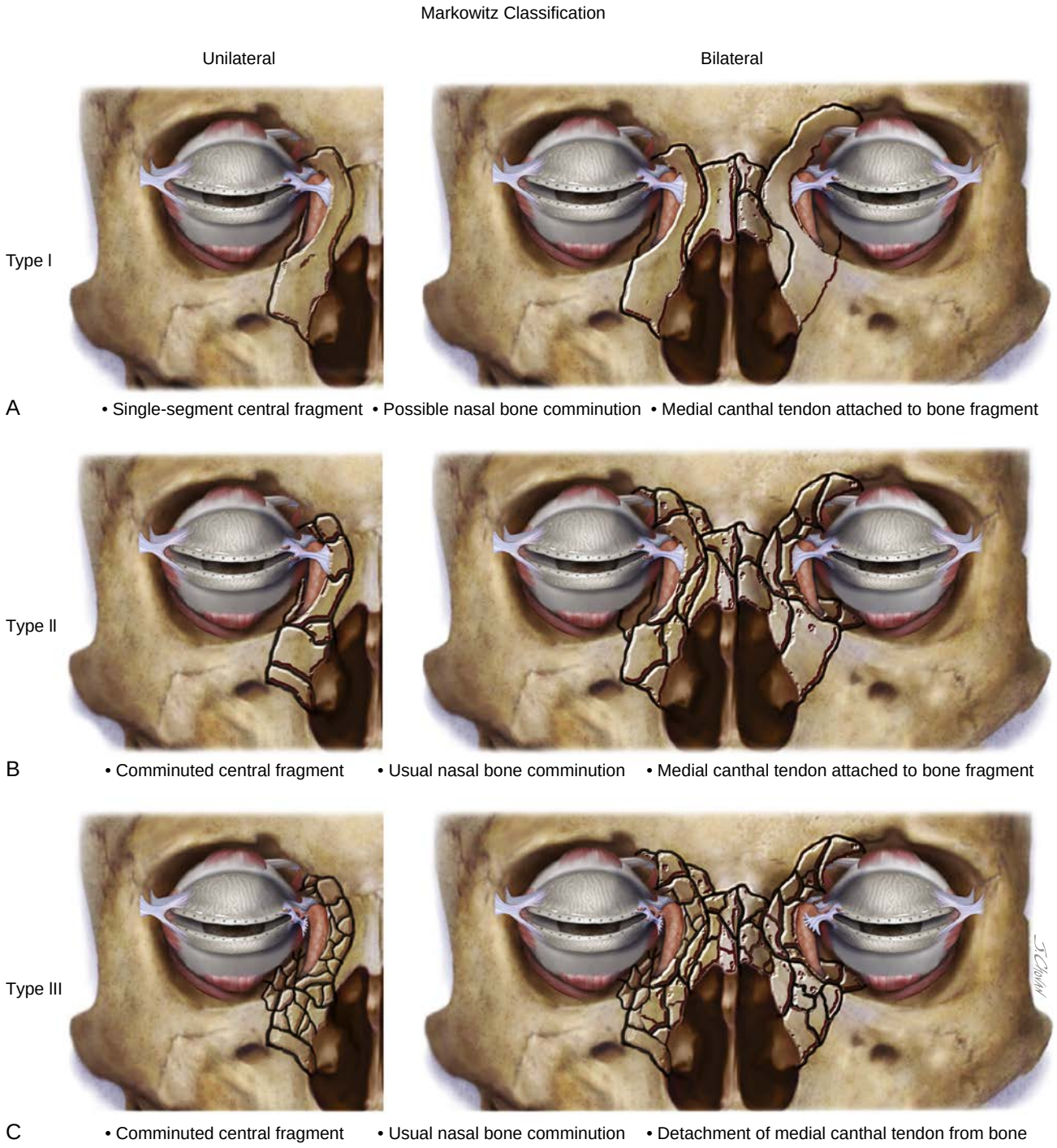
Knowledge of mandibular biomechanics and fracture patterns is required to carefully evaluate imaging in a



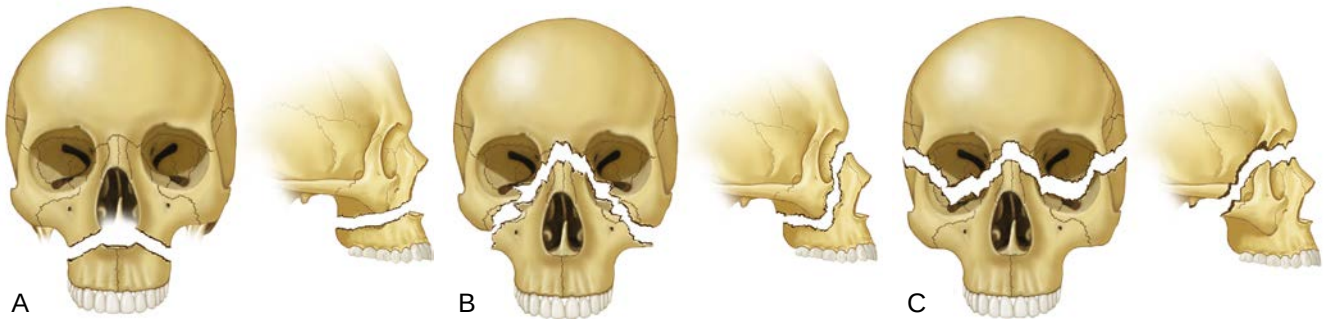
• **Figure 3-11** Naso-orbito-ethmoid (NOE) fracture: type I on right, type II on left. **A**, Axial view shows bilateral nasal bone fractures (*arrows*), disruption of the ethmoid sinus and medial wall of orbit (*arrowheads*). **B**, Coronal image displaying lateral displacement of the nasal processes of the maxilla with displacement laterally (*arrows*). **C**-**E**, Three-dimensional frontal (**C**), right (**D**), and left (**E**) lateral show the right-sided fractures (*arrows*) (type I) and comminution of the left side (*arrowheads*) (type II).

TABLE 3-4 Naso-orbito-ethmoid Classification System

Type	Characteristics
I	Single non-comminuted central fragment, no medial canthal tendon disruption
II	Comminution of central fragment, no medial canthal tendon disruption
III	Comminution of central fragment with medial canthal tendon disruption



have a large central fragment containing the medial canthal tendon (MCT). **B**, Type II fractures have comminution of the central fragment, but the MCT remains attached. **C**, Type III fractures have comminution and disruption of the attachment of the MCT. (From Kademani D, Tiwana P, editors: *Atlas of oral and maxillofacial surgery*, 1e, Philadelphia, 2015, Saunders.)



• **Figure 3-13** Le Fort fractures display classic fracture patterns along three levels. **A**, The Le Fort I fracture occurs along the anterior maxilla extending from the pyriform rims posteriorly through the maxillary sinus to the pterygoid plates. **B**, Le Fort II fractures are referred to as pyramidal when bilateral, as they extend from the nasofrontal suture through the medial orbital wall, floor, and infraorbital rim down to the pterygoid plates. **C**, Le Fort III fractures extend from the nasofrontal suture laterally and include the zygomas, resulting in a craniofacial dysjunction. (From Fonseca RJ, Barber HD, Powers MP, Frist DE, editors: *Oral and maxillofacial trauma*, 4e, Philadelphia, 2013, Saunders.)

patient with a suspected mandibular injury. Because of the U-shape of the mandible, forces applied to a single area of the bone will be transmitted along its contour proximally and distally. This often results in simultaneous fractures of the mandible and contre-coup injuries. Common patterns of fracture include fractures of the angle and contralateral body, bilateral angle fractures, and angle with contralateral subcondylar fractures.

masticator muscle pull. Horizontally favorable fractures are those in which the fracture trajectory is perpendicular to the long axis of the masseter and medial pterygoid fibers. In this pattern, muscle pull will act to reduce the fracture. Horizontally unfavorable fractures are those in which the fracture orientation is parallel to the vector of muscle pull, resulting in displacement with muscle contraction. Vertically favorable fractures are those in which the fracture line, as viewed in the axial plane, is parallel to the medial pterygoid fibers. Unfavorable fractures will be oriented perpendicular to the medial pterygoid muscle fibers (or parallel to the lateral pterygoid fibers).

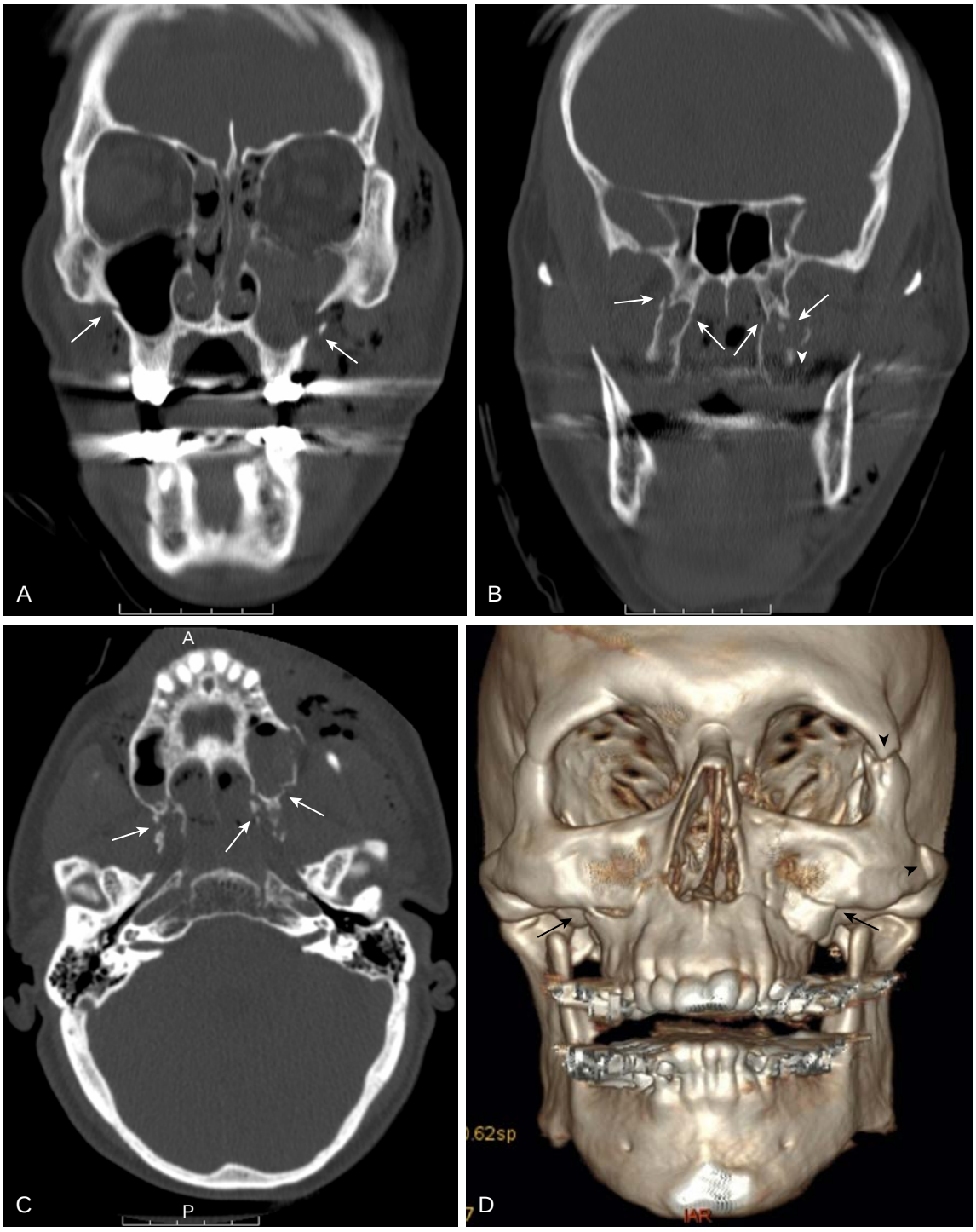
A rare pattern of injury that is of extreme clinical importance is the bilateral parasymphysis pattern, in which the genioglossus muscle attachment is in a single, centralized piece of bone, not attached to the remainder of the mandible. In this setting, the central segment is a "flail segment" that may allow for glossoptosis and airway embarrassment.

Although the majority of patients with facial injuries consistent with mandibular fractures will be imaged with MDCT, isolated mandibular fractures remain one area where plain film imaging may be adequate for diagnosis and management.[48] Regardless of the modality used for imaging, it is our practice to include a panoramic radiographic evaluation on all patients with mandibular injuries. There are two important reasons for this: (1) There are rare documented cases in which mandibular fractures were missed on facial CT due to the orientation of the fracture relative to the CT slice orientation, and (2) most patients with mandibular fractures will be followed with some form of imaging to assess healing for removal of fixation and/or resumption of regular dietary activities. With increasing concerns about cumulative radiation doses, plain film imaging is the modality of choice for following patients, and thus the initial assessment should include a plain film for baseline evaluation.

An isolated mandibular series is useful for imaging patients with a suspected mandibular fracture and no other facial fractures and can be particularly helpful if there is availability of panoramic radiography is available and a CT scan is not clinically necessary. The mandibular series consists of a Towne's view, bilateral oblique views, and posterior-anterior views of the mandible. The Towne's view (anterior-posterior) is an excellent method of visualizing the mandibular condyles/subcondylar region. Oblique views are generally adequate for visualizing the mandibular body, angles, and ramus. The posterior-anterior view is excellent for visualizing the symphysis and parasymphysis.

Condylar Fractures

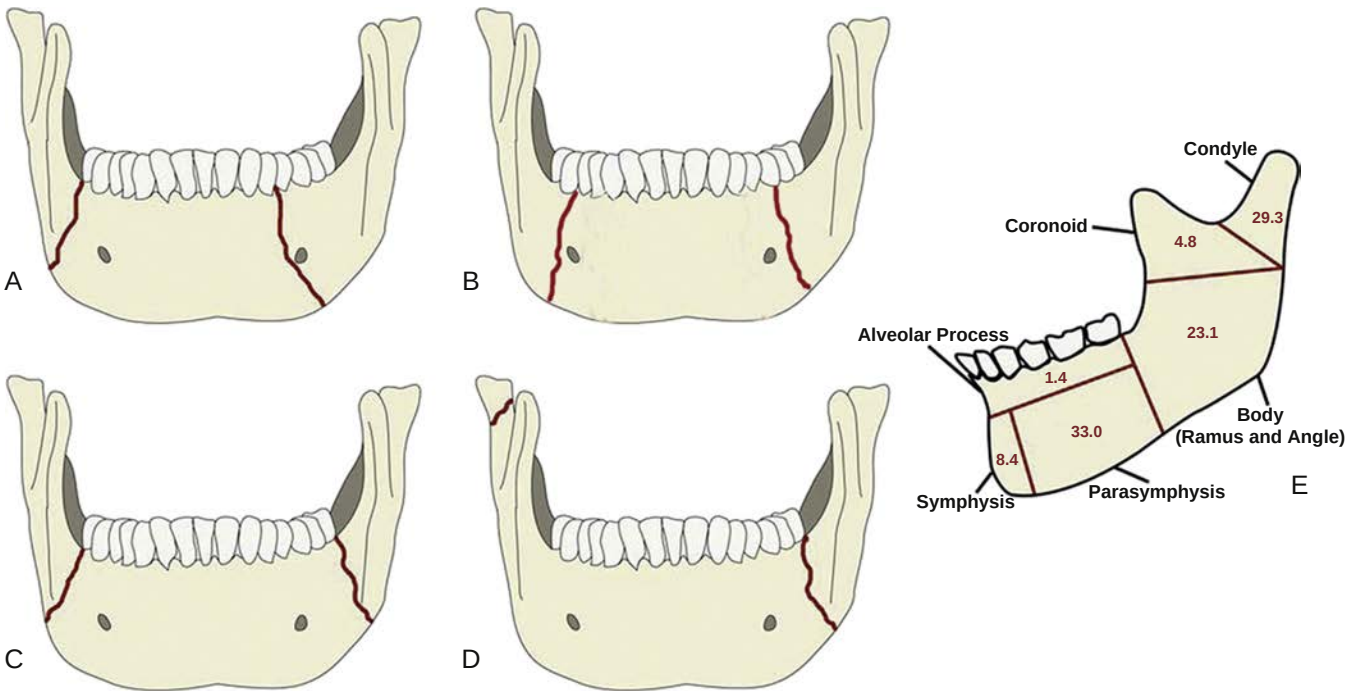
Trauma to other parts of the mandible generally directs force toward the temporomandibular joint and often results in fractures of the condylar process or subcondylar region. Fractures to the area are divided into intra- and extracapsular fractures. Intracapsular fractures are more common in children and can be easily missed on plain films. Fractures that occur below the condylar head within the condylar neck down to the sigmoid notch are considered extracapsular or subcondylar. Unilateral subcondylar fractures often occur with contralateral angle or parasymphysis fractures. A blow to the chin may result in bilateral condylar fractures along with a fracture of the symphysis. The fractured condyles can be displaced in any direction but are often anteromedially displaced due to the pull of the lateral pterygoid muscle (Figure 3-17).



• **Figure 3-14** Le Fort I fracture. **A**, Coronal image shows bilateral fractures through the lateral wall of the maxillary sinuses just above the dentoalveolar segment of the maxilla (*arrows*). **B**-**C**, Coronal image (more posteriorly) and axial image show fractures through the bilateral pterygoid plates (*arrows*). **D**, Three-dimensional reformat showing the fractures extending from the pyriform apertures posteriorly toward the pterygoid plates (*arrows*). There is a concomitant zygomaticomaxillary fracture (*arrowheads*).



• **Figure 3-15** Le Fort II fracture. **A**-**C**, Coronal images moving anterior to posterior show fractures through the nasofrontal suture (*arrows*), pyramid-shaped combination of fracture (*lines*) through the orbital floor and lateral wall of the maxillary sinus, and pterygoid plates (*yellow arrows*). **D**, Axial image showing the pterygoid plate fractures (*arrows*).



• **Figure 3-16** Pattern and incidence of mandibular fractures **A**, Parasymphysis and contralateral body. **B**-**C**, Bilateral body and angle fractures, respectively. **D**, Mandibulary body and contralateral condyle. **E**, Incidence (%) of fractures by location. (From Avery LL, Susarla SM, Novelline RA. Multidetector and three-dimensional CT evaluation of the patient with maxillofacial injury, *Radiol Clin North Am* 49(1):183-203, 2011.)

Plain films can demonstrate disruption of the posterior margin of the condylar neck or loss of vertical height of the condyle-ramus unit (see Figure 3-17, *A*). Intracapsular fractures can be missed and are best found via CT scan (Figure 3-18). Missed intracapsular fractures can have significant articular consequences, particularly in children.

Coronoid Process and Ramus Fractures

Fractures involving the coronoid process and/ramus are rare, accounting for less than 2% of mandibular fractures.[47] The coronoid is protected by the zygoma and arch, whereas the ramus is relatively dense compared to the adjacent subcondylar region and mandibular angle, which are far more commonly fractured.

Mandibular Angle Fractures

Fractures of the mandibular angle are among the most common mandibular fractures. Inherent weaknesses at the mandibular angle, such as the third molar, make the region prone to fracture with blows to the contralateral parasymphysis or ipsilateral mandibular body. The fracture usually extends superiorly from the retromolar region in the area of the third molar posteriorly toward the mandibular angle and is easily detected on plain films such as the panoramic radiograph or ipsilateral lateral oblique view.

Mandibular Body Fractures

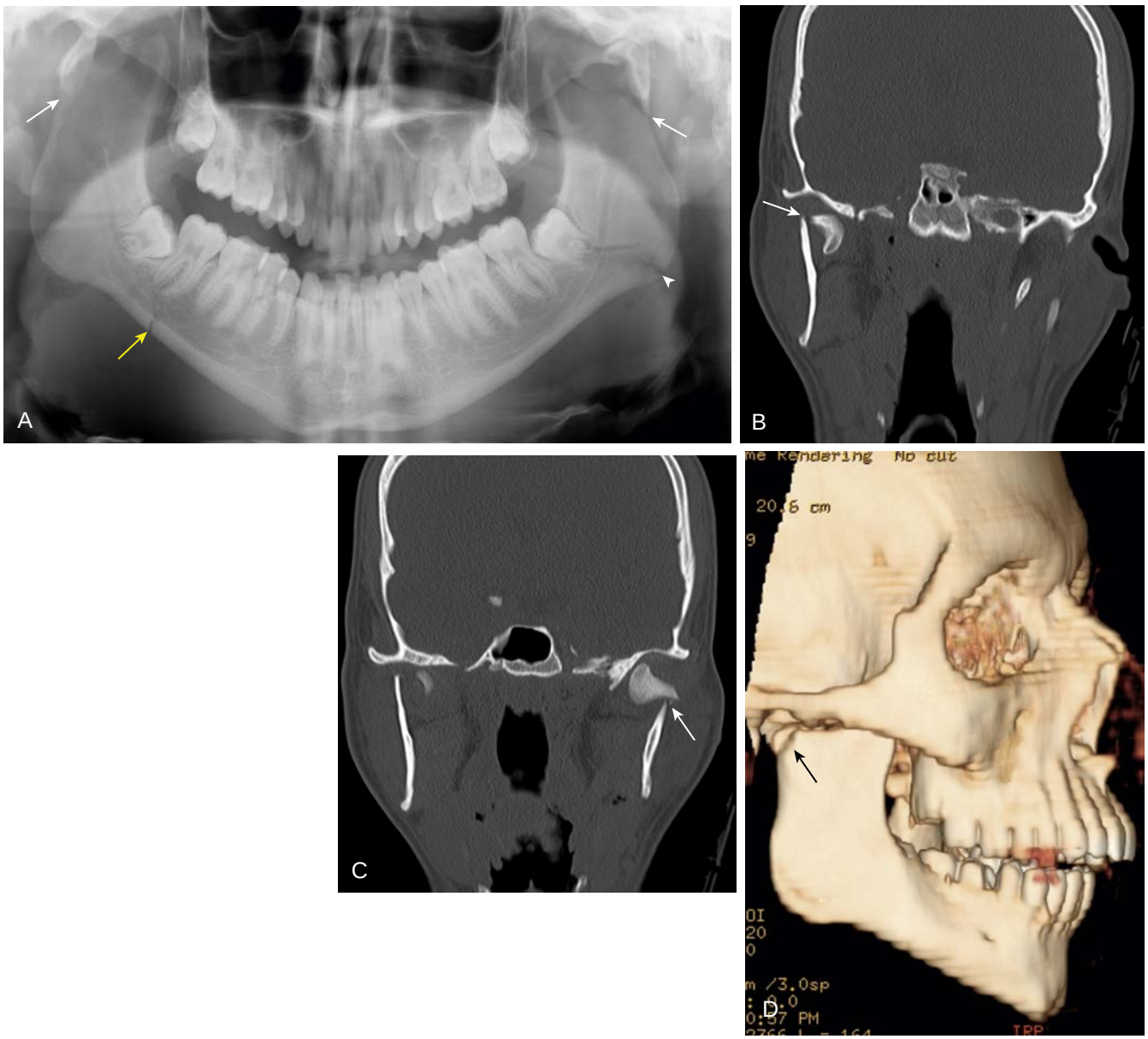
A blow to the ipsilateral mandibular body commonly results in a fracture that traverses through existing teeth. This often results in a step-off the occlusion at the site of fracture and are generally considered compound fractures (Figure 3-19). Edentulous mandibles are particularly prone to mandibular body fractures (Figure 3-20) due to atrophy of the posterior mandibular alveolus with early loss of mandibular teeth.

Mandibular Symphysis Fractures

Mandibular symphysis and parasymphysis fractures occur in the areas between and including the mental foramina. Fractures in this area are often oblique and can be missed on a plain films. The clarity of the image of the mandibular parasymphysis in a panoramic radiograph is variable because of the narrow focal trough. A CT scan is often needed to appreciate the presence and direction of the fracture.

Pathologic Fractures

Mandibular fractures can result from inflammatory or neoplastic processes affecting the structure and integrity of the mandible. Osteoradionecrosis of the mandible can progress to the inferior border and result in a pathologic fracture (Figure 3-21, *A*). Weakening of the mandible after removal of deeply impacted mandibular third molars can lead to

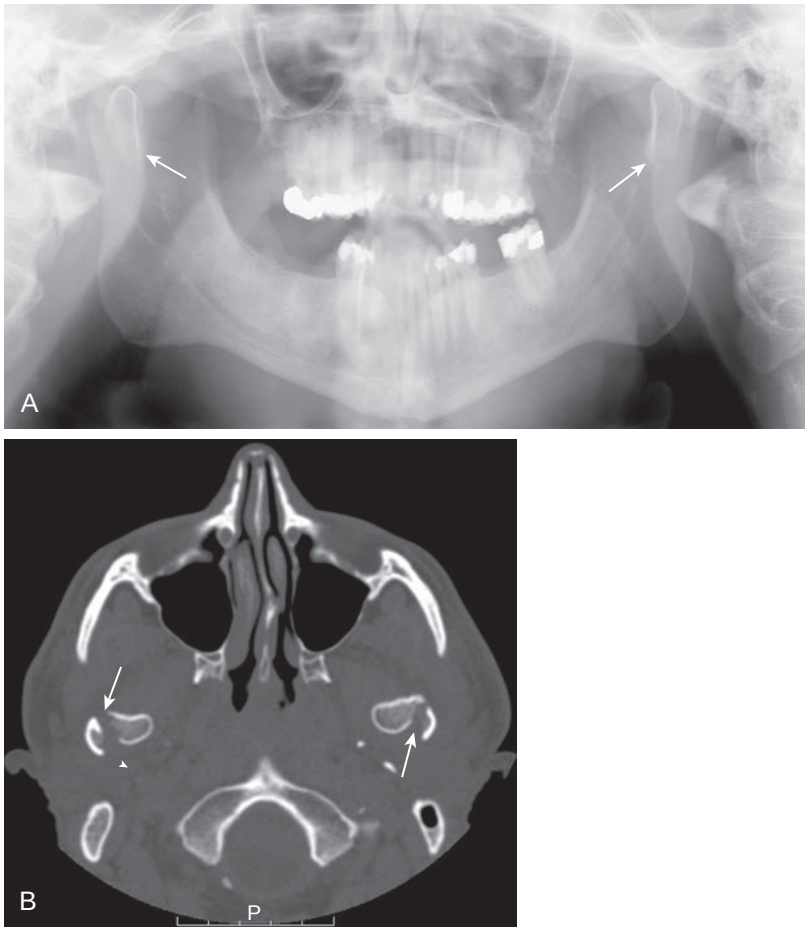


• **Figure 3-17** Multiple mandible fractures. **A**, Panoramic radiograph shows loss of continuity of the bilateral posterior ramus (*arrows*) indicating subcondylar fractures. Fractures are also seen of the left angle (*arrowhead*) through the impacted third molar and right body (*yellow arrow*). **B**, Coronal image shows high right subcondylar fracture with medial displacement of the condylar head out of the glenoid fossa (*arrow*). **C**, Coronal image shows low subcondylar fracture (*arrow*) also with medial displacement. **D**, Three-dimensional view highlights the high right subcondylar fracture with loss of ramus height (*arrow*).

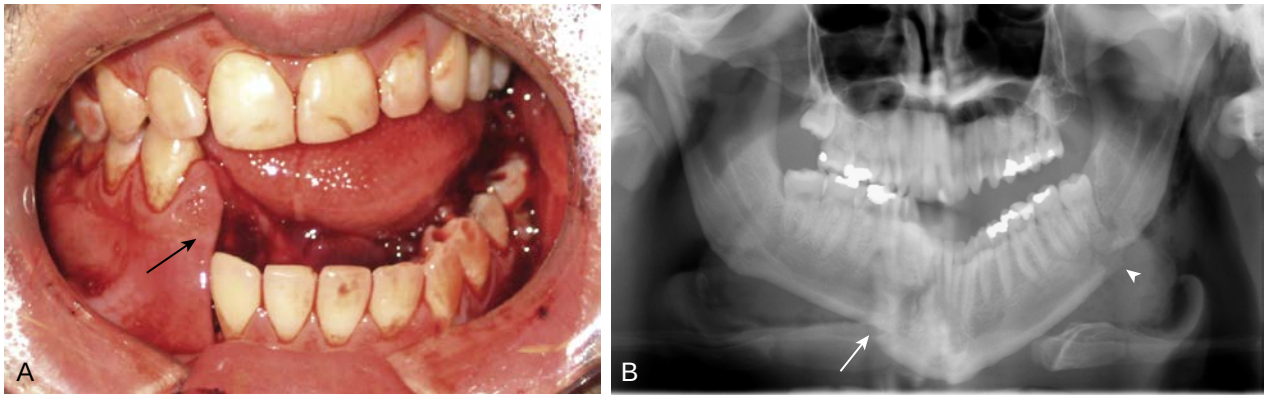
pathologic fracture, particularly in those patients where the third molar makes up a large portion of the vertical height of the mandible (see Figure 3-21, *B*, *C*).

Pediatric Facial Fractures

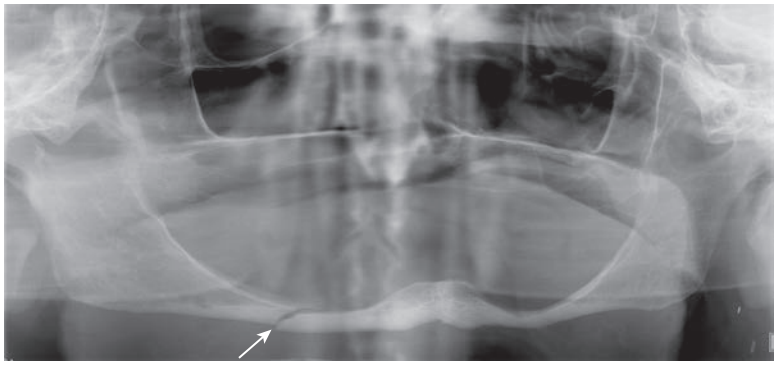
Growth is a confounding variable in the biomechanics of the facial skeleton. The growing facial skeleton has different stress points than the mature facial skeleton, and patterns of fractures are consequently different in children compared to adults.[49-51] Nasal fractures are the most common type of facial fracture in children, but mandibular fractures remain the most frequent cause of hospitalization, as they almost always necessitate some form of treatment. The distribution of mass within the pediatric facial skeleton (prominent cranium, non-pneumatized sinuses within the maxilla) results in more frequent injuries to the condylar/subcondylar regions (Figure 3-22) of the mandible and the frontal bone/orbital roof, with less frequent injuries to the midface.[51,52] When midfacial injuries do occur, they do not follow the



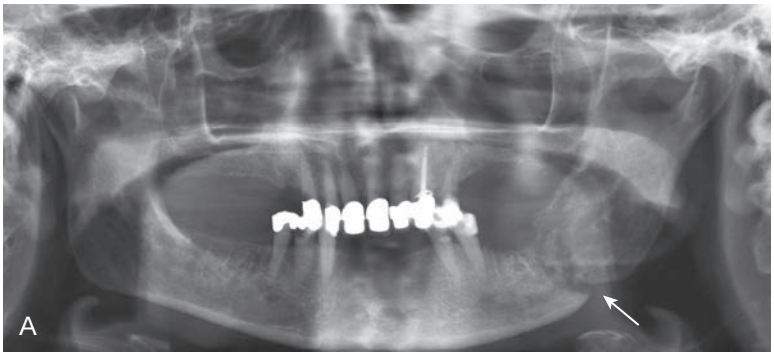
• **Figure 3-18** Bilateral mandibular condyle fractures (intracapsular). **A**, Panoramic radiograph shows disruption of the condylar head with displacement anterior to the articular eminences bilaterally (*arrows*). **B**, Axial image confirms intracapsular condylar fractures with displacement of the bilateral medial poles (*arrows*). The ramus heights are not substantially changed, and the malocclusion was subtle.

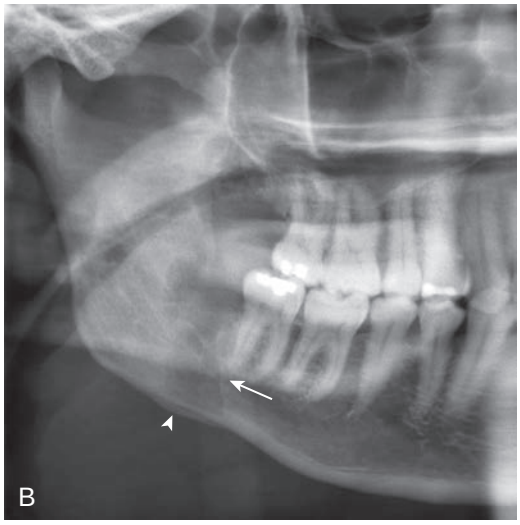


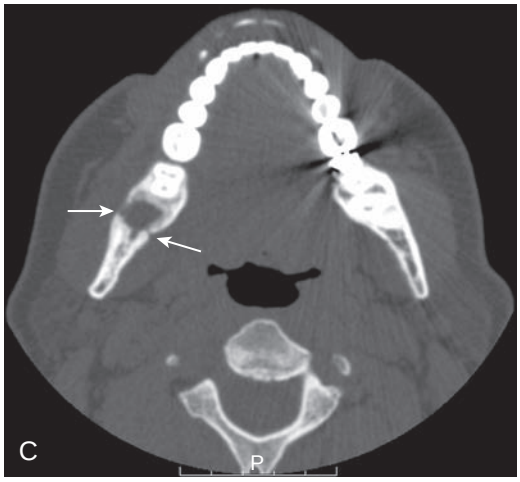
• **Figure 3-19** Mandibular body fracture. **A**, A stepoff in the occlusion (*arrow*) indicates a fracture between the teeth and represents a compound fracture. **B**, Panoramic radiograph demonstrating right mandibular body fracture (*arrow*) and left mandibular angle fracture (*arrowhead*).



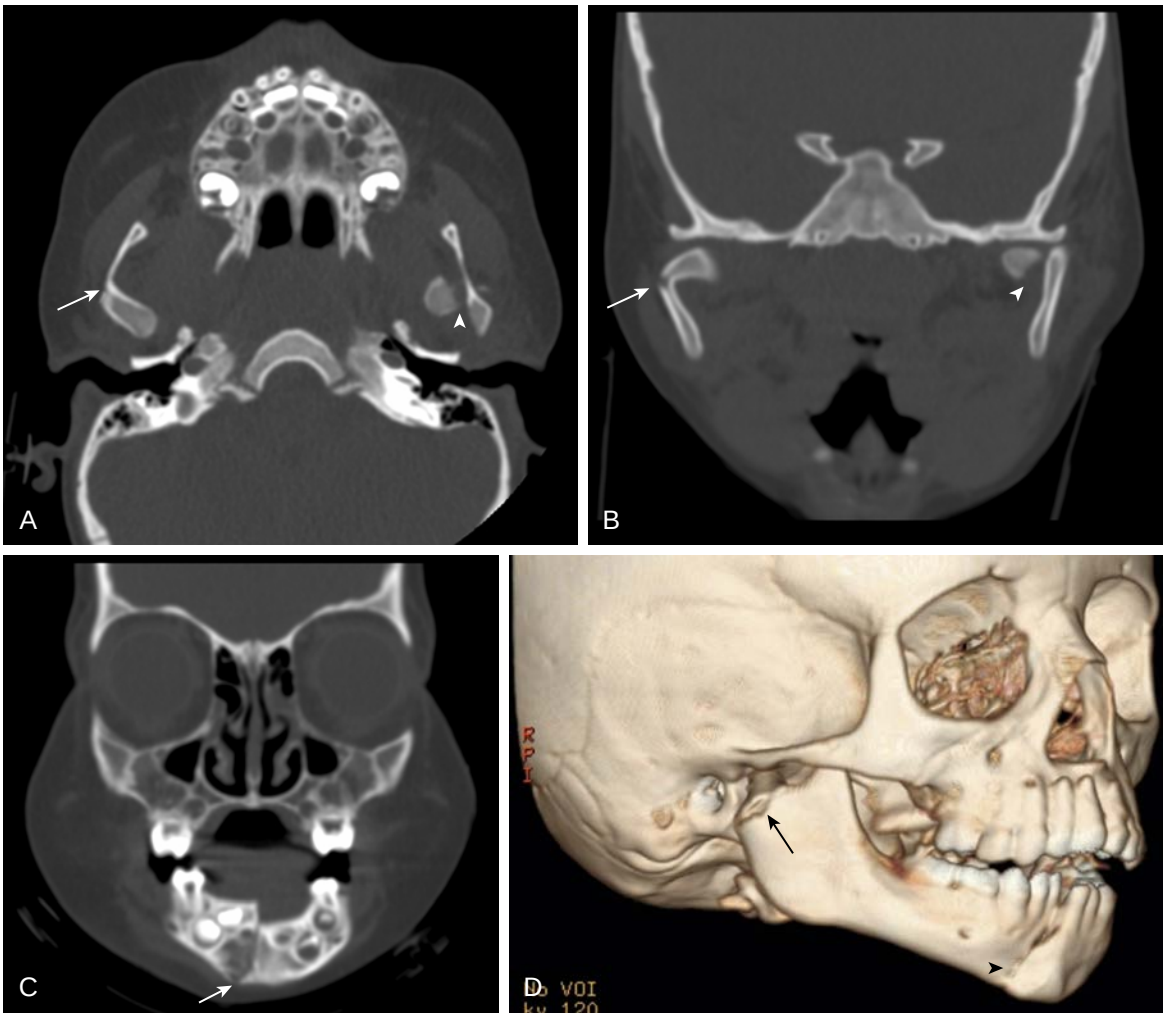
• **Figure 3-20** Fractures of edentulous mandibles typically occur in the region of the mandibular body (*arrow*) after longstanding edentulism of the posterior mandible.







• **Figure 3-21** Pathologic fractures occur in compromised areas. **A**, Osteoradionecrosis has progressed to the inferior border and resulted in a pathologic fracture of the left mandibular body (*arrow*). **B**, After extraction of a deeply impacted third molar, the patient had persistent pain. A panoramic radiograph showed a linear radiolucency (*arrow*) and periosteal reaction (*arrowhead*). **C**, Axial CT image confirmed pathologic fracture through the third molar extraction socket (arrows).



• **Figure 3-22** Pediatric mandibular fractures. **A-B,** Axial (**A**) and coronal (**B**) image shows right subcondylar fracture that is medially displaced with bending without displacement of the medial cortex (*arrows*) along with left intracapsular condyle fracture (*arrowheads*). **C**, Coronal image showing displaced symphysis fracture through tooth buds (*arrow*). **D**, Three-dimensional view of right subcondylar fracture (*arrow*) and symphysis fracture (*arrowhead*).

typical patterns described by Le Fort. Rather, they are more obliquely oriented across the zone of injury. Incomplete ossification of the facial skeleton results in bending in response to stress, with resultant greenstick or incomplete fractures.

Though there are reasonable concerns regarding the use of CT scans in children, CT imaging is the most accurate method of diagnosing facial fractures within this population. Clear discussions between the emergency personnel, surgeon, and radiologist are required to identify the most appropriate method of imaging for a particular injury presentation. Most institutions have diagnostic protocols for low-dose CT imaging for pediatric patients. Such protocols should be used whenever possible.

Children with facial injuries may, unfortunately, be victims of abuse.[49-51] If there is a suspicion of abuse, a skeletal survey to identify other injuries or old injuries in distant parts of the body is required and should be discussed with the radiologist.

Craniomaxillofacial Fractures with Associated Cervical Spine or Intracranial Injury

Among patients who present with facial trauma, 4% to 10% will have concomitant cervical spine injuries and up to 50% will have concomitant intracranial injuries.[53-56] Fractures of the frontal bone and orbital roof are associated with increased incidence of craniocervical injuries. Severe bilateral midfacial injuries are associated with skull-base injuries and death. Unilateral fractures of the nasal, orbital, zygomatic, and maxillary regions have been associated with skull-base fractures and intracranial injuries. Isolated mandibular fractures are associated with cervical spine injury. These associated patterns of injury should prompt the treating clinician to consider additional CT imaging of the cervical spine and head in patients who present with facial trauma.

Summary

Diagnostic imaging has a critical role in the management of facial trauma. Advances in imaging continue to improve the diagnosis and management of maxillofacial trauma.

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4

Soft Tissue Injuries of the Face, Head, and Trunk

PHILLIP N. FREEMAN, JAMES W. WILSON, KEVIN C. GAMS

Facial wounds are among the most commonly encountered problems in emergency departments (ED). Approximately one third of all lacerations occur in adults between the ages of 19 and 35 and predominantly in male patients, with approximately 50% occurring in the head and neck.[1-3] Injury patterns vary greatly, with trips and falls commonly causing isolated soft tissue injuries such as laceration and contusions mainly in children and the elderly.[4] Violence and motor vehicle accidents are among the most common causes of injury in individuals aged 15 to 50 years old.[3-5] Violence is most frequently by sharp injury from glass, knives, and wooden objects. In the United States motor vehicle collisions are the most prevalent cause of soft tissue damage to the face. More than 146,000 patients annually require hospital attention for facial soft tissue trauma.[6] Human and animal bites make up a small but significant percentage of soft tissue injuries. Burns, although infrequent compared to other wounds, also make up a small but significant percentage of facial wounds.

Initial Evaluation

Evaluation and management of trauma patients requires the advanced trauma life support (ATLS) protocol with a primary trauma survey followed by a secondary assessment for concomitant injuries.

A comprehensive head and neck exam should be performed to assess the extent of hard and soft tissue injury to determine the appropriate steps in management. All wounds should be evaluated for depth, size, and status of the wound for contusions, abrasions, crush injury, viability of the wound edges, and contamination. During the assessment period or during treatment of other injuries, the wounds should be kept moist with gauze soaked in saline until final management. Hemorrhage associated with most head and neck wounds may be substantial but can usually be controlled with local measures of pressure and ligation, or electrocautery when vessels are directly visible and can be isolated with a forceps. Persistent bleeding should be evaluated by direct pressure for inspection to prevent damage to other vital structures.

Injured and exposed structures should be identified, evaluated, and documented, with particular attention to cranial nerves V, VII, and XII. This is critical in the conscious patient and must be done prior to the use of any local

damaged, appropriate microsurgical techniques should be used to attempt to restore continuity and ultimate function of the nerve. Always inquire about functional deficits that existed prior to the injury.

Parotid duct injuries should be suspected in any patient with lacerations extending from the pretragal region to the middle half of the upper lip. In patients with a suspected parotid duct injury, the duct should be cannulated intraorally at the level of the second maxillary molar and visualized through the wound. The authors' preference for cannulation is the use of a J-wire followed by an intracatheter placed over the J-wire. If ductal injury is poorly visualized in the wound, liquids such as propofol or methylene blue may be injected into the duct to assess the location of the injury.

Exposed cartilage that cannot be covered initially should be dressed with mafenide acetate (Sulfamylon) 5% or silver sulfadiazine cream. As well, neurovascular structures that cannot be covered should be dressed with nonadherent dressings such as Xeroform gauze or Adaptic gauze with or without bacitracin ointment. Abrasions and superficial burns can be dressed with Adaptic gauze and bacitracin. Deep wounds that cannot be closed can be dressed initially with hydrogel bandages, normal saline Kerlix dressings or iodoform gauze until definitive closure can be obtained. Eyelid avulsion wounds require immediate ophthalmic

antibiotic ointment and an occlusive eye shield to prevent exposure keratopathy.

In isolated soft tissue injuries emergent airway stabilization is rarely indicated. However, in patients with soft tissue injuries that need tracheostomy there is a high associated mortality (11.5%) and a significantly longer hospital stay than in patients with craniofacial fractures.[7] The difference is primarily attributed to neurologic injury, which requires delay of soft tissue repair until after the patient is stabilized. All patients should be assessed for concomitant intracranial, craniofacial, ophthalmologic, and cervical spine injuries. Documentation of the timing and mechanism of injury as well as postinjury signs and symptoms such as loss of consciousness, nausea, and vomiting should be used to guide assessment and management. Increased vascularity of most craniofacial structures limits the risk of infection relative to delays in treatment.[8,9] Time from injury to repair was initially thought to be associated with an increased risk of infection but recently has been shown to be not specifically related to incidence of infections. Berk, Osbourne, and Taylor found that wound age was of little concern in wounds located on the scalp and face.[8] Factors such as diabetes, wound contamination, length greater than 5 cm and location are important risk factors for wound infection.[8]

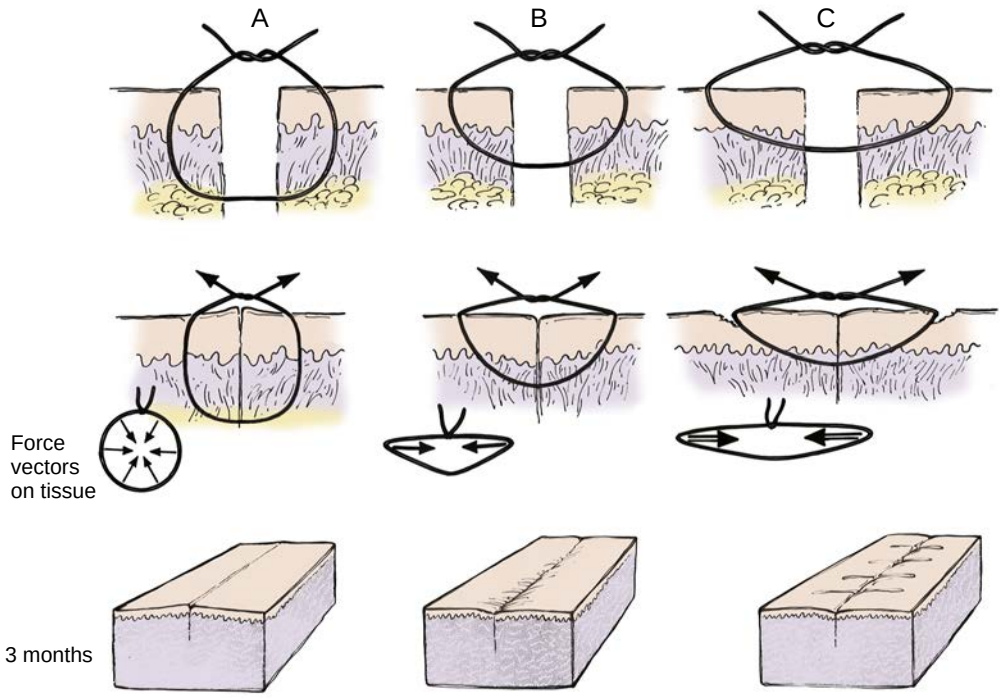
Improvements in decontamination by pressure irrigation over the past 30 years may have led to improved outcome.[10] It is also critically important to assess the mechanism of injury, as certain injuries that are associated with significant debris or wound contamination have been associated with increased incidence of infection. Impact crush injuries, for example, are as much as 100 times more susceptible to infection than are wounds caused by shear force.[11,12] Such wounds require pressure irrigation (< 15 psi) and debridement of all nonviable soft tissue to prevent postoperative infection. Also, photographs prior to injury are useful in identifying preexisting deformities and facial morphology.

Suture Technique and Suture Materials

Wound closure requires a variety of surgical techniques depending on the location of the wound, depth of the wound, anatomy of the wound margins, and presence of tissue edema.

Simple wound closure requires placement of sutures at the proper level in a trapezoidal fashion to create wound eversion. This principle applies to placement of subcutaneous sutures as well. Improper placement results in wound inversion (Figure 4-1). Multiple cutaneous suture techniques may be employed to accomplish the task of wound eversion as shown in Figure 4-2.

Simple wound closure that results in eversion and approximation of wound margins with subcuticular sutures

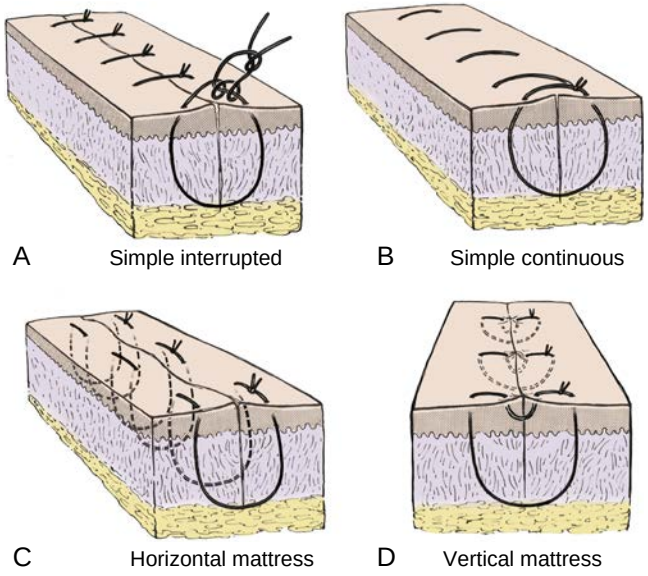


• **Figure 4-1** **A**, Proper placement of cutaneous suture showing equal distribution of tension along entire wound edge. Everted surgical would edges provide esthetic result. **B**, Improper placement of cutaneous suture with surgical bit too far from skin edge and too superficial. This creates vector forces that are greatest in a horizontal direction and produces inverted wound. **C**, Improper placement of cutaneous suture farther from skin edge with more superficial surgical bite. Force vectors on wound are greater in a horizontal direction and create more wound inversion. Additionally, permanent suture marks result in areas of pressure necrosis where wound closure tension is greatest. (From Sykes MJ, Byorth PJ: Suture needles and techniques for wound closure. In Baker SR, Swanson NA, editors: *Local flaps in facial reconstruction*, St. Louis, 1995, Mosby, p 56, Fig. 8, with permission.)

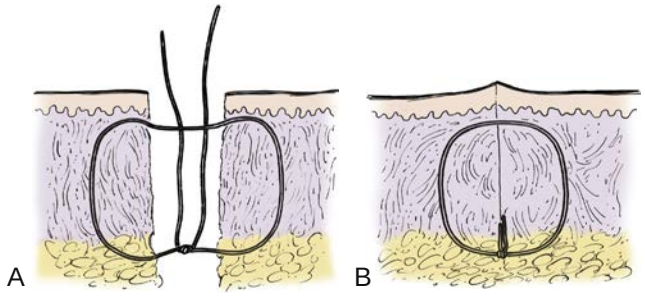
can be supported with paper tape for final closure, as seen in Figure 4-3. Paper tape alone may be used for closure of wounds that are superficial to the subcutaneous level, especially in pediatric patients.

In complex wounds, multilayered closure is required to eliminate dead space and provide wound eversion. This can be accomplished with either an interrupted suture or continuous suture technique as shown in Figure 4-4.

Closure of wounds with skin of unequal thickness requires placement of subcuticular sutures that maximize the cutaneous level and frequently requires modification of cutaneous suture placement (Figure 4-5). Staple closure may be used in a variety of circumstances but is most commonly used in the cutaneous closure of scalp. The proper placement of deep sutures and skin staples is demonstrated in Figure 4-6.



• **Figure 4-2** **A**, Simple interrupted suture. **B**, Simple continuous suture. **C**, Horizontal mattress suture. **D**, Vertical mattress suture. (From Sykes MJ, Byorth PJ: Suture needles and techniques for wound closure. In Baker SR, Swanson NA editors: *Local flaps in facial reconstruction*, St Louis, Mosby, 1995, p 57, Fig. 9, with permission.)



• **Figure 4-3** Schematic diagram of deep suture placement. Placement of deep sutures should eliminate dead space and accomplish wound edge approximation and eversion. (From Sykes MJ, Byorth PJ: Suture needles and techniques for wound closure. In Baker SR, Swanson NA editors: *Local flaps in facial reconstruction*, St Louis, Mosby, 1995, p 56, Fig. 7, with permission.)

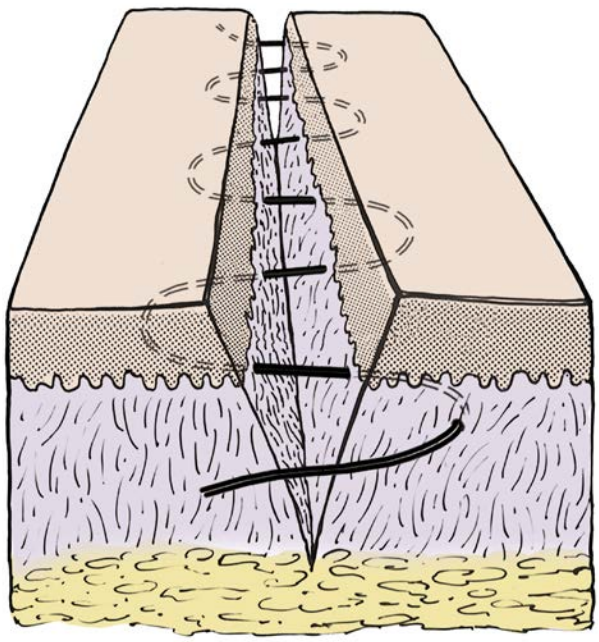
Understanding suture ideal characteristics for both absorbable and nonabsorbable materials is important in selecting the proper suture. There is no ideal suture for all wounds, therefore taking into consideration the ideal characteristics of suture material is important for selection of each particular wound. Box 4-1 lists the ideal suture material characteristics.

Familiarity with suture material terminology gives the surgeon a better understanding of suture material characteristics. This enables the surgeon to choose the suture best suited for the purpose at hand. Table 4-1 lists suture terminology. An excellent regional guide for suture selection is in Table 4-2.

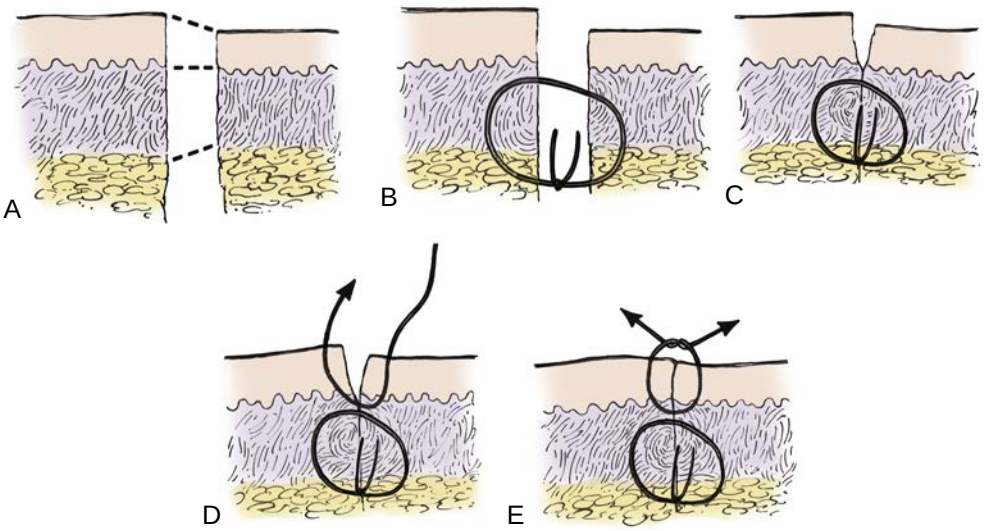
Suture materials are divided into natural fiber and synthetic fiber materials. Natural fibers are absorbable, although silk and cotton are extremely slow to be degraded over a period of several years and therefore considered to be nonabsorbable. Listed in Table 4-3 are natural materials and some of their characteristics, including tensile strength and absorption profile.

Synthetic fiber materials can be either absorbable or nonabsorbable. Absorbable synthetic fibers are polymers that degrade by hydrolysis and therefore cause less inflammation than natural fiber sutures. Listed in Table 4-4 are the absorbable synthetic suture materials and some of their characteristics, including tensile strength and absorption profile.

Synthetic nonabsorbable suture materials such as nylon and Prolene have long been the gold standard for cuticular closure. Nylon has a high level of elasticity and retains the



• **Figure 4-4** Intracuticular continuous suture. Cross-section of skin shows continuous suture at level of dermis to achieve maximal wound edge eversion. (From Sykes MJ, Byorth PJ: Suture needles and techniques for wound closure. In Baker SR, Swanson NA editors: *Local flaps in facial reconstruction*, St Louis, Mosby, 1995, p 58, Fig. 10, with permission.)



• **Figure 4-5** **A**, Schematic diagram illustrating two skin edges of unequal thickness. **B** and **C,** Placement of deep sutures in mismatched tissue to achieve maximal cutaneous alignment. Note suture is placed in dermis at deeper plane of thinner skin edge. **D** and **E,** Placement of cutaneous sutures in mismatched tissue to achieve maximal tissue eversion. (From Sykes MJ, Byorth PJ: Suture needles and techniques for wound closure. In Baker SR, Swanson NA editors: *Local flaps in facial reconstruction*, St Louis, Mosby, 1995, p 58, Fig. 11, with permission.)

most tensile strength of all synthetic materials. Prolene has the most pliability and knot-holding characteristic and is excellent for cuticular closure as well as vascular repair and approximation. Other synthetic suture materials have varied use as subcutaneous sutures for permanent holding characteristics. Table 4-5 lists the nonabsorbable synthetic suture materials and some of their characteristics.

Needle selection can be simplified into three categories: tapered, reverse cutting, and taper cutting. Further needle shapes are important for their particular utility and are divided based on their arc of curvature. Commonly used needles for wound closure include tapered for deep sutures and reverse cutting for skin closure. Tables 4-6 and 4-7 include needle types and shapes with their applications. Tissue sealants will be discussed in the section on postoperative wound care.

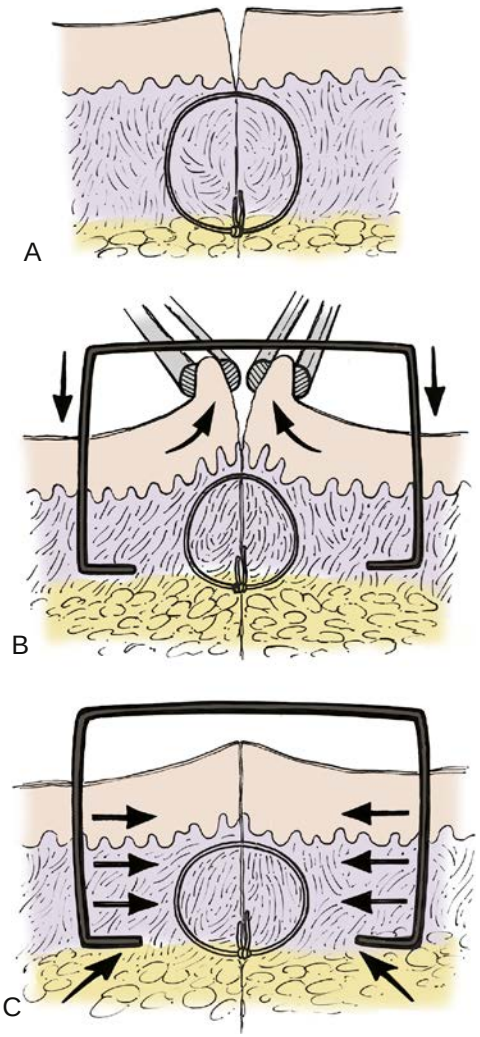
Principles of Wound Closure

Crikelair[14] listed the Halstedian fundamentals of surgical wound closure that apply to the management of any skin wound. These principles are: (1) place incisions to follow tension lines and natural folds in the skin; (2) handle tissue gently and debride only as much as necessary to ensure an adequately clean bed; (3) ensure complete hemostasis; (4) eliminate tension at the skin edges; (5) use fine sutures and remove them early; and (6) allow time for scars to mature before repeat intervention.

Wound closure requires a variety of surgical techniques for managing closure depending on the location of the wound, conformation of the wound (linear vs. curvilinear), depth of the wound, wound margins, and presence of abrasion, contusion, or avulsion. Isolated soft tissue wound closure should be performed as soon as possible, even with significant concomitant injuries. This approach has been shown to have improved postoperative esthetic outcomes.[14,15] Ideally, closure of facial soft tissue injuries should occur within the first 8 hours after injury. Soft tissue swelling associated with delay in wound closure can obscure anatomic landmarks and make primary closure more difficult. Closure in the ED requires meticulous cleaning of debris under nerve block with local anesthesia prior to closure.[16] Contraindications to primary closure in the ED include extensive lacerations, tissue closure that would result in significant tension, wounds that require complex tissue rearrangement, significant wound contamination, concomitant injuries that require general anesthesia (duct and nerve injuries), and inability to achieve adequate hemostasis or visualization in the ED setting. Wounds covering facial nerve or parotid duct injuries should be closed only after operative management of the deeper injury is complete.

Most lacerations can be treated using regional nerve blocks with small quantities of local anesthesia containing epinephrine and supplemented with 1:100,000 epinephrine solution where additional vasoconstriction is needed.[16] Pediatric patients who do not tolerate injection of local anesthesia may require conscious sedation for proper management of soft tissue injuries larger than 3 centimeters in length.

Optimizing wound healing through proper acute wound management involves removal of harmful debris/necrotic tissue, exploration for underlying injuries, control of bacterial burden, and multilayered closure. If wound contamination is present, wounds can be cleaned with a surgical antiseptic, preferably chlorhexidine gluconate.[17,18] Care must be taken not to scrub the wound because this can increase inflammation and result in poor esthetic outcome. Copious irrigation



• **Figure 4-6** **A,** Deep tissue approximation required prior to placement of surgical staple. **B**, Tissue forceps approximating and everting skin edge during application of surgical staple. **C,** Appearance of surgical wound after appropriate placement of surgical staple. Note equal and well-distributed horizontal vector forces on tissue edge after appropriate placement. (From Sykes MJ, Byorth PJ: Suture needles and techniques for wound closure. In Baker SR, Swanson NA editors: *Local flaps in facial reconstruction*, St Louis, Mosby, 1995, p 59, Fig. 12, with permission.)

should be performed in all contaminated wounds and any wounds treated more than 6 hours after injury. Irrigation volumes of 50 to 100 mL per cm of laceration length have been reported to be appropriate for contaminated wounds. Clean, uncontaminated wounds treated early do not benefit from irrigation.[19] Pressure irrigation, which has been shown to improve decontamination of wounds, can be performed in the ED setting using a 35-cc syringe and an 18 gauge catheter. Longmire[21] found that pressures of 13 psi, generated by using a needle and syringe, were effective in reducing inflammation and infection when compared to irrigation using a bulb syringe associated with lower pressures. Pressures of 8-12 psi in the wound are believed to overcome the adhesive forces of the introduced bacterium.[20] After cleansing, all irregular wound edges and devitalized tissues should be debrided. In cases such as crush injuries where the extent of injury is unclear, tissues should be loosely approximated until the wound viability is assured.

• BOX 4-1 Ideal Suture Material Characteristics

- Minimal tissue injury
- Minimal tissue reaction
- Ease of handling
- High tensile strength
- Favorable absorption profile
- Resistance to infection

Marcus BC: Wound closure techniques. In Baker SR: *Local flaps in facial reconstruction,* ed 2, St Louis, 2007, Mosby.

Several key principles are necessary to achieve an optimal result when primarily closing traumatic wounds. First, a layered closure is critical to obliterate dead spaces and also to relieve tension on the epidermal layer. Deep closure can be accomplished with a variety of suture materials. Absorbable suture, generally 3-0 and 4-0, are appropriate for muscle layers, 4-0 or 5-0 absorbable sutures are appropriate for dermal closure, and 5-0 to 7-0 nonabsorbable monofilament sutures are used for skin layers. Cyanoacrylate tissue adhesive such as Dermabond (Ethicon) or use of Steri-Strips (3-M) are appropriate in pediatric patients with uncomplicated, clean lacerations as they have been shown to be time saving, cost effective, and are less painful for the patient.[21,22]

Ideally, definitive repair of bony and soft tissue injuries can be achieved in a single operation, as successive operations rarely improve functional outcomes.[23] In high-velocity or blast injuries, primary soft tissue closure is frequently not possible due to the need for multiple debridements. Clinically superior outcomes result from early soft tissue reconstruction, which prevents significant contracture and provides better coverage for later osseous reconstruction.[24] The presence of contamination has not been associated with an increase in perioperative or long-term complications, therefore contamination should not be considered a contraindication to this treatment approach.[25] Computed tomography angiography (CTA) is needed to evaluate recipient vessels for free flap reconstruction in patients with complex wounds. If palpable pulses are not appreciable and recipient vessels lie in the zone of injury, then CTA is the definitive method to evaluate vessel patency and integrity.

Management of Special Anatomic Units

The general principles apply to most facial lacerations, however, areas with specific facial anatomy require additional consideration. These areas include the esthetic units and subunits of the face (Figure 4-7) as well as the adjacent soft tissue needed for reconstruction. Scalp, although not considered an esthetic unit, also deserves special consideration due to the importance of its hair and the esthetic consequences from injuries.

TABLE 4-1 Suture Material: Definition of Terms

Absorbable Suture

Undergoes progressive loss of mass or volume (does not correlate with loss of tensile strength

Breaking Strength

Limit of tensile strength at which material (or tissue) failure occurs

Capillarity

Extent to which absorbed fluid is transferred along the strand

Elasticity

A measure of a suture's ability to regain its original form and length after deformation

Fluid Absorption

Ability to take up fluid after immersion

Knot Pull Tensile Strength

Breaking strength of a suture material, which can be 10% to 40% weaker after deformation by knot placement

Knot Strength

Amount of force necessary to cause a knot to slip, which is directly proportional to the coefficient of static friction and plasticity of a given material

Memory

A suture's inherent capability to return to or maintain its original gross morphologic shape; it is a function of elasticity, plasticity, and diameter

Nonabsorbable Suture

Undergoes no significant loss of mass or volume (does not correlate with retention of tensile strength

Plasticity

A measure of a suture's ability to deform without breaking and to maintain that new form after relief of the deforming force

Straight Pull Tensile Strength

Linear breaking strength of suture material

Suture Pullout Value

Limit of strength of a particular tissue as measured by the force applied to a loop of suture at which tissue failure occurs

Tensile Strength

A material or tissue's ability to resist deformation and breakage

Wound-Breaking Strength

Limit of tensile strength of a healing wound at which wound separation occurs

Coefficient of Friction

A numeric value that quantifies a material's surface characteristics that act to resist motion against another surface

Marcus BC: Wound closure techniques. In Baker SR: *Local flaps in facial reconstruction,* ed 2, St Louis, 2007, Mosby.

TABLE 4-2 A Regional Guide to Suture Selection

Region	Cutaneous Suture	Subcutaneous/ Fascia Suture	Comments
Eyelid and periorbital	#6-0, #7-0	#4-0, #5-0	Minimal tensile strength requirements Esthetic concerns at a premium
Nose and pinna	#5-0, #6-0	#4-0, #5-0	Small tensile strength requirements Esthetic concerns at a premium
Lip and vermilion	#6-0	#3-0, #4-0	Moderate tensile strength requirements due to highly active region Esthetic concerns at a premium
General facial and anterior neck	#5-0, #6-0 #4-0, #5-0	#3-0, #4-0	Moderate to high tensile strength requirements due to regional mobility Significant esthetic concerns
Nasal and oral mucosa	#3-0, #4-0	#3-0, #4-0	Moderate tensile strength needed due to tissue mobility May select based on ease or no need for removal No esthetic concern
Scalp and posterior neck	#3-0, #4-0	#2-0, #3-0	Tensile strength needed for moderate to heavy tissue and very mobile region Minimal esthetic concern
Superior trunk	#2-0, #3-0	#2-0, #3-0	Tensile strength needed for heavy tissue in a relatively mobile area
Major musculocutaneous flaps	#4-0, #5-0	#1-0, #2-0, #3-0	Maximal tensile strength needed because sutures are often under significant tension May require long-term tensile strength

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TABLE 4-3 **Natural Fiber Sutures**

Name	Source	Special Processing	Filament	Relative Tensile Strength*	Tensile Strength Profile†	Absorption Profile‡	Tissue Reaction	Ease of Use§
Absorbable								
Plain gut	Highly purified (nearly 100%)	None	Twisted	2	75% at 7 days	70 days proteolysis		
Chronic gut	Collagen derived from submucosa of sheep intestines or serosa of beef intestine	Chromium salt treatment resists breakdown Heat treated to speed up degradation	"virtual"	2	75% at 14 days 75% at 5 days	90 days proteolysis	5	4
Fast-absorbing gut			monofilament	2		60-70 days proteolysis		
Plain collagen	Beef achilles tendon	Chromium salt treatment	Twisted "virtual"		75% at 7 days 35% at 14 days	70 days proteolysis	4	3
Chronic collagen		Chromium salt treatment	monofilament			90 days proteolysis		
Nonabsorbable								
Silk	Silkworm	Coating with beeswax or silicone; dyed	Braided	1	Progressive loss over 1 year	Significant at 2 years proteolysis	4	1 (gold standard)
Cotton	Cotton seed		Twisted	1				2
Linen	Flax seed		Twisted	2				2
Surgical steel			Braided or monofilament	5	Significant loss only if kinked		1	5

*Relative tensile strength scale: 1 = least, 5 = greatest strength.
†Represents percentage of original dry, out of package tensile strength.
‡Represents relative tissue reaction: 1 = least, 5 = greatest reaction.
§Represents relative overall ease of use: 1 = easiest, 5 = most difficult.
Marcus BC: Wound closure techniques. In Baker SR: *Local flaps in facial reconstruction,* ed 2, St Louis, 2007, Mosby.

TABLE 4-4 **Absorbable Synthetic Sutures**

Name	Source	Special Processing	Filament	Relative Tensile Strength*	Tensile Strength Profile†	Absorption Profile	Tissue Reaction‡	Ease of Use§
Poliglecaprone 25 (Monocryl, Ethicon)	Synthetic copolymer glycolide and caprolate	Undyed	Monofilament	4 (1)	50-60% at 1 wk 20-30% at 2 wk 20% at 3 wk	90-120 days hydrolysis	2	1—very pliable elastic
Polydioxanone (PDSII, Ethicon)	Synthetic polymer polydioxanone	Undyed	Monofilament	4 (4)	70% at 3 wk 50% at 4 wk 25% at 6 wk	180-210 days hydrolysis	2	3
Polygalactin 910 (Vicryl, Ethicon)	Synthetic copolymer glycolide lactide	Dyed violet or undyed, coated galactin 370	Braid	4 (2)	65% at 2 wk 40% at 3 wk 8% at 4 wk	56-70 days hydrolysis	3	2
Polyglycolic acid (Dexons, Davis & Geck)	Synthetic polymer	Dyed or undyed, coated polycaprolate	Braid	4 (3)	65% at 1 wk 35% at 2 wk 5% at 4 wk	90-120 days hydrolysis	3	2
Polyglyconate (Maxon, Davis & Geck)	Synthetic polymer polytrimethylene carbonate	Dyed	Monofilament	4 (1)	75% at 2 wk 50% at 4 wk 25% at 6 wk	180-210 days hydrolysis	2	2

*Relative tensile strength scale: 1 = least, 5 = greatest strength.
†Represents percentage of original dry, out of package tensile strength.
‡Represents relative tissue reaction: 1 = least, 5 = greatest reaction.
§Represents relative overall ease of use: 1 = easiest, 5 = most difficult.
Marcus BC: Wound closure techniques. In Baker SR: *Local flaps in facial reconstruction,* ed 2, St Louis, 2007, Mosby.

TABLE 4-5 **Nonabsorbable Synthetic Sutures**

Name	Source	Special Processing	Filament	Relative Tensile Strength*	Tensile Strength Profile†	Absorption Profile	Tissue Reaction‡	Ease of Use§
Nylon Dermalon (Davis & Geck) Ethilon (Ethicon)	Synthetic polyamide	Clear or dyed	Monofilament	3	81% at 1 yr 72% at 2 yr 66% at 11 yr	Slow hydrolysis stable at 2 yr	2	2—low coefficient of friction
Nurolon (Ethicon) Surgilon (Davis & Geck)		Dyed, silicone coated	Braided	2	Same as above	Same as above	2†	1
Polybutester Novafi (Davis & Geck)	Synthetic copolymer polyglycol terephthate polytrithylene terephthate	Dyed blue	Monofilament	3	–	None	1	2—very elastic, very low coefficient of friction
Polyester Ticron (Davis & Geck) Ethibond extra (Ethicon)	Synthetic Dacron polyester	Dyed, silicone coated	Braided	3	–	None	2	2
Dacron (Davis & Geck) Mersilene (Ethicon)	Synthetic Dacron polyester	Dyed, uncoated	Braided	2	–	None	2	3
Polypropylene Prolene (Ethicon) Surgilene (Davis & Geck)	Synthetic polymer propylene	Dyed blue	Monofilament	2		None	1	3—very low coefficient of friction

*Relative tensile strength scale: 1 = least, 5 = greatest strength.
†Represents percentage of original dry, out of package tensile strength.
‡Represents relative tissue reaction: 1 = least, 5 = greatest reaction.
§Represents relative overall ease of use: 1 = easiest, 5 = most difficult.
Marcus BC: Wound closure techniques. In Baker SR: *Local flaps in facial reconstruction,* ed 2, St Louis, 2007, Mosby.

TABLE 4-6 Needle Point Types and Applications

	Type	Application
Taper	Aponeurosis Biliary tract Blood vessels Dura Fascia Gastrointestinal tract Muscle	Nerve Peritoneum Pleura Subcutaneous fat Urogenital tract
Conventional or reverse cutting	Dermis Ligament Nasal cavity Oral cavity Pharynx Skin Tendon	
Tapercut (tapered cutting point, very sharp)	Bronchus Dermis Ligament Nasal cavity Oral cavity Ovary Perichondrium	Periosteum Pharynx Sclerotic vessels Tendon Trachea Uterus

Marcus BC: Wound closure techniques. In Baker SR: *Local flaps in facial reconstruction,* ed 2, St Louis, 2007, Mosby.

TABLE 4-7 Needle Body Shapes and Applications

Shape	Application	
¼ circle	Eye Microsurgical	
⅜ circle	Aponeurosis Biliary tract Blood vessel Dura Eye Fascia Gastrointestinal tract Muscle Myocardium	Nerve Perichondrium Periosteum Peritoneum Pleura Tendon Urogenital tract
½ circle	Biliary tract Eye Gastrointestinal tract Muscle Nasal cavity Oral cavity Pelvis	Peritoneum Pharynx Pleura Respiratory tract Skin Subcutaneous fat Urogenital tract
⅝ circle	Cerebrovascular System Nasal cavity Oral cavity Pelvis	Urogenital tract
Compound curved ("J" shaped) Kieth (straight)	Cleft palate repair Eye Gastrointestinal tract Nasal cavity Oral cavity	Pharynx Skin Tendon Vessels

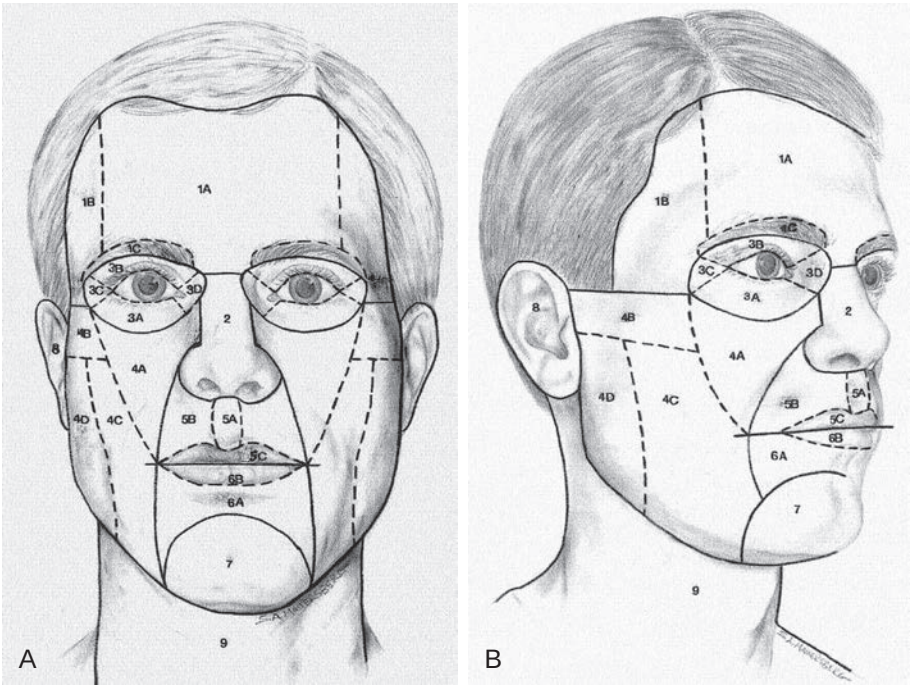
Marcus BC: Wound closure techniques. In Baker SR: *Local flaps in facial reconstruction,* ed 2, St Louis, 2007, Mosby.

Scalp

Scalp lacerations frequently bleed profusely due to the extensive blood supply and require good visualization to gain hemostasis. Head CT should be performed to rule out skull fractures prior to closure of scalp lacerations. Lacerations that are extensive are therefore better repaired in the operation room under more controlled conditions. Scalp lacerations with defects smaller that 3 cm can be closed primarily in most cases. Larger defects may require galea scoring to allow laxity for closure. Closure of the galea is important to achieve proper approximation of overlying soft tissue. Failure to close galea frequently results in a step defect in the scalp as illustrated in (Figure 4-8). Options for closure of larger defects in hair bearing areas include local rotational or advancement flaps, skin grafts provided pericranium is intact, burring the outer table when pericranium absence exposes bleeding bone to allow granulation tissue to form a vascular bed for skin grafting, and rotation of adjacent intact pericranium, galea, or temporoparietal fascia for a vascular base for skin graft coverage. This can later be followed with staged tissue expansion of the hair bearing areas for definitive scalp reconstruction. Pedicle flaps or free tissue transfer can be performed for large defects that cannot be managed solely with tissue expansion. Avulsion wounds of the scalp that are a result of blunt or shear forces have poor prognosis due to the vascular intimal damage that propagates proximal and distal within the vessels, and in such cases microscopic revascularization is generally unsuccessful. However, in large scalp avulsion injuries attempts should be made to revascularize when possible because reconstruction of hair bearing areas remain difficult without like tissue.

Forehead

Lacerations of the forehead should be comprehensively evaluated with special attention to cranial nerves V and VII. This is critical in the conscious patient and must be done prior to the use of any local anesthetic. Closure of wounds should follow the general principles described previously using conservative debridement and multiple layered closure. Avulsion defects that are smaller can be managed with rotational flaps or advancement local flaps based off the supraorbital or supratrochlear vessels. Larger tissue defects can be closed with split-thickness skin grafts followed by secondary tissue expansion for improved management of color and texture match with forehead skin. In cases where the entire esthetic unit is avulsed, skin grafting can result in an acceptable outcome without further treatment with distant flaps which often have poor color and texture match.



• **Figure 4-7** **A**, Frontal and **(B)** profile views of the esthetic units and subunits of the face. *1,* Forehead unit (*1A,* central subunit; *1B,* lateral subunit; *1C,* eyebrow subunit); *2,* nasal unit; *3,* eyelid units (*3A,* lower-lid unit; *3B,* upper-lid unit; *3C,* lateral canthal subunit; *3D,* medial canthal subunit); *4,* cheek unit (*4A,* medial subunit; *4B,* zygomatic subunit; *4C,* lateral subunit; *4D,* buccal subunit); *5,* upper-lip unit (*5A,* philtrum subunit; *5B,* lateral subunit; *5C,* mucosal subunit); *6,* lower-lip unit (*6A,* central subunit; *6B,* mucosal subunit); *7,* mental unit; *8,* auricular unit; *9,* neck unit. (From Fattahi TT. An overview of facial aesthetic units, *J Oral Maxillofac Surg* 61:1207–1211, 2003.)

Eyelid

Management of eyelid lacerations requires accurate identification of injury to all components of the eyelid. This involves upper lid, lower lid, medial canthus, lateral canthus, tarsal plates of upper and lower lid, levator aponeurosis, and lacrimal apparatus, as well as thickness of the injury and loss of tissue.[26] Timing of closure is not a critical factor owing to the excellent tissue vascularity in the periorbital area and in most cases a delay of 12 to 36 hours will not alter the outcome of the primary closure. Simple lacerations are closed anatomically in layers based on the tissues injured.[27] Closure materials include 5-0 and 6-0 plain gut for conjunctiva and orbicularis followed by 5-0 or 6-0 fast-absorbable plain gut or 6-0 nonabsorbable sutures for skin closure.

Lacerations of the lid margin and tarsal plate must be approximated anatomically and the lid margin everted with vertical mattress sutures using 6-0 silk to prevent notching (Figure 4-9). In lower lid lacerations anatomic approximation and support are important to prevent ectropion. The use of an orbicularis muscle sling sutured to lateral orbital rim using 5-0 Vicryl provides excellent support when laxity is present during repair. In upper lid lacerations levator aponeurosis integrity is important to establish to prevent postoperative ptosis. Presence of orbital fat implies a beach of the orbital septum indicating possible damage to the underlying levator palpebrae superioris muscle (Figure 4-10).



• **Figure 4-8** Poor outcome from scalp repair as a result of failure to close the galea in an anatomic closure.

When necessary, anatomic approximation of the aponeurosis with the tarsal plate can be performed with 6-0 or 7-0 polyglactin sutures placed central, medial, and lateral.[27] Medial lid lacerations require evaluation of the lacrimal ducts and canaliculi and appropriate ophthalmologic consultation for repair. Partial-thickness loss greater than



• **Figure 4-9** **A,**Through and through upper eyelid laceration managed with **(B)** closure of the palpebral conjunctiva using 6-0 plain gut with knot buried below conjunctiva. This is followed by tarsal plate repair with 6-0 polyglactin and skin closure with 6-0 polyprolene. Care must be taken to approximate margin anatomically and evert the gray margin using a horizontal mattress suture with 6-0 or 7-0 silk.

50% of either upper or lower lid requires full-thickness skin graft. Donor sites from the contralateral eyelid when adequate skin exists or postauricular (as opposed to retro auricular) full-thickness skin from the contralateral eyelid when available provide satisfactory match in thickness and color. Donor site deformities need to be prevented in both sites when using this technique. Local advancement flaps can be used in full-thickness tissue loss greater than one third of the upper lid in combination with lateral canthotomy and cantholysis. Greater loss of tissue may require myocutaneous flaps, whereas eyelid loss in excess of one half of the lid may require lid-sharing procedures of additional grafting, or both can be used for closure of defects up to 50% of the lid length (Figure 4-11). Avulsion injuries of eyelid can be repaired primarily if the horizontal length is less than one fourth of the upper lid or one half of the lower lid. Lower lid defects that are larger require lateral canthotomy and cantholysis or tarsal strip to allow for tension-free closure. A variety of single pedicle or bipedicle myocutaneous flaps from the apposing eyelid have been described for reconstruction of both upper and lower lid avulsion defects. Complete or near complete avulsion of upper and/or lower eyelid defects require switch flaps, composite flaps, cheek flaps, or forehead flaps. In complete upper and lower lid avulsion wounds it is critically important to protect the eye from further injury. Ophthalmic antibiotic ointment and protective shields should be employed for protection followed by early reconstruction. Establishment of medial and lateral canthus attachments is necessary to provide lid contour for globe protection.

Complete eyelid reconstruction can be achieved using microvascular transfer of dorsalis pedis with septal cartilage[28] or radial forearm flaps with palmaris longus tendon.[29] With severe injuries involving loss of the globe a complete prosthetic eye constructed by a maxillofacial prosthodontist is an excellent option and should be considered.

Lateral and medial canthus injuries occur frequently in lid injuries when lacerations in the adjacent area are full thickness. Repair requires primary canthopexy or canthoplasty when possible, but with more extensive injuries alternative repair may become necessary. Lateral canthus can be recreated with suture repair of the lower lid tarsus to the lateral orbit placed inside the rim. Medial canthus lacerations frequently involve the canaliculi or lacrimal apparatus and should be addressed with ophthalmologic consultation and the Jones dye test. A Jones I test can be performed using fluorescein dye placed in the eye and assessed for the presence of fluorescein in the nose after 5 minutes. If dye is present in the nose, a functional lacrimal apparatus is present. Without dye present, a Jones II test is performed by irrigating the nasolacrimal system with saline and having the patient expectorate the irrigation solution into a basin, where it is then checked for the presence of fluorescein. In the absence of a lacrimal apparatus injury, repair of the medial canthus is done with a method similar to that used in repair of Type III nasoorbitoethmoidal (NOE) injury.

Nose

Principles for repair of the nose are similar to those that apply to other special anatomic areas. With simple lacerations, anatomic approximation is performed using 5-0 chromic for mucosal lacerations and 5-0 or 6-0 nonabsorbable sutures for skin. The skin and soft tissues of the nasal tip and alar rim tend to be thick and relatively stiff, making primary closure of these regions more difficult. When cartilage lacerations are present, simple approximation with



• **Figure 4-10** Eyelid lacerations that appear innocuous with small skin loss as shown in **A** need to be explored as shown in **B**. As seen in **B**, there is a discontinuity of the levator aponeurosis and conjunctival laceration. Complete ophthalmologic exam needs to be performed before completion of repair. **C,** Completion of repair of the levator aponeurosis with 5-0 polydioxanone followed by repair of palpebral conjunctiva with 6-0 plain gut. This is followed by repair of the lid skin with advancement flap for final lid repair.



• **Figure 4-11** Complete loss of full-thickness lower lid as seen in **A**. Reconstruction with Hugh's tarsoconjunctival flap for posterior lamella and anterior lamella reconstructed with full-thickness skin graft from ipsilateral postauricular skin **(B).** Tarsoconjunctival flap is similar to an Abbey flap for lip reconstruction, however, division in inset is performed at 3 weeks.

monofilament absorbable sutures can prevent collapse of nasal ala and tip and improve esthetic outcome. The authors' have found that splinting significant lacerations that involve the alar margin and lower lateral cartilage with intranasal packs and external splints can reduce scar formation that results in external valve stenosis (Figure 4-12).

With tissue loss, successful reconstruction of soft tissue defects requires addressing all osseocartilaginous injuries or defects. Multiple algorithms have been devised for the evaluation and reconstruction of nasal defects.[30,31] Opinion varies with regard to reconstruction of the esthetic subunits of the nose. In the past, general consensus was that if a defect greater than 50% of a subunit is compromised, then the remainder should be excised so that the entire subunit can be reconstructed. Opinion is now shifting in favor of retaining as much of the anatomic structures of the nose and doing only esthetic subunits of the nose.[32] Partial-thickness defects over subunits with thinner skin can be closed using postauricular full-thickness skin grafts with reasonable esthetic outcome. Thicker skin defects of nasal tip and alae can be reconstructed with retroauricular full-thickness skin grafts; however, a better option is preauricular full-thickness grafts, which have better thickness and color match. With larger defects involving more than just tip, local and regional flaps such as dorsal nasal, cheek advancement, nasolabial, and paramedian forehead flaps are used for repair (Figure 4-13).

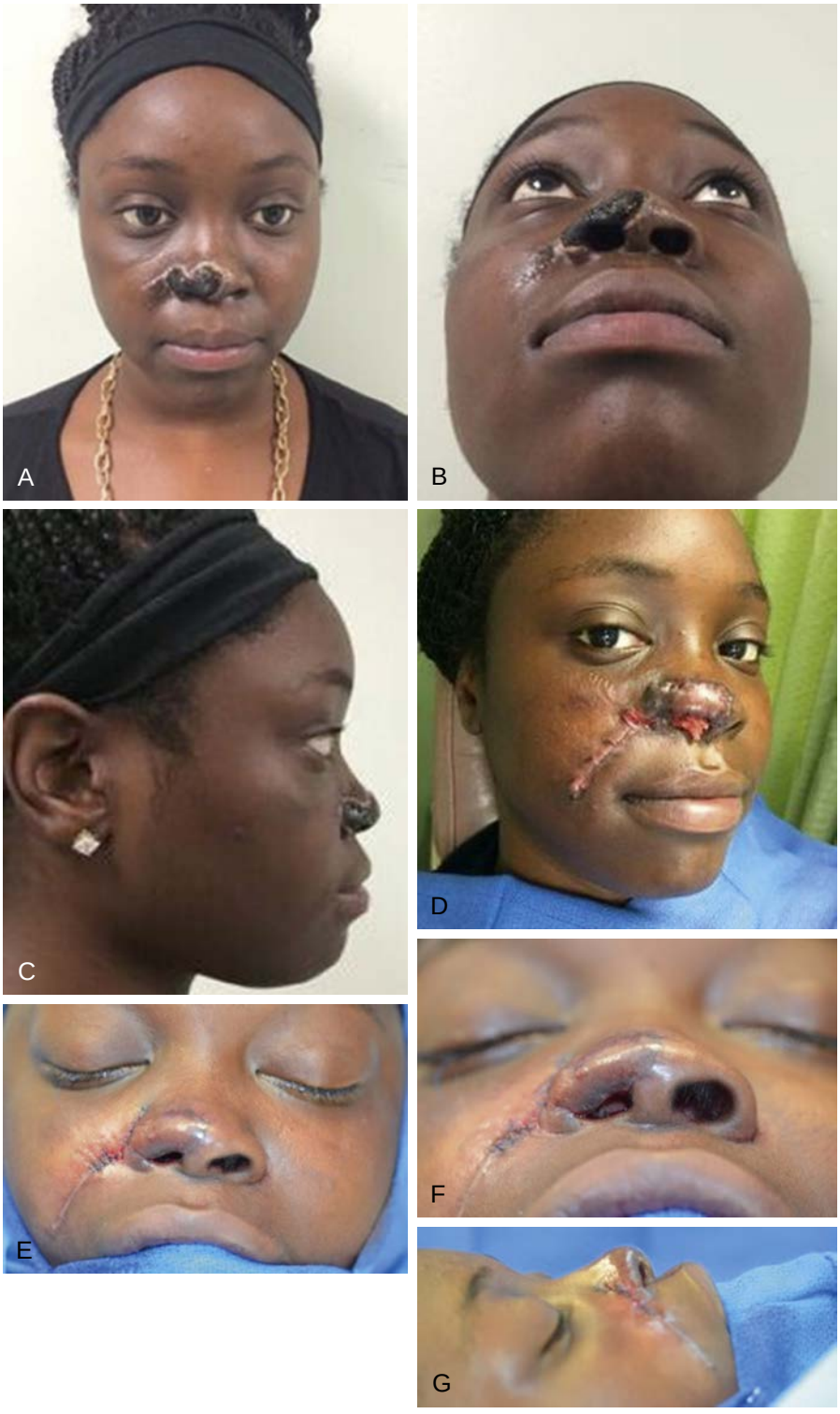
Extensive avulsion of soft tissue resulting from high-velocity projectiles or amputation from mechanical devices that cannot be closed with local or regional flaps requires bone graft and free flap reconstruction and often produces less than desirable esthetic results. In such cases, as with total avulsion of eyelid and ear defects, total nasal prosthetic reconstruction by a maxillofacial prosthodontist is an excellent option (Figure 4-14).

Lips

Anatomic landmarks are key to proper management of lip lacerations in restoring esthetics, motor function, and sensory function. Identification and marking of key landmarks such as the vermillion border, Cupid's bow, and commissure prior to injection of local anesthesia is important. Alignment of vermillion border is critical to the final esthetic outcome because the human eye can detect as little as 1 mm of discrepancy in vermillion continuity. Simple lacerations of the lips can be managed using the basic principles of wound closure. After thorough irrigation and wound debridement, closure of skin can be performed using 4-0 polyglactin or polydioxanone suture for deep tissue and intradermal approximation with 6-0 permanent monofilament skin sutures. If lip mucosa only is involved, irrigation and debridement is performed followed by closure with 3-0 or 4-0 chromic gut in a single layer fashion. Through and through lip lacerations should be closed from inside out. Following irrigation and debridement, mucosal closure can be performed with 3-0 or 4-0 chromic gut in a running locking fashion creating a watertight seal. If necessary, several interrupted sutures can be placed for proper anatomic alignment prior to placement of the running suture. Irrigation is performed extraorally to minimize oral bacterial contamination. Approximation of muscle with interrupted 3-0 or 4-0 polyglactin or polydioxanone is followed by intradermal approximation with 4-0 or 5-0 polyglactin or polydioxanone. Skin approximation should be accomplished with intradermal sutures to align the epidermis and prevent tension, followed by closure of skin with 6-0 cuticular sutures.



• **Figure 4-12** **A,** Complex nasal laceration with tacking suture used for temporary closure before definitive repair in the operating room. Repair requires minimal debridement and multiple layered anatomic closure. Extensive laceration with upper lateral cartilage avulsed from nasal bones, septum separated from upper lateral cartilages, septum fractured and separated from upper and lower lateral cartilages, and left lateral crus of lower lateral cartilage transected seen in **(B)**. Complete repair with suture repair of septum and lower lateral cartilage with 5-0 polydioxanone, transnasal repair of mucosa with 5-0 chromic, and layered closure of skin with 4-0 polygalactin and 5-0 polypropylene seen in **(C)**.



• **Figure 4-13** Composite loss of nasal tip involving portions of lateral crus, caudal septum, and nasal tip skin and mucosa **(A-C).** Patient at 1 week postoperative after reconstruction with nasolabial flap with auricular cartilage grafts from conchal bowl for medial and lateral crus reconstruction, and bipedical nasal mucosal flap for intranasal lining **(D).** Patient seen immediately postoperative following modification of the nasolabial flap inset to reestablish an esthetic nasofacial groove **(E-G).** Note the marked improvement of the nasolabial scar at 6 months.

Lip wounds may suggest significant tissue loss on first impression; however, by a careful approximation, it becomes apparent in many cases that most if not all of the tissue is present. When avulsion wounds exist in the lips it is important to assess the quantity of missing tissue. The lower lip is functionally more important than the upper lip because it maintains oral secretions and prevents drooling. The lower lip can tolerate up to one third loss of tissue and still be managed with primary closure. Upper lip avulsions are similar, with the exception of reestablishing normal Cupid's bow and philtral column anatomy. Esthetic outcome from upper lip loss is much less desirable than in the lower lip.



• **Figure 4-14** Patient with prosthetic nose following traumatic loss of all external nasal tissue.

Management of lip avulsion wounds can be accomplished with lip switch procedures such as the Abby-Elslander and reverse Abby-Elslander technique for defects of upper and lower lip, respectively. Lip switch procedures have major advantage in that lost tissue is replaced with like tissue. Bilateral and unilateral Karapanzic flaps can be employed for larger avulsion defects greater than one half the lip length, with the ultimate outcome dependent on the neurovascular supply of the lip for its functional maintenance.

In significant loss of upper and/or lower lip from large avulsion wounds such as gunshot wounds, it is often necessary to create lip tissue from distant free tissue transfer. Microvascular reconstruction with radial forearm and anterolateral thigh (ALT) can provide necessary tissue for lower lip with good outcome.[33,34]

Ears

Lacerations of the ear typically involve both skin and cartilage because of the thin nature of ear skin and its strong adherence to the underlying cartilage. As with all facial lacerations, the basic principles of wound management apply. Debridement of cartilage should be kept to a minimum because extensive cartilage removal results in significant deformities. Simple lacerations require skin closure only with skin adherence acting as a splinting mechanism. Permanent nonabsorbable sutures are used in most cases, but in young children and infants fast-absorbing gut is preferable.

Complex lacerations that lack support from cartilaginous injury require cartilage sutures. Absorbable monofilament 5-0 sutures such as PDS are preferable due to its absorption properties (Figure 4-15). Suture knots should be placed on the posterior of the cartilage repair, as knots on the anterior surface are visible and frequently become exposed. This is due to the tighter adherence of skin on the anterior surface versus the posterior skin. Following complex repair of ear



• **Figure 4-15** **A,** Complex forehead, lateral eyelid, cheek laceration, abrasion, contusion. Repair required copious irrigation, debridement of foreign material and nonviable severely contused cheek tissue with preservation of frontal branch of cranial nerve (CN) VII followed by multiple layered repair of soft tissue reapproximation with 5-0 polydyoxalene and multiple 6-0 prolene seen in **(B)**. Postoperative wound dressings included Bacitracin, adaptic gauze, 4-by-4 gauze, and Tegaderm occlusive bandage for management of the abrasion.

lacerations it is wise to apply a contouring bandage to provide support as well as prevent hematoma or serosa formation under the skin, which can result in a cauliflower ear deformity. The authors' preference for contour bandages is bacitracin-saturated cotton ball that can be placed into the contours of the ear from conchae to helical fold. Once the contours are filled, applications of 4-by-4 gauze front and back are placed followed by a mastoid bandage, as shown in Figure 4-16. The bandage is kept in place for 5 to 7 days.

Partial loss of ear skin can be repaired with split-thickness skin grafts taken from the contralateral ear postauricular skin. Adequate splinting to prevent hematoma and seroma is essential for survival of the graft (Figure 4-17). Lacerations that result in near avulsion should first be assessed for arterial inflow as well as venous outflow. In partial amputation with relatively large pedicle, the prognosis is good following conservative debridement and meticulous repair. If the pedicle is narrow, the chance of venous congestion is much higher. When outflow is inadequate, venous micro

this period. As with complete avulsion of the scalp, mechanism of injury is a strong predictor of success. Injuries that are sharp avulsion have much better success of revascularization than those that are shearing and crushing in nature.

In complete traumatic loss of the ear excellent results can be obtained by implant-retained auricular prosthesis (Figure 4-19).



• **Figure 4-16** Mastoid bandage placement provides excellent support and compression over ear repairs and reconstructions. Bandage consists of cotton balls saturated in antibiotic ointment and placed in the contours of the ear anatomy followed by 4-by-4 gauze behind and covering the ear. This is followed by Kerlex wrapped as shown and tied in place over the forehead with suture or umbilical string.

Parotid Duct

Lacerations of the cheek that lie in a line from the tragus to the ipsilateral mid-upper lip and extend deep to the superficial muscular aponeurotic system (SMAS) need to be explored for parotid duct injuries and facial nerve injuries.[35]

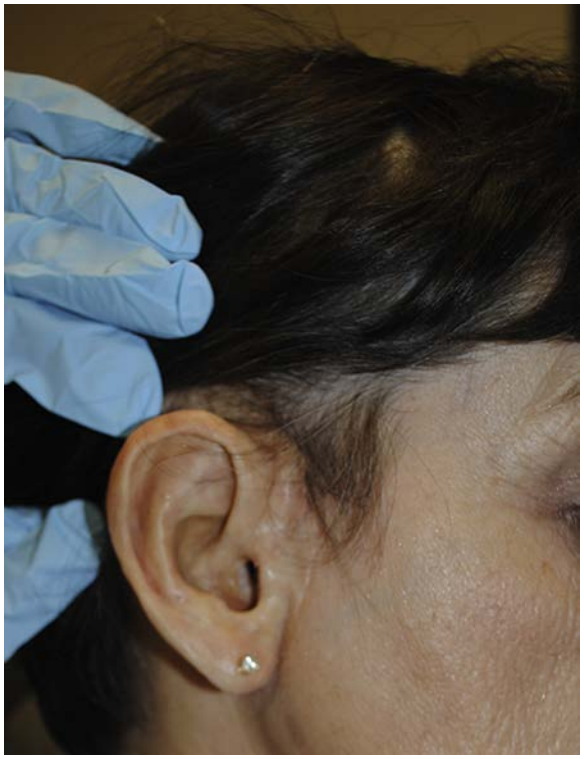
Lacerations through parotid fascia in this area have high probability of duct injury. Cannulation of Stinson's duct, located adjacent to the first molar tooth, should be done and visualized in the open wound. Cannulation can most easily be performed with a J-wire and followed by a catheter placed over the J-wire. Injection of materials such as methylene blue or propofol allows documentation of duct injury. Direct visualization is difficult without adequate lighting and hemostasis, therefore this type of laceration repair should be done in the operating room. If duct laceration is within the hilum of the gland, stick tie suture ligation should be placed in the hilum, followed by ligation of the distal stump of the duct. If the ductal injury is more distal, anastomosis should be performed over the catheter with 8-0 nylon under microscopic or loop magnification. The catheter should be sutured in place intraorally and left



• **Figure 4-17** Ear partial skin avulsion seen in **(A)** before repair. Split-thickness skin graft reconstruction placed over pericondrium but without adequate splinting failed. The wound was allowed to granulate resulting in a cauliflower ear deformity seen in **(B).**



• **Figure 4-18** **A,** Near complete avulsion of ear. **B,** Superior pedicle with marginal blood supply after reattachment showing moderate cyanosis. **C,** Leech therapy applied to attempt for adequate venous outflow.



• **Figure 4-19** Excellent esthetic reconstruction with complete auricular prosthesis following total loss of auricle.

for a minimum of 2 weeks. Antibiotics and antisialogogues should be prescribed.

Sialocele is not uncommon with duct or gland injury. Initial management is with pressure dressing and antisialogogues.[36]

Facial Nerve

Laceration of the facial nerve can result from penetrating injuries to complex facial lacerations that involve structures deep to the SMAS (superficial musculoaponeurotic fascia). Complete examination of all branches of the facial nerve function should be performed on initial exam. If injury is proximal to the parotid gland, the main trunks of facial nerve may be involved and must be repaired. The use of local anesthesia should be delayed until the function of the facial nerve has been established. Injuries proximal to a vertical line drawn from the lateral canthus require exploration and repair. If anterior to the parotid gland, the branches of facial nerve are examined under loop magnification or operating microscope. The nerve stimulator is useful for identification of the distal segment within 48 hours of injury. After 48 to 72 hours, the distal nerve segments will no longer conduct the impulse.[37] Early microscopic epineural and perineural repairs with 9-0 or 10-0 nylon result in the best clinical outcomes and therefore should be the primary objective if facial nerve transection is identified. If both proximal and distal ends cannot be identified, suture tags should be placed for future exploration. (A more in-depth discussion is beyond this chapter and will be deferred.)



• **Figure 4-20** Penetrating neck injury dissecting in a subcutaneous level that extends for the mandibular border to below the level of the cricoid cartilage anteriorly and posterior to the sternocleidomastoid muscle. Computerized tomographic angiography was negative.

Neck

coid cartilage, zone II extends from the cricoid cartilage to the angle of the mandible, and zone III extends from the angle of the mandible to the base of the skull. Injuries to the neck can involve deep structures affecting the vascular, respiratory, digestive, neurologic, endocrine, and skeletal structures. If injury of major vessels is suspected, computerized tomographic angiography (CTA) should be performed before exploration (Figure 4-20). Imaging triage can now accomplish what operative or selective evaluation could not: a safe and noninvasive evaluation of critical neck structures to identify or exclude injury based on trajectory, the key to penetrating injury management. A comprehensive physical examination combined with CTA is adequate for triage to effectively identify or exclude vascular and aerodigestive injury after penetrating neck trauma.[38]

Postoperative Care

Routine use of antibiotics should not necessarily be employed as a component of postoperative care in most facial lacerations; however, antibiotic prophylaxis is recommended in patients with prosthetic joints, patients at risk for endocarditis, patents receiving corticosteroid therapy,

TABLE 4-8 Characteristics of Tetanus-Prone Wounds

Clinical Features	Tetanus-Prone Wounds	Nontetanus-Prone Wounds
Age of wound	More than 6 hours	6 or fewer hours
Configuration	Stellate wound	Linear wound
Depth	More than 1 cm	1 cm or less
Mechanism of injury	Missile, crush, burn, or frostbite	Sharp surface (eg, knife)
Signs of infection	Present	Absent
Devitalized tissue	Present	Absent
Contaminants (dirt, feces, soil, saliva)	Present	Absent
Denervated or ischemic tissue or both	Present	Absent

From Edlich RF: Principles of emergency wound management, *Ann Emerg Med* 17(12):1284–1302, 1988, with permission.

and in immune compromised patients (e.g., diabetes mellitus, HIV, chemotherapy).[39] Other risk factors for infection include increased age, puncture wounds, impact wounds, presence of foreign bodies in the wound, heavy contamination, jagged wound edges, lacerations deeper than the subcutaneous layer, and wide gaping lacerations. These categories should strongly be considered for antibiotic therapy.[40-42] Through and through lacerations involving oral mucosa require clinical judgment. The choice of antibiotics should contain an active agent against staphylococci and β-hemolytic streptococci, such as a first-generation cephalosporin or penicillinase-resistant penicillin.[43] Wounds that have gross contamination and/or delay in time of wound closure should be considered for antibiotic therapy. A controlled study by Ichikawa found baseline wound infection rates that varied by degree of contamination: 2.6% in clean-contaminated, 5.8% in contaminated, and 20.8% in dirty wounds. Tetanus prophylaxis should be given according to the patient's immunization history (Tables 4-8 and 4-9).

Current CDC guidelines recommend a tetanus vaccine for wound management based on vaccination history and wound severity. All patients with an unknown vaccination history or who have received fewer than three doses should receive a tetanus diphtheria vaccine (Td). Inadequately vaccinated patients with anything other than a clean, minor wound should also receive tetanus immune globulin (TIG). Patients who have received three or more tetanus vaccines prior to the injury only need Td vaccination if their previous dose was more than 10 years ago for clean, minor wounds or 5 years for other wounds.

TABLE 4-9 Recommendations for Tetanus Prophylaxis

	DTP* (0.5 mL IM)	TIG (250 U IM)	TD¶ (0.5 mL IM)	TIG (250 U IM)
History of adsorbed tetanus toxoid (for children < 7 yr)				
Unknown or < 3 doses	Yes†	Yes‡	Yes†	Yes
3 or more doses	No¶	No	No¶	No

NOTE: All dog and cat wounds should be considered tetanus-prone wounds.
*Use diphtheria, tetanus (DT) if pertussis vaccine is contraindicated.
†The primary immunization series should be completed.
‡Administer in contralateral extremity.
¶Use diphtheria, tetanus, pertussis (DTP) for children <7 years old (DT if pertussis vaccine is contraindicated); TD is preferred to T if patient is ≥ 7 years old.
¶Yes, if > 5 years since last dose. (More frequent boosters are unnecessary and may accentuate side effects.)
§ Yes, if the routine immunization schedule has lapsed or if more than 5 years since last dose of tetanus toxoid.
IM, intramuscular; *TIG,* tetanus immune globin.
From American College of Emergency Physicians: Tetanus immunization recommendations for persons seven years of age or older, *Ann Emerg Med* 15:1111–1112, 1986; and American College of Emergency Physicians: Tetanus immunization recommendations for persons less than seven years old *Ann Emerg Med* 16:1181–1183, 1987, with permission.

Animal and Human Bites

Animal and human bite wounds are common and can cause [44] caused by dogs, with approximately 800,000 bite wounds per year in the United States, followed by cat wounds at 400,000 per year, and then human bite wounds[45,46] (Box 4-2). Appropriate wound management is the single most important factor in preventing infection in this patient population, and increasingly, dog bite wounds are a source of litigation due to improper management.[45,47]

Most dog bite wounds occur in children. The head and neck is the most common site of injury in children younger than 9 years old, whereas in children 10 years or older the

• BOX 4-2 Dog Bite Statistics

- 77.5 million dogs in the United States
- 4.5 million dog bites each year
- 1 in 5 bitten; 885,000 require medical attention
- Half of these are children:
  - Age 5 to 9 years; mostly boys
  - Face, head, and neck: 50% to 70%
- Adult victims, 5% to 15%: face, head, and neck
- In 2012, 27,000 underwent reconstructive surgery
- Most dog bites occur in or close to home and known to child/family

Gilchrist J, Sacks JJ, White D, Kresnow MJ: Dog bites: still a problem? *Inj Prev* 14(5):296-301, 2008; Centers for Disease Control and Prevention (CDC): Nonfatal dog bite-related injuries treated in hospital emergency departments—United States, 2001; *MMWR Morb Mortal Wkly Rep* 52(26):605-610, 2003.

TABLE 4-10 Retrospective Review of Bite Wounds for 2013 at Memorial Hermann Hospital TMC Houston, Texas

Soft Tissue Injuries	Total: 90	Hard Tissue Injuries	Total: 5
Face	31	Skull	1
Eye	18	Nasal	1
Lip	16	Dental	1
Scalp	11	Jaw	2
Nose	6		
Neck	5		
Ears	3		

extremities are the most commonly involved site[48] (Table 4-10). Dog bites occur most frequently in the victim's home and the dogs are most often known by the victim. Dog bite forces can vary considerably from 310 kPA to nearly 31,700 kPA in trained attack dogs.[49] Due to the high bite forces with these injuries, the possibility of underlying bony injury must not be overlooked.

Due to their rounded teeth and strong jaws, dog bite wounds are often crush-type injuries.[50] The wounds are most often polymicrobial with *Pasturella multocida*, *Pasturella canis*, *Streptococcus* species; *Staphylococcus* species and *Capnocytophagia canimorus* being the most commonly isolated pathogens[50] (Box 4-3). Amoxicillin/clavulanic acid (Augmentin) provides coverage for some penicillin-resistant *S. aureus* species and *Pasturella* species and is the preferred prophylactic antibiotic[49] (Box 4-4). Whether empirical prophylaxis is required for all bite wounds is unclear based on available literature; some authors argue for routine prophylaxis and others for prophylaxis in only high-risk cases.[51,52] Due to the rich vascular supply of facial tissue, immediate closure of bite wounds is typically safe even with old

• BOX 4-3 Microbiology of Bites

- Oral flora of dog and skin of human
- Common pathogens in order of prevalence:
  - *Pasturella multocida*: soft tissue inoculation, septic arthritis, osteomyelitis
  - Staphylococci
  - Streptococci
  - Anaerobic bacteria
  - Capnocytophaga: sepsis, meningitis

• BOX 4-4 Empiric Intravenous Antibiotic Therapy

Options for empiric gram-negative and anaerobic coverage include:

- Monotherapy with a beta-lactam/beta-lactamase inhibitor:
  - Ampicillin-sulbactam 3 g every 6 hours 50/mg/kg/dose (based on ampicillin component) every 6 hours
  - Piperacillin-tazobactam 4.5 g every 8 hours 125 mg/kg/dose (based on piperacillin component) every 8 hours
  - Ticarcillin-clavulanate 3.1 g every 4 hours 50 mg/kg/dose (based on ticarcillin component) every 4 hours
  - A third-generation cephalosporin in such as ceftriaxone 1 g IV every 24 hours

PLUS

- Metronidazole 500 mg IV every 8 hours (Metronidazole 10 mg/kg/dose every 8 hours)

OR

- A third-generation cephalosporin in such as ceftriaxone 100 mg/kg/dose every 24 hours

• Box 4-5 Rabies

- Neurotropic viruses: rhabdoviridae family
- Animal quarantine
- Rare in United States: 47 deaths from 1990 to 2005
- Geographic variation: U.S./Mexico border
- Wound care: Soap and water; povidone iodine, rabies vaccines; rabies immune globulin

injuries.[53] Grossly contaminated crush wounds with delayed presentation (> 24 hours) deserve careful consideration of primary versus delayed closure. Good lighting, sterile technique, thorough irrigation of wounds using tap water or normal saline, removal of foreign bodies, and debridement of tissue are the mainstays of wound management. Cultures are indicated only in grossly infected cases.[49] The CDC recommends observation of healthy animals for 10 days and human vaccination only if the animal shows symptoms of rabies. In unprovoked bites or animals demonstrating other rabid behavior immediate vaccination is recommended[54] (Box 4-5). Tetanus immune globulin and toxoid are recommended in bite victims who have had two or fewer primary immunizations. Tetanus toxoid alone is recommended in



• **Figure 4-21** Superficial dog bite wound management. Initial wound management includes copious irrigation with normal saline, when contaminated, followed by debridement of all nonviable tissue. Wound cultures are only necessary when wound is infected. In dog bite wounds, prophylaxis consists of oral amoxicillin clavulanate for 3 to 5 days and tetanus immune globulin and tetanus toxoid as listed in Tables 4-8 and 4-9. Primary closure can be performed in noninfected wounds.

patients who have completed the primary immunization series but have not received a booster within 5 years.[55]

Some differences but many similarities exist between cat and dog bite wounds. Cat bites are more likely to cause a puncture injury with deep penetration, leaving only a small opening through which fluids can drain.[49] For this reason, cat bites are associated with a twofold higher risk of infection than dog bites.[49,50] Bacteria commonly isolated from cat bite wounds include: *P. multocida, Bartonella henselae* (the causative organism of Cat-scratch disease), *Streptococcus*, and *Staphylococcus* species. Copious irrigation of wounds with normal saline or tap water is recommended along with primary closure in the majority of cases. As with dog bite wounds, Augmentin is the prophylactic antibiotic of choice with good coverage of the most common pathogens.[49] Clindamycin should not be used alone due to poor coverage of *Pasturella* species. Similar tetanus and rabies prophylactic measures are recommended.

Human bite wounds often compress the skin, but rarely cause avulsion injuries as in dog or cat bites. However, left untreated, open human bite wounds can cause significant morbidity.[49] The most common pathogens associated with human bites include *Streptococcus* and *Staphylococcus* species as well as anaerobic bacteria *Eikenella*, *Fusobacterium*, *Peptostreptococcus*, and *Prevotella*. The prophylactic antibiotic of choice is Augmentin. Clindamycin should not be employed due to poor coverage against *Eikenella* spp.

Several cases are presented to illustrate the nature and management of these bites. Superficial dog bite wound management includes copious irrigation with normal saline, close inspection, debridement of nonvital tissue, use of appropriate antibiotic therapy, application of rabies and tetanus toxoid protocol, and primary closure in noninfected wounds (Figure 4-21).

Complex dog bite wounds by their nature involve greater loss of tissue, larger surface area, and damage to underlying structures such as bone, glands, nerves, and muscle. Two concepts should be kept in mind for pediatric patients. First is to achieve closure of the wound with either approximation or skin grafts in order to minimize scar tissue (Figure 4-22). In this case extensive undermining was done, which resulted in excessive tension on the surface. Although there was dehiscence early, at 8 months there was appreciable improvement eliminating the need for revision. In addition, by not using aggressive flap procedures one keeps more options on the table for use at a later time.

Another concept for pediatric patients is that the soft tissue scars tend to grow with the patients. Individual judgment is needed to choose between early or late revision. Certainly, degree of disfigurement and psychological needs must be factored in. Figures 4-23 and 4-24 represent a case where wide scar bands occurred following reapproximation of tissue where excessive tissue was lost initially. At 1 year, a decision was made for excision of the scar with advance flap closure. The results 6 months later helped mitigate the patient's psychological distress.

In cases where there is extensive loss of tissue and late sequela will result in major deformities, local flaps, and in some cases free flap reconstruction, should be considered. Loss of major parts of special anatomic structures such as nose, eyelids, and ears requires such management. Early nasal reconstruction with local flaps such as nasolabial or axial pattern forehead flaps results in superior esthetic outcomes than when management is delayed. Axial pattern forehead flaps can provide coverage of tissue loss of multiple esthetic units (Figure 4-25), whereas nasolabial flaps are limited to isolated reconstruction for smaller areas. Eyelid avulsion wounds require early intervention in order to protect vision. In extensive avulsion wounds of both upper and lower eyelid, local cheek flaps similar to the Mustarde flap can be used for lower eyelid reconstruction. Axial pattern forehead flaps or radial forearm free flap reconstruction can be used for upper lid reconstruction (Figure 4-26), resulting in less scar contracture and improved esthetic appearance. The reader is encouraged to review multiple reconstructive options for complex avulsion wounds of special anatomic areas prior to deciding on which method will be the best.



• **Figure 4-22** Reapproximation of tissue. This case is an example of a complex wound with gaping margins and partial avulsion **(A)**. In this case, extensive wound undermining is done with tight closure **(B)**. Although dehiscence occurred at one year postoperative, it is much improved **(C, D).** An important concept for pediatric wounds is obtaining wound closure by whatever means necessary (undermining, or skin grafts) because of positive impact to reduce the amount of scarring.



• **Figure 4-23** Wound (**A**), immediate closure (**B**), and one year postoperative (**C**).



• **Figure 4-24** A, Scar excision at 12 months post operative. B, Wound closure under minimal tension after extensive undermining prior to closure. C, Appearance at 18 months postoperative without revisions. Use caution in determining timing for revision. Revision is necessary because of wide scar ban.



• **Figure 4-25** **A-B,** Dog bite avulsion wound of the nasal tip. **C-D,** forehead flap reconstruction. (Courtesy Phillip Freeman, DDS, MD)



• **Figure 4-26** Scalp-forehead flap reconstruction. (Courtesy Phillip Freeman, DDS, MD)

Facial Burns

Facial burns produce significant changes in the physical features that are central to the human being. Features of facial expression, communication, feeding, phonation, and special sensory altered by burns can change the patient's entire individual identity. Early evaluation and management is critical in order to maintain or restore facial features essential to identity. There are many types of burns caused by different mechanisms, such as thermal, radiation, chemical, or electrical. Burns can occur at

n injury

and can produce mild to moderate pain depending on the level of burn. First-degree burns affect only the epidermis, or outer layer of skin. The burn site is red, painful, dry, and with no blisters. Long-term tissue damage is rare and usually consists of an increase or decrease in the skin color.

Second-degree burns involve skin and superficial dermis and are referred to as "partial thickness." Second-degree burns involve the epidermis and part of the dermis layer of skin. The burn site appears red, blistered, and may be swollen and painful. Partial-thickness burns may be further divided into superficial and deep depending on the level. Typically, second-degree burns form fluid-filled blisters, which result in the separation of the epidermis and dermis and produce moderate to intense pain.

Third-degree burns refer to full-thickness skin and extend though the dermis into subcutaneous tissue and classically are insensate and pale to translucent in appearance. Third-degree burns destroy the epidermis and dermis. Third-degree burns may also damage the underlying bones, muscles, and tendons. There is no sensation in the area because the nerve endings are destroyed. Third-degree injuries are beyond the scope of this chapter and the reader is encouraged to review more comprehensive literature for details.

Because the face involves orifices with both respiratory and gastrointestinal tract epithelium, it is essential to evaluate all areas in the advanced trauma life support (ATLS) secondary survey. Airway evaluation should include observation for signs of singed nasal hair, nasal and oropharyngeal soot, erythema of the oropharynx, carbonaceous sputum, dysphonia, stridor, dyspnea, rhonchi, and wheezing. Initial arterial blood gas (ABGs) and chest x-ray (CXRs) should be done as a baseline. Fiberoptic evaluation of the airway should be performed and, if clinical signs and symptoms of the above are present, intubation should be performed for airway protection. Oropharyngeal exam may show similar findings of edema, erythema, or carbonaceous material with signs of dysphagia. Ophthalmology examination should be performed to evaluate for singed eyelash and brow hair, lid edema and blistering, conjunctival edema and injection, corneal exam, visual acuity, and funduscopic exam. Incidence of ocular injury in facial burns approaches 27%.[56,57]

Evaluation of ears, nose, and eyelids for deep partial-thickness and full-thickness burns dictates specific treatment protocol.

Management

Prevention of airway compromise and death caused by pulmonary injury from facial burns should be the first priority. Humidified 0_2 by face shield, elevation of head of bed, and suction for excess secretions should be initiated early. Simultaneous to pulmonary resuscitation, attention should be given to fluid resuscitation. Burn resuscitation is beyond the scope of this chapter and the reader is encouraged to review literature that deals with such.

In the acute phase, gentle debridement of loose skin and debris should be performed and antiseptic soap (TechniCare Surgical Scrub Care-Tech Laboratories, Inc.) should be used to clean and decontaminate the burned skin. Reduction in the bacterial count with antiseptic soap reduces the risk of conversion of burn wound depth from bacterial infection. The use of chlorhexidine gluconate offers optimum antisepsis, rapid onset of action, and broad spectrum coverage for gram-positive, gram-negative, and virucidal activity.[58]

The use of topical antimicrobials that control and limit burn wound antimicrobials ideally should be broad spectrum; should exhibit long duration, low toxicity, and good penetration; and should be inexpensive and easy to use. By providing good penetration and broad-spectrum coverage, topical antimicrobials prevent conversion of burn wounds from zone of stasis to zone of coagulation necrosis, thus reducing the need for debridement and subsequent grafting.

Topical agents commonly used are silver preparations such as silver sulfadiazine, silver nitrate, and Acticoat (Smith Nephew, Hull, UK). Mafenide acetate (Sulfamylon, Bertek Pharmaceuticals, Morgantown, WV), a sulfonamide, provides fast, deep penetration with excellent antimicrobial spectrum. Antibiotic preparations such as Neosporin, Polysporin, and Bacitracin are the most commonly used agents for superficial burns. Polysporin and Bacitracin in combination with enzymatic debriding agents provides clean burn wounds in partial-thickness burns and results in outcomes superior to those obtained by silver sulfadiazine.[59] However, the use of enzymatic debriding agents in facial burns remains controversial and produces variable results.[60] Multiple alternative methods have been described including amnion,[61] honey,[62,63] sucralfate,[63] beta glucans,[64] and aloe vera.[65] Aloe vera appears to accelerate the sound healing process in both first- and second-degree burns compared to traditional topical treatments. Cadaveric allografts appear to be a superior biologic dressing for superficial and deep partial-thickness burns when compared with traditional management with silver sulfadiazine.[66] Bioengineered skin substitutes have also been compared to traditional management and show similar efficacy.

Once wound closure is achieved, early rehabilitation is begun before scar formation demonstrates hypertrophy. Therapeutic intervention includes pressure garments, masks, and orthotic devices. Such pressure devices improve scar maturation and redistribution of collagen fibers. Compliance with such devices is the primary challenge in the rehabilitative phase; however, without adequate post-burn rehabilitation outcomes are universally less than desirable.

The most common form of facial compression is the use of a mask in combination with compression garments. Openings are made in the garment and mask for nasal obturators and oral commissure spreaders to give continuous pressure in this area. Garments and masks are worn for up to 1 year or more, with modifications made every 6 to 8 weeks to maintain adequate compression. Garments and masks are removed only for short periods for bathing, eating, oral hygiene, and exercise.

Recent developments in the management of burn scars with the use of fractionated CO_2 laser have shown promise in early outcomes. Further studies need to be conducted to compare the efficacy of different rehabilitative modalities.

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5

Diagnosis and Management of Trigeminal and Facial Nerve Injuries

THOMAS SCHLIEVE, MICHAEL MILORO, ANTONIA KOLOKYTHAS

Introduction

The face and perioral regions are among the body regions with the highest density of peripheral nerve receptors, and this feature makes neurologic disturbances less tolerable in the head and neck than other body parts. The 5th (trigeminal) and 7th (facial) cranial nerves innervate the vast majority of structures involved in sensation and function of the face. The trigeminal nerve is the largest cranial nerve, with three main divisions including the ophthalmic, maxillary, and mandibular branches. It is a mixed motor (special efferent and proprioceptive) and sensory (general afferent) peripheral nerve. Injury to the peripheral branches of the trigeminal nerve can be devastating because of the effects on speech, deglutition, mastication, and taste, as well as impact on social interactions. The facial nerve innervates the muscles of facial expression in addition to providing taste sensation and parasympathetic stimulation to the lacrimal, submandibular, and sublingual salivary glands. Damage therefore not only is cosmetically and functionally cataclysmic but has detrimental effects on psychological, social, and economic well-being.

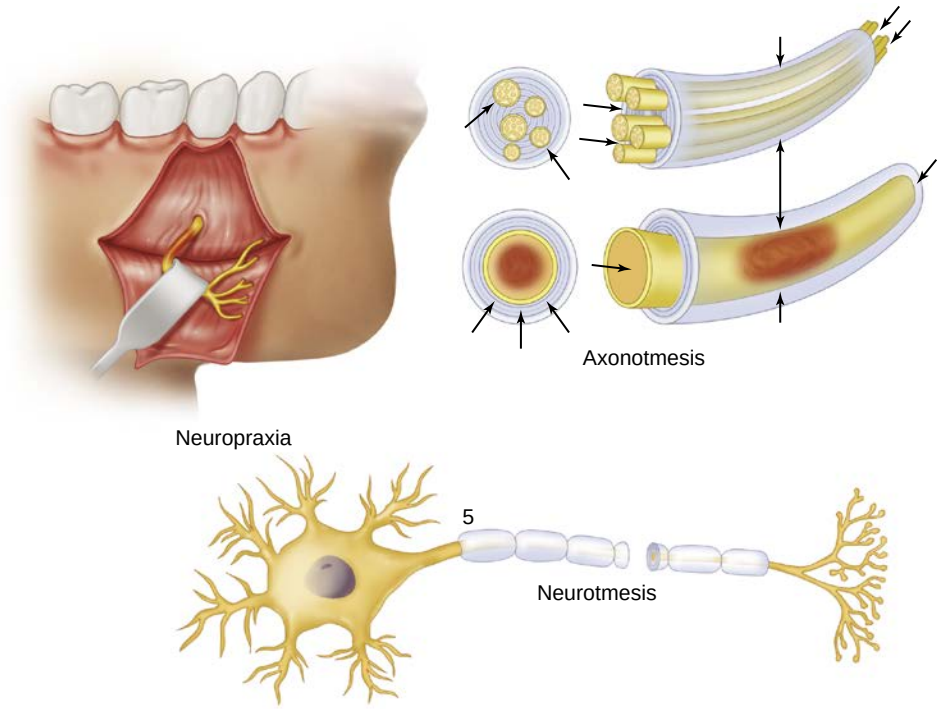
Unfortunately, injury to the trigeminal and facial nerve can occur rather easily from trauma, infection, or pathology, or from commonly performed procedures in the maxillofacial region. Throughout their careers, oral and maxillofacial surgeons often encounter patients with trigeminal and/or facial nerve injuries and should be proficient in diagnosing and managing these cases appropriately because successful outcomes from nerve injuries are critically time-sensitive. In this chapter the following topics are presented: an overview of the anatomy of the trigeminal and facial nerve; a basic overview of peripheral nerve microanatomy to assist the reader's understanding of the events following injury and a nerve's regenerative properties; the available imaging modalities; several potential causes of nerve injury; and the neurosensory testing available for appropriate evaluation and classification of nerve injuries. Finally, the treatment of trigeminal and facial nerve injuries and the expected outcomes are discussed.

Classification of Nerve Injuries

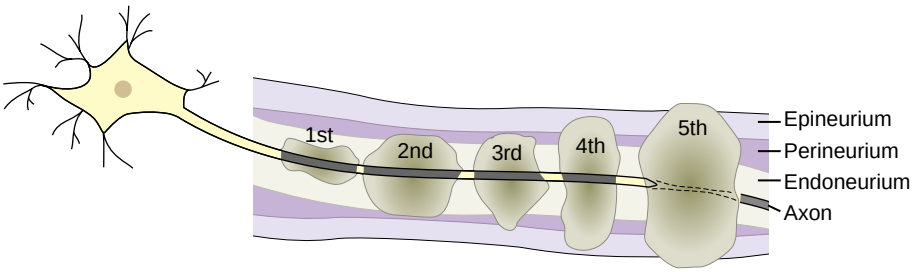
Several complex cellular events occurring in and around the nerve structure are responsible for the response to trigeminal and facial nerve injury and are required for the regeneration and restoration of neurosensory function. Two nerve injury classification schemes, Seddon and Sunderland, are described and provide for a correlation between the clinical symptoms and the histologic changes observed within the nerve structure at the time of injury. Seddon's classification is based on the time between injury and recovery and the degree of recovery, whereas Sunderland places an emphasis on the specific histologic degree of damaged neural structures.

Seddon Classification System

The Seddon classification system includes three levels of nerve injury (Figure 5-1): neuropraxia, axonotmesis, and neurotmesis.[1] In neuropraxic injuries, the integrity of the axon is maintained, and the injury indicates a local conduction block from a transient anoxic event due to acute vascular interruption of the epineurial or endoneurial vasculature. Neuropraxia is usually the result of a mild nerve manipulation, traction, or compression injury and is characterized by a reversible conduction block, with a favorable outcome and complete recovery within days to weeks of the event. No axonal degeneration occurs in neuropraxic injuries, and damage is confined to the endoneurium only. Axonotmesis involves axonal damage, corresponds to degrees II-IV Sunderland injuries, demonstrates variable



• **Figure 5-1** Seddon classification system including examples of neuropraxia with nerve stretching; axonotmesis with variable degrees of axonal injury; and neurotmesis with nerve transection. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)



• **Figure 5-2** Sunderland classification system showing the five degrees of nerve injury with progressive injury beginning with damage confined within the endoneurium (1st degree injury) and extending outward to the perineurium (2nd degree), then through the perineurium (3rd degree), and to the epineurium (4th degree), and finally through the epineurium with discontinuity (5th degree). (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

degrees of demyelination and axonal injury, and therefore, spontaneous recovery varies significantly in this category of injuries. More details are provided in the following discussion of Sunderland's classification of nerve injuries. Finally, neurotmesis implies complete or near-complete nerve transection that includes epineurial discontinuity. Spontaneous recovery is unlikely, whereas neuroma formation is common.

Sunderland Classification System

(Sunderland's degree I-V nerve injury) based on histologic findings of the degree of nerve involvement[2] (Figure 5-2). A first-degree Sunderland injury is the same as Seddon's neuropraxia described earlier, and was further divided by Sunderland into three types based on severity and recovery time. First-degree Type I injury is the result of nerve manipulation that causes transient blood supply interruption that, once restored, allows for full sensory recovery after only a few hours. First-degree Type II injury involves intrafascicular edema formation, from fluid exudate or transudate, as a result of moderate traction or compression on the nerve. Sensory recovery follows edema resolution within a few days. First-degree Type III injury results from more aggressive nerve manipulation and may involve segmental demyelination with recovery requiring a few days to weeks.[3] Second-degree injuries involve axonal and myelin interruption with an intact endoneurium, epineurium, and perineurium, allowing for axonal regeneration. Recovery is a relatively slow process and may take up to 1 year for

TABLE 5-1 Classification of Nerve Injuries and Associated Findings

Injury Type	Histologic Findings	Response	Recovery Pattern	Recovery Rate	Treatment
First degree (Seddon neuropraxia)	Transient ischemia, anoxia, ± segmental demyelination, intrafascicular edema	Conduction block	Complete	Fast (hours to weeks)	None indicated
Second degree (Seddon axonotmesis)	Axon and myelin interruption (intact endoneurium, perineurium, & epineurium)	Wallerian degeneration distal to injury	Complete	Slow (weeks)	None indicated
Third degree	Injury involves endoneurium (intact perineurium & epineurium)	Wallerian degeneration and some degree of neuron cell death	Variable	Slow (weeks to months)	Nerve exploration may be considered
Fourth degree	Injury involves endoneurium and perineurium	Wallerian degeneration, neuron cell death, neuroma formation and intrafascicular fibrosis	None	Spontaneous recovery not likely	Microneurosurgery
Fifth degree (Seddon neurotmesis)	Complete nerve transection, continuity disruption	Wallerian degeneration, cell death neuroma, fibrosis	None	No spontaneous recovery possible	Microneurosurgery

complete return to normal sensation, but is possible because of the intact supporting connective tissue structures. These injuries are caused by traction or compression on the nerve. In third-degree injuries, the endoneurium is involved in the injury while the epineurium and perineurium remain intact. The usual etiologies are the same as for first- and second-degree injuries, and some spontaneous recovery is expected. Complete recovery is unlikely, and surgical exploration may be considered. Fourth-degree injuries caused by traction, compression, needle injection, or chemical injury lead to disruption of the endoneurium and perineurium, while the epineurium remains intact. These injuries are associated with a poor potential for spontaneous recovery and a high probability of neuroma formation and intraneural fibrosis. Surgical intervention is required for these injuries, especially if there is no improvement within 3 months following the injury. A fifth-degree injury in Sunderland's classification system corresponds to Seddon's neurotmesis. It implies nerve transection, avulsion, or laceration with complete disruption of all components of nerve organization with little to no chance of spontaneous recovery. Extensive fibrosis, neuroma formation, or neuropathic changes occur in these serious clinical situations, and microneurosurgery is indicated. In cases of witnessed nerve transection, immediate surgical intervention is warranted. Table 5-1 summarizes the types of injuries, corresponding histologic changes, responses, recovery pattern, rate of recovery, and recommended treatment.

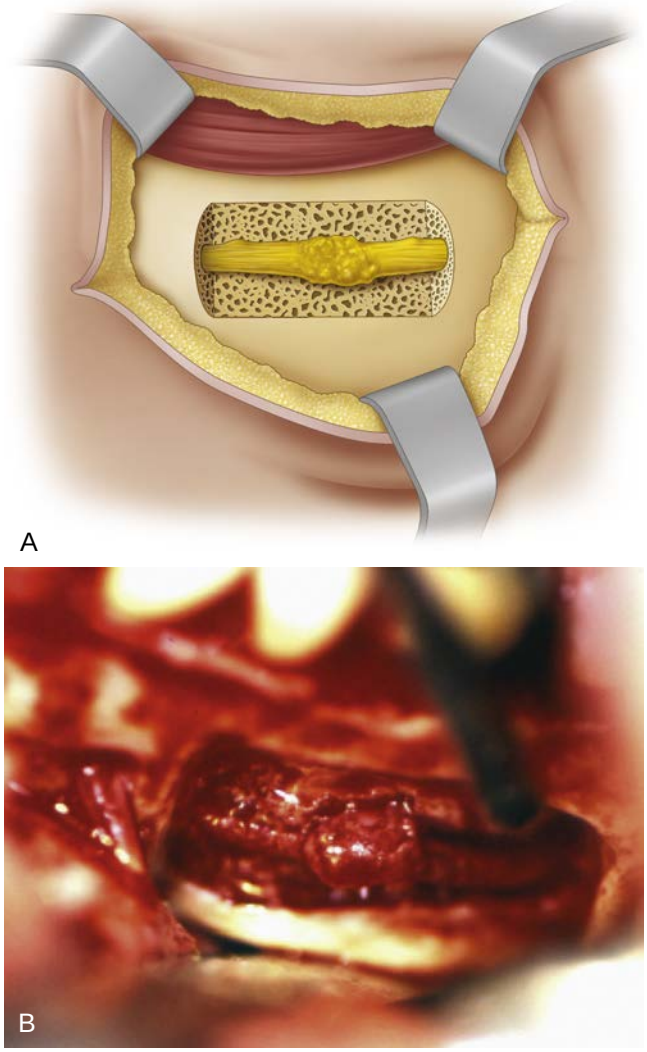
Axonal and Cellular Response to Injury

Nerve injury involves several events and variable responses, but the basic process of nerve healing remains the same and involves a sequence of degeneration followed by regeneration.[4,5] Within hours of axonal injury, a series of events occur at the primary site of injury, as well as at the distal and proximal portions of the axon and the cell body. The changes within the cell body and the nerve fiber proximally depend on the proximity of the injury to the cell body as well as the severity of the injury. Within 6 hours of the injury, the metabolic rate of the cell body increases significantly. This results in edema and migration of the nucleus toward the periphery of the cell body, upregulation of the rough endoplasmic reticulum (Nissl substance), and increased protein synthesis. These events are collectively known as chromatolysis and represent the histologic correlation of RNA and protein synthesis, a programmed event intended to ensure cell survival that peaks within 14 to 21 days following acute injury.[6-14] Chromatolysis signals the proliferation of perineural glial cells that, along with macrophages, phagocytes, and Schwann cells, begins the cleanup process of cellular debris at the injury site.[4,5,15]

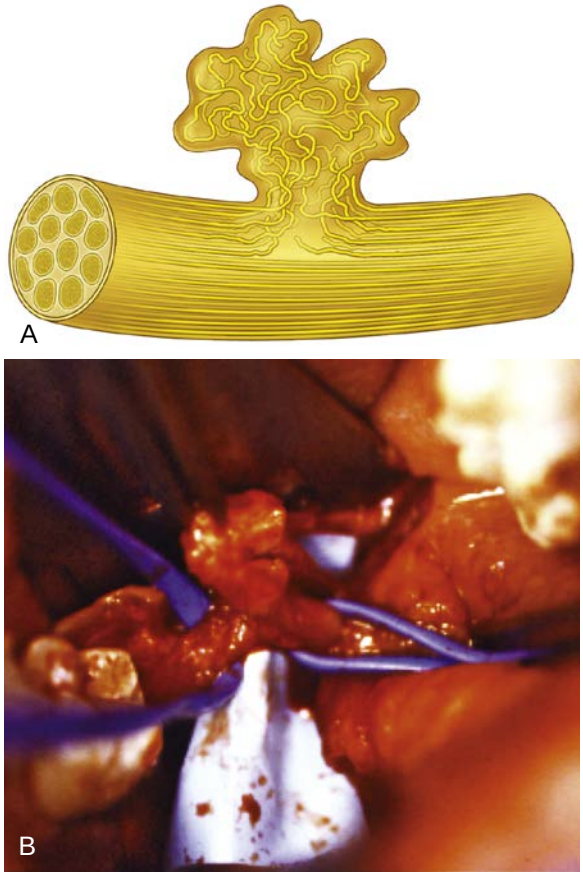
When the injury involves the axonal fibers (Sunderland II-V grade injuries), a series of molecular and cellular events occur, either simultaneously or consecutively, and collectively result in wallerian degeneration.[16] These events occur throughout the distal nerve trunk as well as the small portion of the proximal end close to the injury site. The distal portion of the axon becomes edematous, so its ends are sealed, while the myelin that surrounds the axon breaks down into droplets.[17] The debris is phagocytosed by Schwann cells with enhanced proliferation and activity levels as well as recruited macrophages. These events, which are a prerequisite for nerve regeneration to occur, are initiated within hours of the injury and are completed within 1 week following the nerve injury.[18-24] Neural degeneration occurs in both the distal and proximal nerve ends, so the final result is empty endoneurial tubes that act as conduits for nerve regeneration; these tubes are present up to the site of the injury.[17,21,25-27]

Proximally, the transected axon forms sprouts, or axonoplasmic extensions, that mimic the axon growth cones observed during embryonic neural development. Several substances produced by neural and supportive tissues are required, and these ultimately lead to the growth and regeneration of the axon toward its receptor target.[20,28-31] Each axon may have as many as 50 collateral axonal sprouts. The high proliferative activity of the Schwann cells noted during these phases is thought to be required for the production of new myelin that will host the new axon. This theory has been challenged by Yang and colleagues, who demonstrated that Schwann cell proliferation may not be an absolute requirement for nerve regeneration, but rather that this is achieved via existing Schwann cells that survive the insult but do not divide, and that the regeneration is axon-driven and axon-dependent, as opposed to a predominant Schwann cell influence.[19]

In any case, if these processes take place in the appropriate chronological order, spontaneous nerve regeneration will be achieved. In cases when there is interruption or unfavorable sequencing of these events, the outcome will be failure of reinnervation of target receptors and possible neuroma formation. Neuromas represent a disorganized mass of collagen fibers and nerve sprouts that are randomly oriented.[32-36] Neuromas can be of the following types: amputation (stump neuroma), neuroma-in-continuity (central or fusiform neuroma) (Figure 5-3), or lateral (lateral exophytic, or lateral adhesive neuroma) (Figure 5-4). Neuromas may be painful or asymptomatic, and histologic differentiation between the two clinical scenarios is not possible. What appears to distinguish the painful and non-painful neuromas is their neurophysiologic properties.[37-39] Last, consideration must be given to the mechanism of injury and the resultant nerve injury. For clean lacerations of the nerve, primary repair is usually indicated, but for avulsive-type injuries, a delayed primary repair is preferred. A delayed primary repair is typically performed at 21 days following the injury, as this allows time for the area of injury to become defined macroscopically, levels of neurotrophic and neurotropic factors are at their highest, and the nerve is most amenable to repair.



• **Figure 5-3** **A,** Diagram of a fusiform neuroma-in-continuity. **B,** Clinical example of an inferior alveolar nerve neuroma-in-continuity at the apex of a mandibular first molar following endodontic therapy with nerve injury. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)



• **Figure 5-4** **A,** Diagram of a lateral exophytic neuroma. **B,** Clinical example of a lateral exophytic neuroma of the lingual nerve due to third molar removal. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

Trigeminal Nerve Anatomy

Macroanatomy

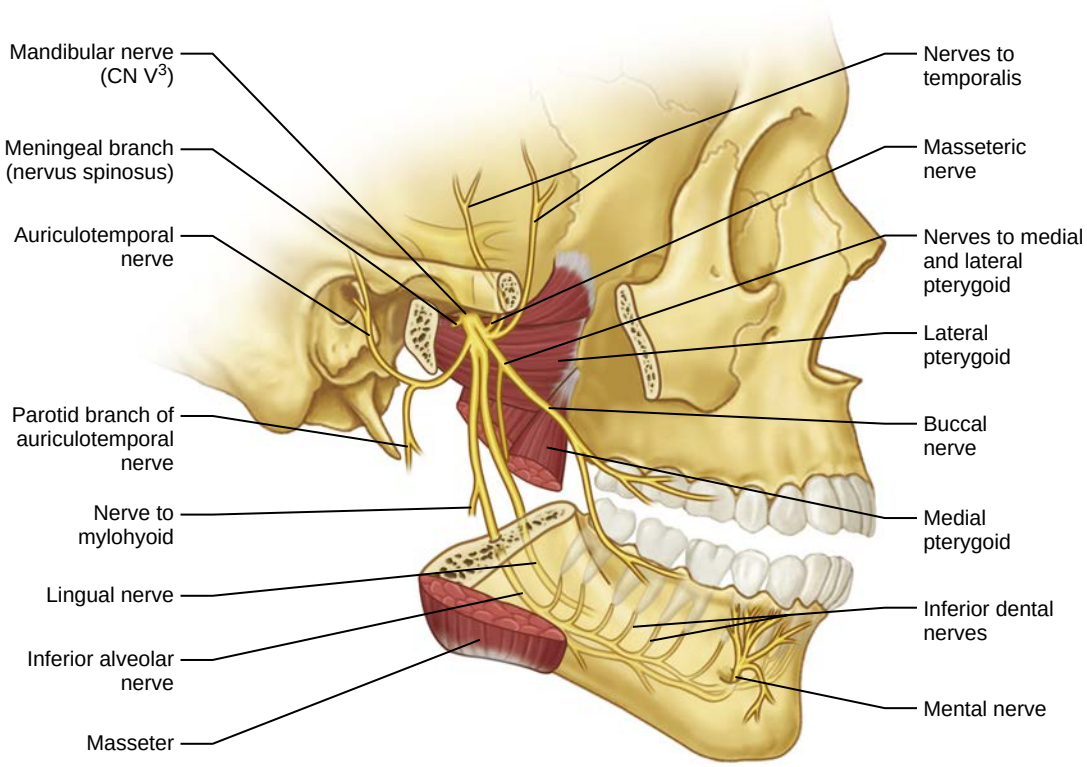
Inferior Alveolar Nerve

The largest of the three branches of the mandibular division of the trigeminal nerve (V3) descends between the medial pterygoid muscle and the medial ramus and enters the mandible at the mandibular foramen (Figure 5-5). At the lingula (the bony landmark for the mandibular foramina along the medial surface of the ramus), the inferior alveolar nerve (IAN) has the greatest diameter of 2.4 ± 0.4 mm. At the mandibular foramen, the IAN diameter is 2.0 ± 1.1 mm. The mental nerve exits the mandible at the mental foramen, and the course of the bony canal appears to be fairly predictable.[40-42] Between the mandibular foramen, where the IAN enters the mandible, and the second premolar region, the IAN follows an S-shaped course. The nerve is most lateral in the third molar region and then approaches the lingual plate in the first molar region. In the premolar region, the IAN returns toward the buccal cortex before exiting the mandible through the mental foramen.

In their study of the mandibular canal, de Oliveira and colleagues analyzed the bi- and tridimensional position of the canal through multiplanar computed tomographic (CT) scan morphometric analysis and provided useful average distances of the canal to the buccal and lingual cortices, the inferior border, and the alveolar ridge. The locations of the mandible for the measurements were selected to represent areas of commonly performed maxillofacial procedures associated with high risk for nerve injury, specifically extraction of third molars, sagittal split osteotomy, and dental implant placement. The authors did not find significant differences between the right and left sides, whereas in edentulous patients the typical values were lower in females than in males, and in older patients (ages between 51 and 75 years) than in younger individuals (ages 25-50 years).[43]

According to Cutright and co-workers, the mental foramen was found to be apical to the second premolar in about 51% of the cases. It was noted that in whites the foramen females for the three studied foramina (mental, infraorbital, and supraorbital).[44] In the sagittal plane, the course of the IAN in the mandible begins superiorly and lingually at the lingula, approximately 10 mm from the sigmoid notch, and it reaches its lowest point at the first molar-second premolar region, with the distance from the inferior border of the mandible of 7.5 mm ± 1.0 mm, where it splits into the incisive and mental nerve branches. The incisive dental branch continues forward toward the incisors, whereas the mental nerve ascends and loops backwards for a variable distance (3-7 mm) to exit at the mental foramina through the buccal cortex.[45,46]

Classically, the mental nerve is described as having two branches (range between one and four branches) with the largest being the labial branch running on the orbicularis oris



• **Figure 5-5** Regional anatomy demonstrating the peripheral trigeminal nerve system. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

muscle fibers, and a smaller mucosal branch that runs posteriorly on the buccinator muscle fibers. The labial branch innervates the lip and chin mucosa and overlying skin, and it may re-enter the mandible to innervate the mandibular incisors and even cross the midline,[47] The mucosal branch innervates the buccal mucosa and gingiva of the mandible as far posteriorly as the first and second molar where cross innervation with the buccal nerve may occur. Throughout its course in the mandible, the IAN provides branches for innervation of the mandibular teeth.[48]

Lingual Nerve

The lingual nerve (LN) branches from the posterior division of the third division of the trigeminal nerve, medial to the lateral pterygoid muscle, and it is located medial to the IAN. It supplies sensory and special sensory function to the anterior two thirds of the ipsilateral tongue, floor of mouth, and lingual mandibular gingiva. The LN is joined by the chorda tympani as it passes through the pterygotympanic fissure, which provides taste (anterior two thirds of the tongue) and carries special visceral afferents (preganglionic parasympathetic fibers from the facial) to the submandibular and sublingual glands. Kim and associates, in their study of the topographic relationship of the LN and IAN at the infratemporal fossa and paralingual space in 32 cadaveric hemi-sectioned heads, noted four patterns of furcation between the two nerves in men ovale and the hamulus. The bifurcation was identified to occur on average 14.3 mm (range: 7.8-24.1 mm) inferior to the foramen and 16.5 mm superior to the tip of the hamulus (range: 4.9-24.3 mm).[49] This variation in the bifurcation patterns between the IAN and the LN, as well as the collateral nerve branches at the retromolar region identified in 81.2% of the cases in the study by Kim and colleagues, is thought to contribute to the reported failure rate of mandibular anesthesia.[49,50]

TABLE 5-2 Types of Furcation of IAN and LN

Type of Furcation between IAN and LN	Level of Furcation between Sigmoid Notch and Lingula	Percentage per Type
Type I	Separation occurs above notch and inferior to otic ganglion	65.6% (21/32)
Type II	Separation occurs below notch and at superior half of distance between notch and lingula	28% (8/32)
Type III	Separation occurs below notch and at inferior half of distance between notch and lingula	3.1% (1/32)
Type IV	Separation occurs in a plexiform pattern	6.3% (2/32)

Kim SY, Hu Ks, Chung IH, et al: Topographic anatomy of the lingual nerve and variations in communication pattern of the mandibular nerve branches. *Surg Radiol Anat* 26:128-135, 2004.
IAN, Inferior alveolar nerve; *LN*, lingual nerve.

The LN then passes into the pterygomandibular space between the ramus and the medial pterygoid muscle, where it is surrounded by mesoneurial fat throughout its course. It enters the oral cavity over the superior pharyngeal constrictor, styloglossus, and mylohyoid muscles at the anterior border of the medial pterygoid muscle. As the nerve approaches the third molar region, it courses from a more lateral to a more medial position following the oblique flaring of the ramus. The exact location of the LN at the third molar region has been studied extensively, with some controversial findings between cadaveric studies, clinical observation during third molar surgery, and high-resolution magnetic resonance imaging, with regard to its proximity to the mandible.[51-58] Table 5-3 summarizes the reported distances and relationship of the nerve to the mandible at the third molar region. In this location, the nerve has a diameter between 2.0 and 5.0 mm and may be round, oval, kidney-bean shaped, elliptical, or ribbon-like in cross section, with a predominance of one shape versus another varying among the studies.[49,56,58]

At the second molar region, the LN crosses Wharton's duct from a lateral to medial direction traversing below the duct and hypoglossal nerve in the submandibular triangle. The nerve in this location gives off the preganglionic parasympathetic fibers (from the facial nerve) to the submandibular ganglion. These fibers are transected during submandibular gland excision so the gland can be released from the nerve. It has been reported that the risk of LN injury during submandibular gland excision or sialodochoplasty of the Wharton's duct ranges between 1.4% and 4.8%, and the nerve is in danger from both intraoral and extraoral approaches.[59-62]

After looping under Wharton's duct, the LN passes upward onto the genioglossus muscle and enters the oral tongue muscular substance. With the exception of one or two large branches that proceed toward the tip of the tongue, all other branches to the tongue and adjacent lingual mucosa and gingiva are of small diameter (generally no more than 1-2 mm). The larger branches provide the greatest density of innervation to the tip and medial portions of the anterior two thirds of the tongue, compared to the posterolateral, dorsal, and ventral portions, and this difference is developmentally driven.[63]

Buccal Nerve

The buccal nerve (BN) is a branch of the mandibular division of the trigeminal nerve that carries sensory fibers to the lower buccal sulcus, gingival, buccal, and cheek mucosa and may contribute to the cutaneous supply of the cheek. The nerve travels between the two portions of the lateral pterygoid muscle, beneath or through the lower part of the temporalis muscle deep to the mandible, then crosses over the external oblique ridge at the anterior border of the masseter muscle and merges with the same branch of the facial nerve. It is this

area where the nerve crosses over the external oblique ridge that places it at risk for injury, most commonly from third molar surgery. A rare variation that supports the IAN as the origin of the BN is described by Turner, Singh, and Jablonski and their colleagues, who identified the nerve exiting the mandible through a small foramen at the retromolar fossa.[64-67] As the nerve reaches the surface of the buccinator muscle, it divides into a superior division that supplies the muscle and an inferior division that provides the sensory innervation of the mucosa, as stated earlier.

Hendy and colleagues, in their study of the course and relationships of the BN in 20 cadaveric specimens, noted the following: The nerve was found to have 4 to 8 major branches with a mean number of 3 branches where it crosses the external oblique ridge. The nerve trunk was found to cross the ridge as close as 3 mm from its deepest concavity of the external oblique ridge in 70% (14 of 20) of specimens. In the remaining cases, the distance ranged between 7 and 12 mm below that point. The authors postulated that the nerve is at risk from incisions in this region even if these are placed as far away as 12 mm from the external oblique ridge. The variation of the branching patterns of the nerve, in addition to the high mechanosensory threshold noted on the buccal mucosa, may result either in a small area of damage or in the injury going unnoticed by the patient.[66,68,69]

Infraorbital Nerve

The infraorbital nerve (ION) is a major branch and the termination of the second division of the trigeminal nerve that emerges on the face via the infraorbital foramen. The foramen is on average 2.7 cm from the facial midline and 6 to 8 mm from the inferior orbital rim. In males the foramen is larger than in females, with some differences in the distances from the midline and infraorbital rim identified in anatomic studies.[44,70] In the study by Kazkayasi and co-workers, a single foramen was found in 90% of cases, two canals in 5%, and three canals in the remaining 5%. The shape of the canal was found to be oval in 30%, round in 40%, and semilunar in 30% of cases.[71] The ION enters the orbit via the inferior orbital fissure and transverses the orbital floor in the infraorbital canal (IOC) for 22 mm. The canal may not be complete, as the cortical thickness of its roof ranges between 0.1 and 6.0mm and thus the nerve may be exposed without a discrete superior bony wall. The combination of a groove and a canal is found in 50% of the cases, and the remainder demonstrate a complete canal.[71] Racial and gender variations have been reported in the location and shape of the foramen as well as the length of the canal.[70,72,73] After it exits the infraorbital foramen, four branches of the ION have been identified and correspond to the areas of the midface, nose, upper lip, and lower lid innervated by the nerve.[74] The ION is at risk for injury during approaches for reconstruction of the orbito-zygomatico-maxillary complex following traumatic events and during maxillary orthognathic surgery. Orthognathic-related injuries are typically transient and reversible, whereas sensory changes from entrapment of the nerve encountered in midface trauma may cause more problematic, long-term neurosensory changes.

TABLE 5-3 Distances and Relationship of Lingual Nerve (LN) to Mandible at the Third Molar Region

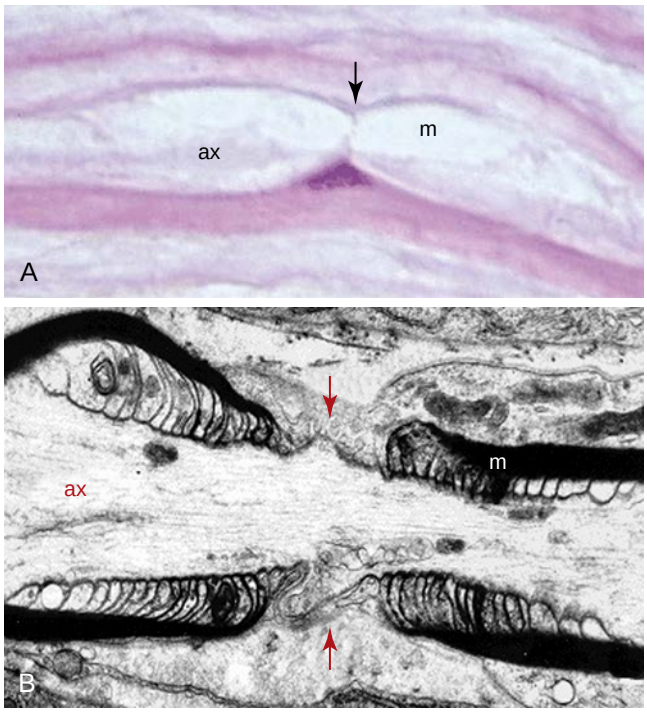
Authors Number of Nerves Method of Evaluation	Vertical Measurement (mm)	Horizontal Measurement (mm)	% of LN above Alveolar Crest	% of LN in Contact with Lingual Plate
Kiesselbach, Chamberlain:* 34 cadaveric and 256 in vivo nerves	2.28 ± 1.96	0.58 ± 0.9	17.6	62
Pogrel and Le:† 40 cadaveric nerves	8.32 ± 4.05	3.45 ± 1.48	15	0
Behnia et al:‡ 669 cadaveric nerves	3.01 ± 0.42	2.06 ± 1.10	14.05	23.27
Holzle and Wollfe:§ 68 cadaveric nerves	7.83 ± 1.65	0.86 ± 1.00	8.82	57.4
Karakas et al:‖ 21 cadaveric nerves	9.56 ± 5.28	4.19 ± 1.99	4.7	0
Miloro et al:¶ 20 in vivo nerves (HR-MRI)	2.75 ± 1.00	2.53 ± 0.67	10	25

*Kiesselbach JE, Chamberlain JG: Clinical and anatomic observations on the relationship of the lingual nerve to the mandibular third molar region, *J Oral Maxillofac Surg* 42:565-567, 1984.
†Pogrel MA, Le H: Etiology of lingual nerve injuries in the third molar region: a cadaver and histologic study, *J Oral Maxillofac Surg* 64:1790-1794, 2006.
‡Behnia H, Kheradvar A, Shahrokhi M: An anatomic study of the lingual nerve in the third molar region, *J Oral Maxillofac Surg* 58:649-651; discussion 652-653, 2000.
§Holzle FW, Wolff KD: Anatomic position of the lingual nerve in the mandibular third molar region with special consideration of an atrophied mandibular crest: an anatomical study, *Int J Oral Maxillofac Surg* 30:333-338, 2001.
‖Karakas P, Uzel M, Koebke J: The relationship of the lingual nerve to the third molar region using radiographic imaging, *Br Dent J* 203:29-31, 2007.
¶Miloro M, Halkias LE, Slone HW, Chakeres DW: Assessment of the lingual nerve in the third molar region using magnetic resonance imaging, *J Oral Maxillofac Surg* 55:134-137, 1997.

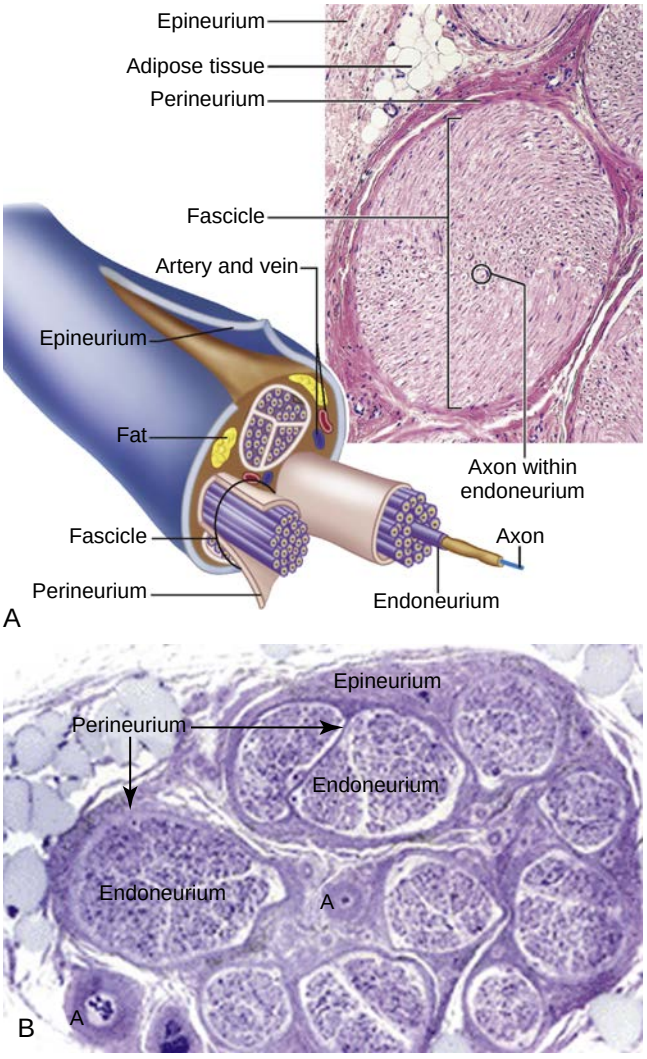
Microanatomy

The microanatomy of the trigeminal and facial nerves is the same, with sensory and motor nerves containing myelinated and unmyelinated fibers in a ratio of 1:4. The difference between the two types of fibers is the number of Schwann cells that surround each fiber with nodes of Ranvier that permit rapid saltatory nerve conduction (Figure 5-6). In the myelinated fiber, the ratio of nerve axons and Schwann cells is 1:1, whereas in the unmyelinated fiber the Schwann cell envelops several axons. The membrane, or basal lamina, created by the Schwann cell as it wraps around the axon, runs the entire length of the axon, is called a band of Büngner (laminar myelin sheath) and is crucial in the process of nerve regeneration. Although myelin may be destroyed during the nerve injury, the Schwann cells survive and play a major supportive role in nerve recovery and repair. The length of the axon surrounded by a single Schwann cell is known as the internode, and the small area (0.3 μm to 2.0 μm) between the internodes, where the axon is not myelinated, is known as a node of Ranvier. In each node of Ranvier, diffusion of ions occurs, resulting in nerve depolarization and repolarization. This allows for the conduction of nerve impulses along the nerve fiber. Conduction occurs only between the nodes of Ranvier (saltatory conduction) and is responsible for the rapid impulse transmission noted in myelinated nerve fibers (up to 150 m/s) compared to the nonmyelinated nerve fibers (2-2.5 m/s). Typically, unmyelinated axons are also smaller, with diameters ranging between 0.15 and 2.0 μm.

Collagen provides the framework that surrounds the nerve and creates the structural architecture within the nerve (Figure 5-7). The endoneurium is the first organized outer layer of connective tissue supporting the nerve, along with some elastic fibers, creates the external epineurium or



• **Figure 5-6** Hematoxylin and eosin **(A)** and silver stain **(B)** demonstrating the organization of a peripheral myelinated nerve in longitudinal section in the area of a node of Ranvier (*arrows*). *ax*, Axon; *m*, myelin. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)



• **Figure 5-7** **A,** Schematic representation of nerve organization. **B,** Low power cross-section of polyfascicular nerve showing the organization of the nerve with individual nerve fibers surrounded by endoneurium, fascicles surrounded by perineurium, and the investing epineurium. The mesoneurium is visible surrounding the entire nerve sheath at the periphery, with adipose tissue (upper left). *A,* Perineurial and endoneurial blood vessels. (**A** from Patton K, Thibodeau G: *Anatomy and physiology*, ed 7, St. Louis, 2010, Mosby. **B** from Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

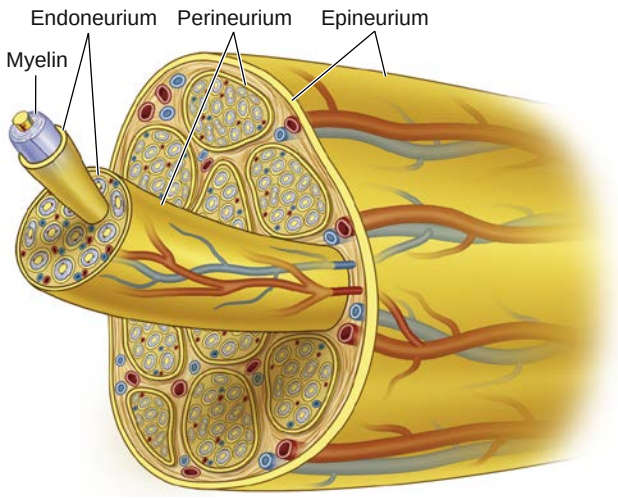
the nerve and provides some protection against compression. The final layer of connective tissue, which is continuous with the epineurium and surrounding tissue bed and is responsible for allowing some freedom of movement of the nerve, is known as the mesoneurium, or adventitia of the nerve.[75]

Peripheral nerves are often distinguished based on their fascicular pattern. A monofascicular pattern has only one large fascicle (an example is the chorda tympani); an oligofascicular pattern contains only a few fascicles (2 to 10; an example is the labial branch of the mental nerve); and a polyfascicular pattern has several different-sized fascicles, more than 10 in total (examples include the facial, IAN, lingual, and buccal nerves). The mean number of fascicles and the cross-sectional area of the trigeminal nerve branches decreases proceeding from proximal to distal nerve.[76-79]

A rich interconnecting vascular network of extrinsic and intrinsic systems provides blood supply for each neuron. The vessels reach the extrafascicular epineurium, via the vasa nervosum, after entering the mesoneurium and create a plexus that runs longitudinally at this level. The vessels continue their course toward the axon by passing in an oblique angle through the subsequent connective tissue layers and forming a longitudinally running plexus during their course at each level. This configuration allows for the individual fascicles to have their independent and rich blood supply analogous to an individual nerve fiber (Figure 5-8).[80,81] This passage of the vasculature between the layers of connective tissue may become an area of compromise within the intrafascicular layers. There are no associated draining lymphatics running with the vascular plexuses.

Trigeminal Nerve Imaging

Objective, noninvasive, radiologic imaging modalities in the preoperative assessment of the patient at risk for nerve injury, as well as a monitoring methods for post-injury and post-repair phases of neurosensory recovery, are highly desirable.[82] Radiologic assessment can be categorized with regard to the timing of the imaging period: that is, pre-injury, post-injury, and post-repair phases. Pre-injury assessment refers to the documentation of the in situ position of a nerve prior to any surgical intervention that places that nerve at risk for iatrogenic injury (e.g., third molar removal, tumor extirpation). Intraoperative monitoring of nerve function during a surgical procedure that involves a specific nerve may also be used, most commonly with functional study of nerve conduction and electrophysiologic status such as somatosensory evoked potentials (SSEP). Post-injury imaging is divided into a primary phase (i.e., following nerve injury and allowing for spontaneous neurosensory recovery without microneurosurgical intervention) and a secondary phase (i.e., following surgical nerve exploration and repair). Primary post-injury imaging may be clinically significant if it can correlate objective (radiologic) findings with subjective (clinical examination) findings, and thereby guide the need for surgical intervention, and possibly aid in treatment planning (i.e., the need for an interpositional nerve graft).



• **Figure 5-8** Schematic representation of vascular supply between the layers of the connective tissue surrounding the axon. *Red*, arteries; *blue*, veins; *yellow*, axons. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

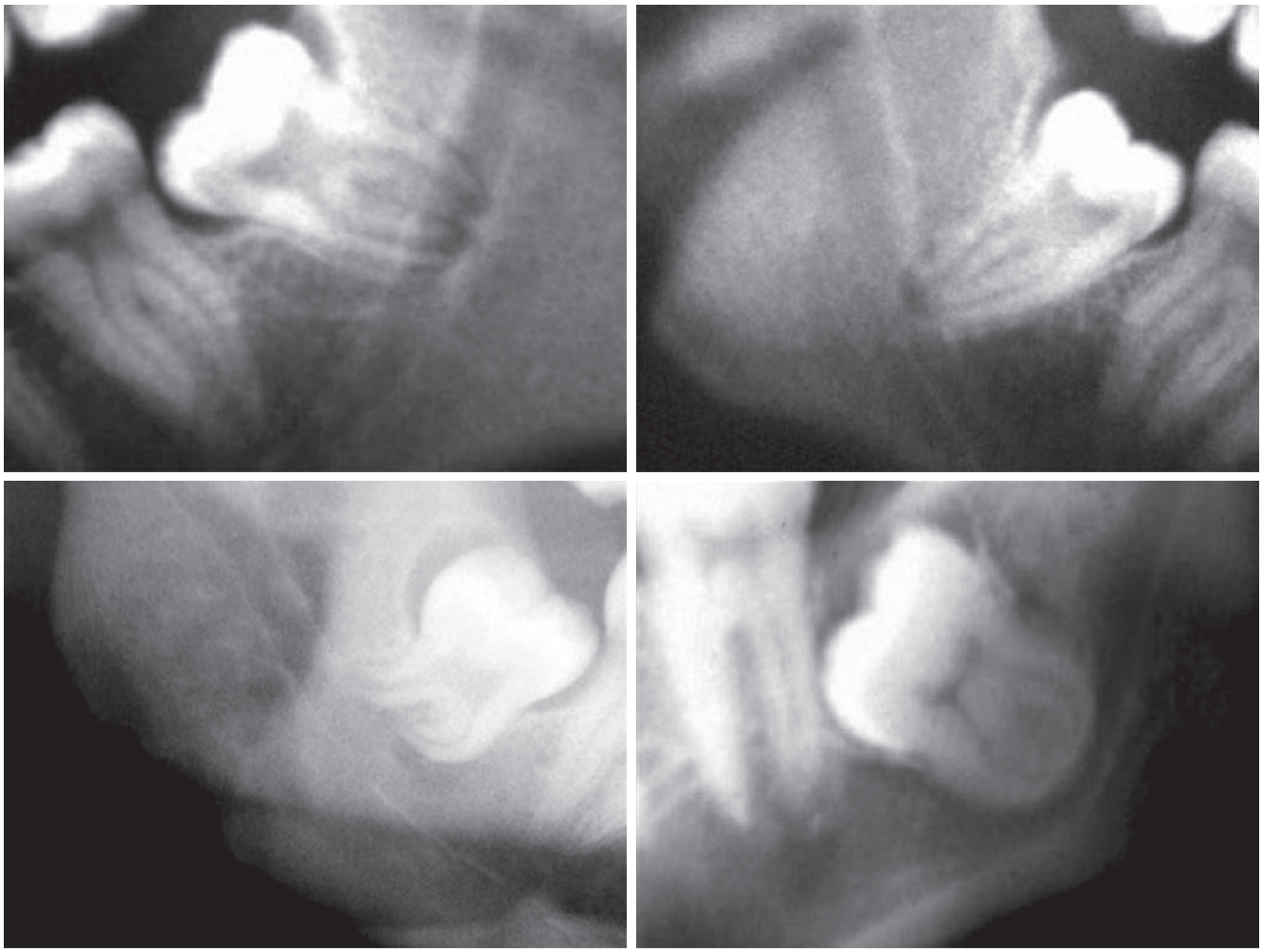
Panoramic Radiography

Preoperative assessment of the position of the inferior alveolar nerve during patient consultation has been routinely performed with the use of a panoramic radiograph. Obviously, information gained from this study is extremely limited because of the two-dimensional nature of the image, the variable magnification of the bony anatomy (for the inferior alveolar nerve), and the complete inability to visualize the position of the lingual nerve. Valuable information can be obtained from the panoramic radiograph as a stand-alone imaging modality in regard to the relationship of the IAN in the vertical plane, but not in the horizontal dimension. The most useful aspect of the panoramic radiograph is in assessing increased potential for inferior alveolar nerve injury during third-molar extraction based on the presence of several radiographic predictors[83,84] (Figure 5-9).

The post-surgery assessment of the nerve-injured patient usually includes a panoramic radiograph that may demonstrate a variety of clinically significant findings. The presence of a foreign body in the region of one or both nerves must be ruled out; these may include metallic foreign bodies from rotary instruments or amalgam particles from neighboring teeth, as well as retained tooth or root fragments following third-molar surgery. The presence of iatrogenic surgical disturbance of the nerves may be indicated by evidence of bone removal in proximity to the inferior alveolar neurovascular bundle or the lingual nerve (Figure 5-10). A panoramic radiograph or any other plain film is rarely used, however, to monitor progression following injury or repair.

Computed Tomography

The use of computed tomography (CT) in the assessment of nerve injuries is very limited. An evaluation of bone



• **Figure 5-9** Panoramic radiographs showing examples of Rood radiographic predictors of root proximity to the inferior alveolar canal, including root darkening, root narrowing, root deflection, loss of the superior white line of the canal, and diversion of the canal. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

window attenuation images may indicate violation of the cortical outline of the inferior alveolar canal, either from implant placement or following facial trauma involving the posterior mandible (Figure 5-11), but yields little information regarding the condition of the nerve or neurovascular bundle.[85] The use of soft tissue window images for the lingual or inferior alveolar nerves is compromised by very poor detail resolution that precludes its routine application in neural assessment. Furthermore, dental artifacts often impose severe limitations on obtaining accurate information regarding the position of the LN relative to the lingual cortex of the mandible in critical areas, even in the soft tissue windows and despite with the current high-resolution image acquisition.

In 1998 cone beam CT (CBCT) technology, until then used only in angiography, was employed in the United States as a potential imaging modality for the maxillomandibular complex. The use of CBCT for presurgical evaluation of an impacted mandibular third molar and its relationship to the IAN has gained popularity over CT scans and plain panoramic radiographs[86-90] (Figure 5-12).



• **Figure 5-10** Panorex following third molar removal showing the presence of preoperative radiographic predictors of root proximity to the canal, and evidence of the use of a drill distal to the crown of the extraction site in a patient with right lingual nerve injury.

The need for accurate imaging with the lowest possible dose of radiation (following the ALARA rule: as low as reasonably achievable) seems to be well satisfied with this technology. CBCT provides the desired three-dimensional representation of the anatomic location of interest with minimal distortion compared to traditional plain films and by simpler acquisition compared to CT systems.[91,92] Similar to the panoramic radiograph, CBCT can be used for preoperative risk assessment in various dentoalveolar procedures such as third-molar surgery or dental implants and pre-prosthetic surgery.[93-95] A major limitation remains the inability to visualize the lingual nerve, as no accurate soft tissue information can be obtained with use of CBCT.

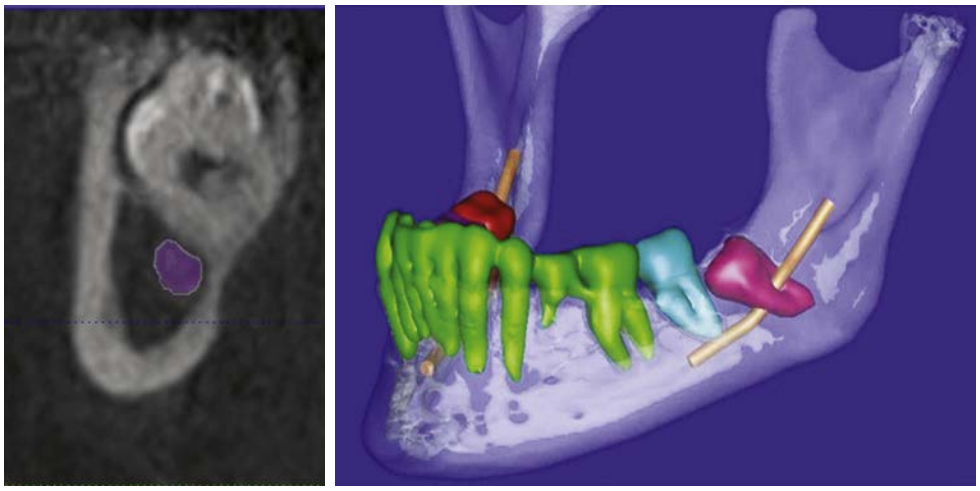
Postoperative investigation of the surgical site for examination of the integrity of the IAN canal or presence of material, tooth or root fragments, within the canal could be superior and more reliable with CT or CBCT imaging than traditional panoramic imaging. Direct investigation of the integrity of the LN cannot be reliably performed with either modality because of the limitations discussed. Disruption of the lingual cortex of the mandible at the third-molar region that may be noted in a postoperative panoramic radiograph, and may imply trauma to the LN in the region, can be reviewed in more detail with CT or CBCT. Direct comparison of pre- and postsurgical images can be made and added to the information gathered from the clinical examination to potentially assist in the decision for need of exploration in the region.



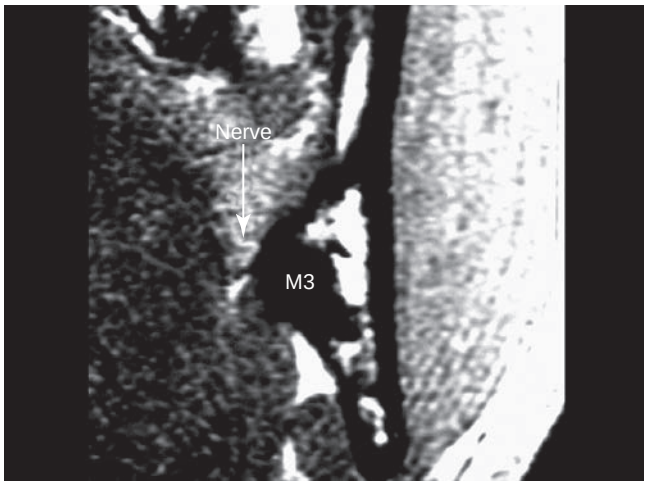
• **Figure 5-11** Coronal CT scan through a mandibular body fracture showing canal involvement. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is the method of choice for visualization of all cranial nerves (CN), and each nerve segment can be seen and examined in detail with specific sequences. Because of the complexity of the course and surrounding anatomic structures, detailed examination of the CNs is possible only with careful planning and MRI technique selection. The imaging plane, coil selection, slice selection, in-plane resolution, and use of special techniques can be tailored based on the CN and the segment of interest so the highest quality image possible is obtained. The course of the lingual and inferior alveolar branches of the mandibular division, after it exits from foramen ovale, can be followed with high-resolution contrast-enhanced T-weighted (T1W) or T1W three-dimensional fast field echo (T1W 3D-FFE) sequences in the axial, coronal, and sagittal or parasagittal



• **Figure 5-12** Cone-beam CT scan showing the proximity of the inferior alveolar canal to an impacted third molar, and 3D reconstruction of the scan to highlight the canal passing between the roots of the impacted third molar tooth. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)



• **Figure 5-13** High-resolution MRI showing a kidney bean–shaped lingual nerve (*Nerve*) superior to the lingual crest, and in contact with the lingual plate in the third molar (*M3*) region. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

planes.[96-100] MRI is the preferred imaging modality for examination of the status of the CNs in the presence of a disease process or injury.[97,101-104]

In an attempt to document the in situ position of the lingual nerve in the third molar region, high-resolution MRI has been studied. Ten patients (20 sides) of healthy adult volunteers without prior dental surgery were imaged using an MRI sequence that enabled visualization of the lingual nerve (Figure 5-13). This study documented that the lingual nerve position, while variable, was found to be superior to the lingual crest in 10% of cases, and in direct contact with the lingual plate in 25% of cases.[56]

The application of MRI in the assessment of the trigeminal nerve post-injury is in its early trial phases. Presumably, with improved resolution, a variety of anatomic changes in the nerve could be visualized. First, a change in nerve diameter may be visualized in cases of nerve injury with wallerian degeneration of the nerve segment distal to the site of injury with an acute or gradual decrease in nerve diameter. Second, an acute change in nerve position may be seen—for example, where the lingual nerve is retracted into the region of the third-molar socket with the formation of a lateral adhesive or exophytic neuromatous segment. Third, a change in nerve shape may be able to be visualized—for example, in the case of a fusiform neuroma-in-continuity, with a change in shape of the nerve for a certain distance with return to normal shape distal to the neuroma.[105]

The application of MRI to post-injury neural assessment is hindered by a variety of factors. The degree of image resolution and magnification significantly limits lution from currently available techniques. Also, while the lingual nerve lies within soft tissue and its course is unaccompanied, the inferior alveolar nerve lies within a cortical bony conduit and is joined by an artery and a vein throughout its course.

Ultrasonography

Several reports have described the use of ultrasound and high-resolution ultrasound technology mainly for assessment of peripheral nerve lesions. This real-time advanced technology with the high-resolution probes now available can offer compound imaging without radiation and in a relatively inexpensive manner. Although ultrasonography (US) has not been employed or investigated as a potential preoperative risk assessment tool for the trigeminal nerve, it has been demonstrated to be valuable in identification and safe advancement of the needle in brachial plexus and sciatic nerve blocks.[106]

Mechanisms of Injury to the Trigeminal Nerve

Several commonly performed procedures in the maxillofacial region are associated with potential injury to the terminal branches of the trigeminal nerve.

Local Anesthetic Injection

Injury to both the IAN and LN is possible during administration of mandibular block local anesthesia. Interestingly, prolonged sensory alterations are rare, considering the number of blocks administered daily by dental professionals. The ratio of injuries to injections has been estimated at between 1:26,762 to 1:160,571, although this may not represent the actual incidence because not all cases of sensory disturbances are reported.[107,108] Harn and Durham in 1990 reported an incidence of transient sensory disturbance of 3.62%, with only 1.8% incidence of long-duration changes (over 1 year).[109] The proposed mechanisms that result in this injury are multiple, the exact cause remains unclear, and there is no reliable way of avoiding these types of injuries. Direct penetration of the nerve by the needle, hematoma formation from vessel laceration, direct laceration of the nerve from a barb on the tip of the needle after repeated injections and needle contact with cortical bone, and chemical injury from intraneural injection are reasonable possibilities.[109-111] Direct toxicity of the local anesthetic solution (specifically 4% articaine and 4% prilocaine), especially when deposited within the confines of the epineurium, has been associated with cases of sensory changes after mandibular blocks.[112-115] Box 5-1 lists conclusions that can be made based on the current understanding of injection-related nerve injuries. These cases are usually associated with only a limited distribution of neurosensory alteration, reflecting the small number of fascicles insulted or involved in this type of injury.[116]

• BOX 5-1 Clinically Based Conclusions on Local Anesthesia-Related Nerve Injuries

1. Not predictable, possibly preventable
2. Painful response upon injection (electric-shock sensation) does not always accompany an injury
3. More common in female patients
4. More commonly result in dysesthesia than hypoesthesia
5. May follow a non-anatomic distribution (involvement of more than one division of the trigeminal nerve) due to segmental demyelination
6. More common with higher-concentration anesthetic solutions (e.g., 4% articaine)
7. Surgical exploration is not indicated due to nature and location of injury
8. Lingual nerve is more commonly affected than the inferior alveolar nerve
9. Spontaneous recovery usually occurs within 8 weeks of the injury
10. Less than one third of cases lasting longer than 8 weeks will recover fully
11. Pharmacologic management is indicated for unpleasant sensations (dysesthesia)

Third Molar Surgery

Complications associated with third molar removal are the most common cause of trigeminal nerve injury reported and can occur during any stage of the actual procedure (Figure 5-14) as well as during postoperative care.[117-121] The overall incidence of IAN injury during third molar surgery is estimated to be between 0.41% and 7.5%, resulting in temporary sensory changes in 2% to 6%, and permanent disturbances in 0.5% to 2% of cases. Stretching or manipulation of the lingual nerve from tissue retraction during third molar surgery is reported to cause temporary sensory disturbances at rates from 6.4% to as high as 15%, but less than 1% result in permanent changes.[116,122-128] Several risk factors associated with increased risk of IAN injury during this procedure have been discussed in the literature and include advanced age, female gender, tooth angulation, depth and type of impaction, integrity of the lingual cortex, complexity of the procedure, and surgeon experience.[129,130] Rood and Shehab in 1990 described seven radiographic predictors of potential proximity of a third-molar to the IAN on panoramic radiograph that may be helpful in the decision-making process regarding extraction versus more conservative approaches such as coronectomy or observation.[84] These radiographic predictors include darkening, deflection, or narrowing of the tooth root; diversion, narrowing, or interruption of the white line of the IAN canal; and a dark or bifid root apex. The most significant radiographic findings of potential nerve injury included root darkening, root deflection, and interruption of the white line of the IAN canal. It is important to note that subsequent studies have reported controversial findings, in both support and opposition of the value of these radiographic predictors in nerve injury (Figure 5-15).[131,132] In any case, these radiographic findings are neither highly sensitive nor specific for nerve injury.

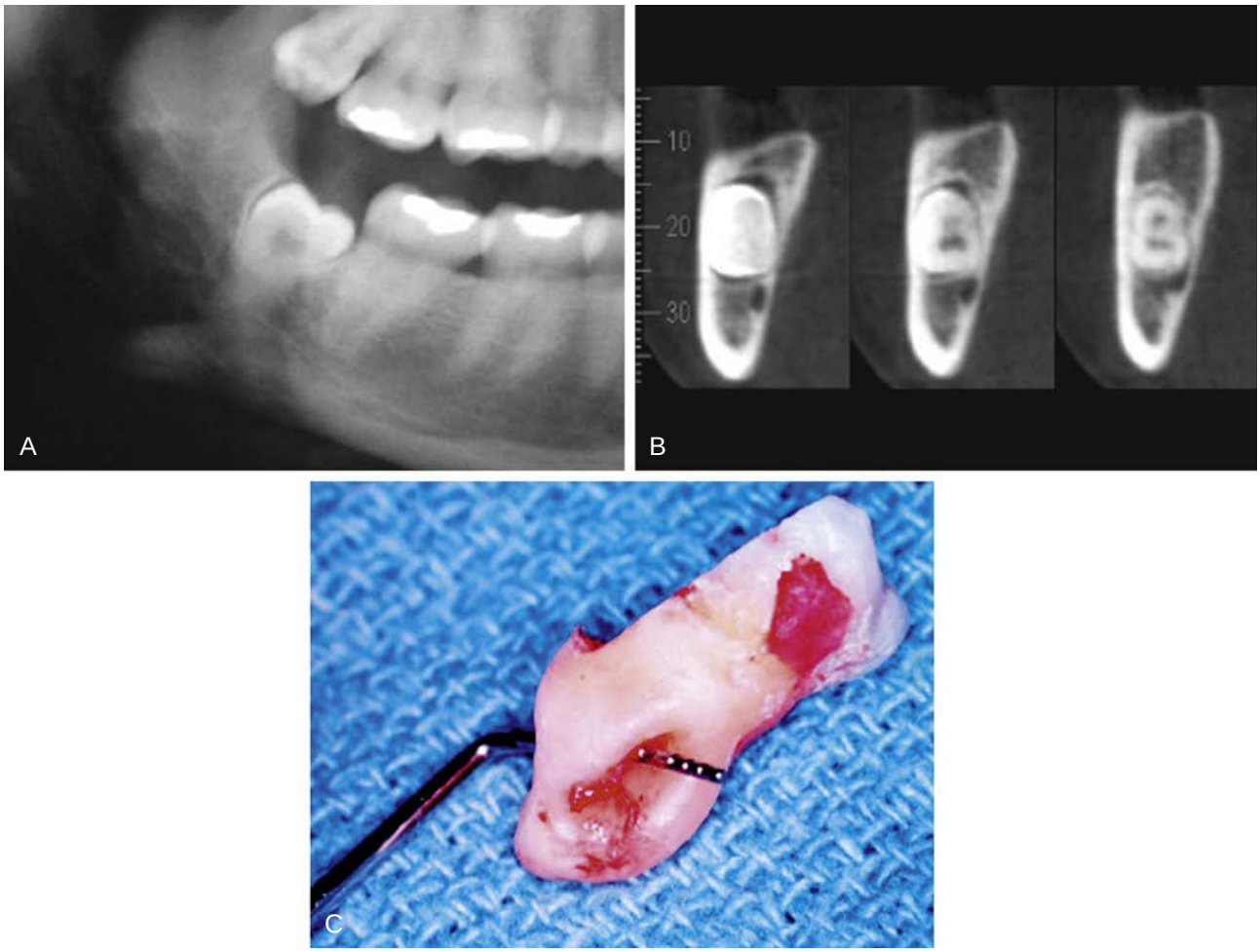


• Figure 5-14 Diagram showing possible iatrogenic injury of the inferior alveolar nerve during extraction of a deeply impacted third molar. (From Hupp JR, Ellis E, Tucker MR: *Contemporary oral and maxillofacial surgery*, ed 5, St. Louis, 2008, Mosby.)

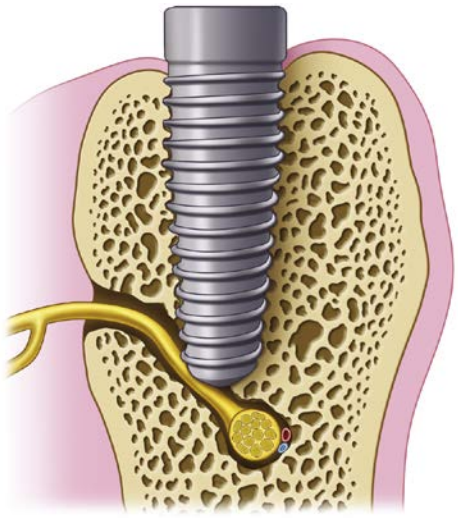
Dental Implant Surgery

With the wide utilization of dental implants for dental rehabilitation throughout the world, injury to the IAN is a fairly common occurrence with a 0% to 40% reported incidence of nerve injury due to implant placement, depending on location (Figure 5-16); and, patient management can be problematic.[133,134] The IAN, in particular, is at risk in the molar region as well as anterior to the mental foramen, especially in edentulous patients because of the associated alveolar ridge resorption. In addition, the surgeon should consider the anterior extension, or genu, of the neurovascular bundle beyond the foramen when placing dental implants in this region. These injures can result from surgical exposure, during preparation of the osteotomy site, or at the time of implant placement. Mechanical compression of the neurovascular bundle can result from overextension of and canal violation during the osteotomy. This can cause infracture of the cortex of the canal at the site and direct pressure on the IAN (Figure 5-17). Alternatively, bleeding within the canal from a laceration of the inferior alveolar vein or artery with an implant drill can cause pressure similar to a compartment syndrome. Finally, direct compression on the neurovascular bundle following restoration of the implant and mastication or prior clot formation and subsequent ectopic calcification may occur. Although extensive literature is available regarding the use of modern imaging modalities for treatment planning in implant dentistry, data are lacking on the most appropriate modality for nerve injury risk assessment, as discussed earlier.[42,134-139]

Management of these injuries is tailored individually based on the mechanism of injury and may involve implant removal as soon as such an event is recognized, or the use of pharmacologic therapy as indicated for dysesthesia. Immediate implant replacement with a shorter implant may be considered, but it is dependent on the exact cause of the trauma and the need or lack of need for nerve canal exploration as well as the timing and recognition of the occurrence.[117,134,140-143]



• **Figure 5-15** **A,** Panorex showing root proximity to the inferior alveolar canal. **B,** Cone-beam CT showing root proximity to the inferior alveolar canal. **C,** Third molar following removal with a periodontal probe showing the location of the inferior alveolar neurovascular bundle. Despite an attempt to section the tooth to avoid nerve injury, the nerve was transected during the extraction. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)



• **Figure 5-16** Diagram showing implant-related nerve injury that can occur when the implant is in proximity to the closed canal with possible bleeding, edema, and the development of a compartment syndrome that causes deleterious effects on the nerve even in the short term. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

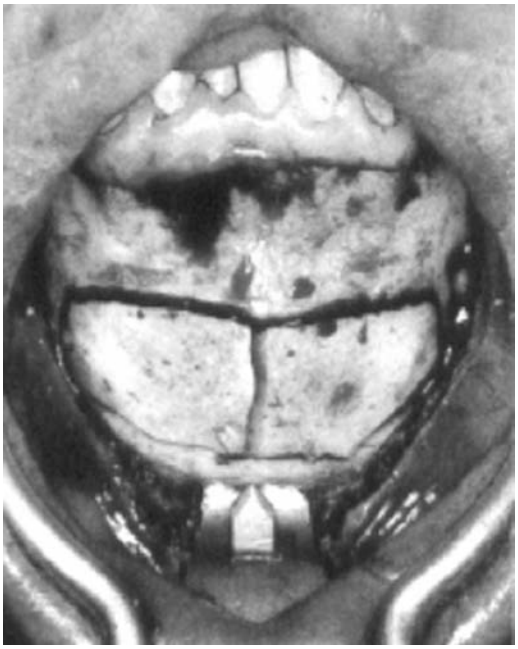


• **Figure 5-17** Panorex showing the distal implant placed within the confines of the inferior alveolar canal in a patient with inferior alveolar nerve paresthesia. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

Procedures aimed at augmenting the alveolar bone height in the posterior mandible or improving the site to facilitate implant placement, such as bone grafting, distraction osteogenesis (DO), or IAN nerve lateralization carry their own risks for nerve injury. During bone harvesting from the mandibular ramus (Figure 5-18) or chin region (Figure 5-19), the IAN or mental nerves could be inadvertently injured, especially when a large area requires augmentation. When small, single tooth-sized grafts are harvested and appropriate preoperative radiographic examination of the area is undertaken, this risk appears to be minimal.[144] The same branches of the trigeminal nerve are at risk when securing autogenous or allogeneic bone graft material at the recipient site, either from direct compression of the nerve from the graft or from hardware (plates and screws) used to secure the graft in place. Distraction osteogenesis (DO), another method employed for alveolar ridge height augmentation, may lead to nerve injury, again either at the time of the osteotomy or directly from the device used for the distraction. The actual response of the IAN to the DO process has been studied in animal models, and it has been shown that several events occur at the cellular level, including activation and proliferation of Schwann cells as well as a limited degree of axonal degeneration and regeneration. The result is minor nerve injury that is reversible with no long-term sequelae.[145-147]



• **Figure 5-18** An example of a ramus graft procedure that places the inferior alveolar nerve at risk for injury due to its lateral location in this region of the mandible. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)



• **Figure 5-19** An example of a genial bone graft harvest that may sacrifice the incisive branch of the inferior alveolar nerve and result in paresthesia to the anterior mandible dentition. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

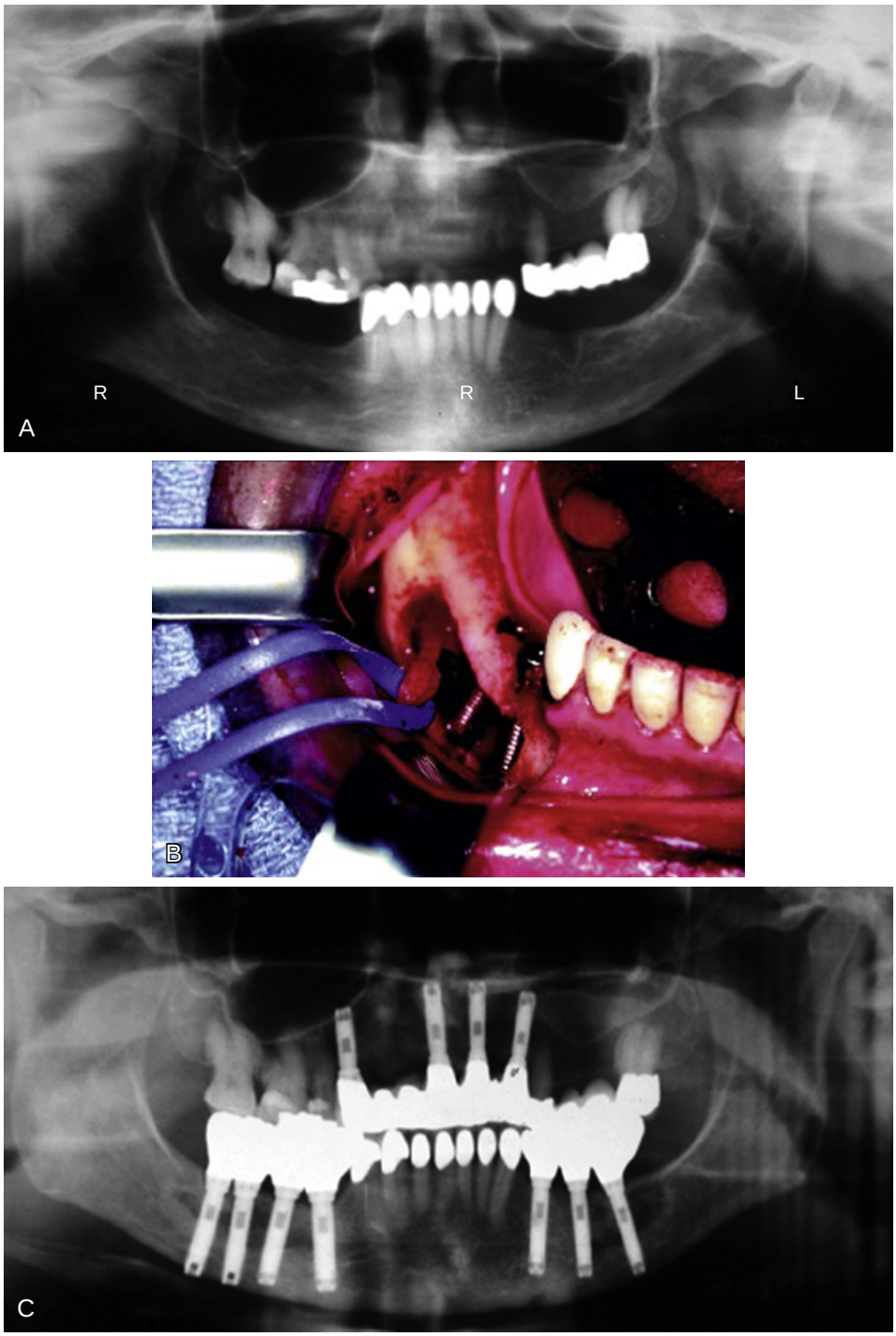
Nerve lateralization for facilitation of implant placement is a viable option in select cases. With this approach, the lateral cortex of the mandible is removed and the IAN is exposed and lateralized so that implants of adequate length can be placed (Figure 5-20). The procedure inevitably causes some neural trauma, but the injury is "controlled," while the risk of compartment syndrome is eliminated along with risk of direct injury to the neurovascular bundle from the implant placement itself. The procedure is associated with a high incidence of neurosensory changes, some permanent, but with excellent implant stability, success, and high patient satisfaction.[148-154] If the nerve lateralization procedure requires release of the mental nerve from the mental foramen, then the incidence and degree of neurosensory dysfunction is increased over a transposition of the nerve posterior to, and not involving, the mental foramen. Recovery after nerve lateralization should be expected within 3 to 6 months, although up to 30% to 40% of patients, especially older individuals, may experience long-term neurosensory dysfunction.[154] The use of piezosurgery in a cadaveric study (10 sheep mandibles with 20 lateralizations) showed no disturbance of structures beyond the epineurium, and the overall degree of injury was found to be less than when the procedure was performed with conventional burrs.[155]

Maxillofacial Trauma

Maxillofacial trauma and surgery for the correction of facial injuries may result in disturbances of the peripheral branches of the trigeminal nerve in the vicinity of the traumatic injury. The overall incidence of neurosensory impairment has been reported to be 70.9%. In cases of nondisplaced fractures, the incidence was found to be 54.4%, while a significant increase was noted in displaced fractures of 88.2%. As expected, cases of direct injury had 100% neurologic impairment.[156] Fractures of the mandible may result in neurosensory alterations due to laceration, traction, or compression of the IAN from bony segment displacement (Figure 5-21) or treatment of the fracture with iatrogenic

injury to the nerve canal (Figure 5-22). Similarly, midface fractures or soft tissue trauma, lacerations, or avulsions may violate the infraorbital canal and damage the ION, leading to transient or permanent sensory alterations[156-159] (Figure 5-23). In a study by Kloss and colleagues, hypoesthesia of the ION was found in 10% of single, and 16% of multiple, midface fractures.[160]

Reduction of fractures with alignment of segments and removal of loose bony segments that impinge on the nerve will assist in spontaneous neurosensory recovery.



• **Figure 5-20** **A,** Panorex showing posterior mandibular edentulism with insufficient bone height above the canal and inadequate interocclusal clearance for implant placement. **B,** Nerve repositioning procedure results in a neuropraxic injury in a controlled fashion during implant placement. **C,** Panorex showing bilateral inferior alveolar nerve repositioning with restored implants that engage the superior and inferior borders of the posterior mandible for stability. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

Unfortunately, treatment of facial fractures may cause further injury to branches of the trigeminal nerve due to nerve retraction or inadvertent placement of plates and screws.

Orthognathic Surgery

Neurosensory alterations are common sequelae of orthognathic surgery for correction of dentofacial deformities, especially mandibular procedures.[161] During sagittal split osteotomy (SSO), the IAN and LN can be injured at several locations and during the various steps of the procedure. These include during medial dissection at the lingula region, during the actual osteotomy procedure, or during mobilization or fixation of the segments. If the IAN is found to be located in the proximal segment after the osteotomy, then it may need to be mobilized, and this may cause further injury. The location of the IAN in relationship to the inferior border of the mandible, the ramus height, the dentofacial deformity to be corrected, and the patient's age and gender have all been associated with various incidences of neurosensory disturbances.[162-165] In addition, the incidence of neurosensory alterations during mandibular orthognathic surgery has been found to increase with intraoperative complications, most commonly unfavorable splits.[166] Furthermore, IAN sensory alterations appear to occur more frequently with additional procedures (e.g., genioplasty in addition to SSO), but these are transient, and spontaneous full recovery is usually reported within 6 to 12 months.[161,167,168] Interestingly, a substantial difference has been demonstrated between subjective and objective findings regarding sensory alterations after SSO with normal sensation reported in 73.7% of osteotomy sites, while objective testing revealed normal sensation in only 34.2% of cases.[169]

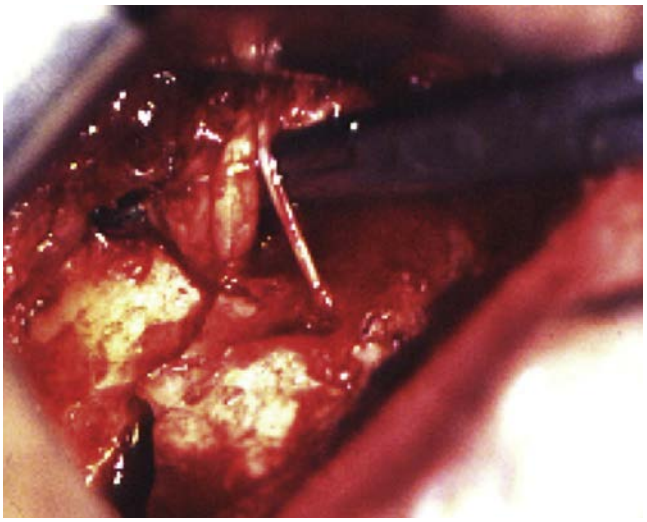
During maxillary or midface procedures, the ION is at risk for injury, most commonly due to soft tissue flap retraction rather than direct injury, and results in sensory changes of the upper lip, cheeks, lateral aspect of nose, and infraorbital region. Based on the nature of the injury (traction, compression, or pressure), full recovery is expected and usually achieved without intervention.[168] Segment fixation with plates and screws could theoretically cause direct injury to the ION or LN from bicortical screw overpenetration (Figure 5-24), but this is an event that is easily avoidable with adequate exposure, visualization, and protection of the nerve.



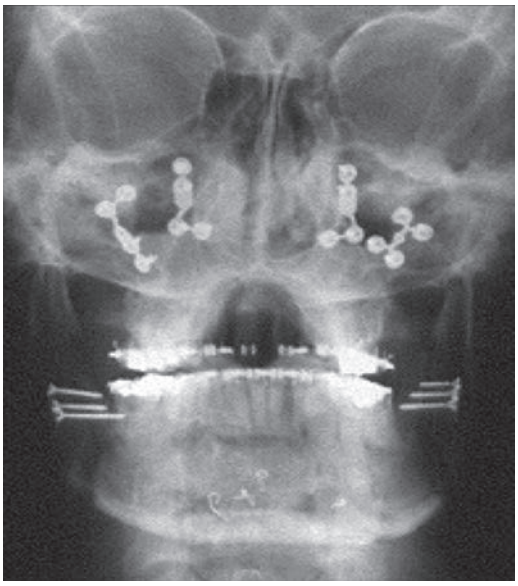
• **Figure 5-21** Panorex showing an open displaced unfavorable left mandible angle fracture. Note the displacement of the inferior alveolar canal. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)



• **Figure 5-22** Panorex showing fixation of a right mandibular body fracture with screws that penetrate the inferior alveolar canal in a patient with right inferior alveolar nerve dysesthesia. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)



• **Figure 5-23** Intraoperative view of compression of the terminal branches of the right infraorbital nerve exiting from the infraorbital foramen in a patient with a displaced right zygomaticomaxillary complex fracture. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

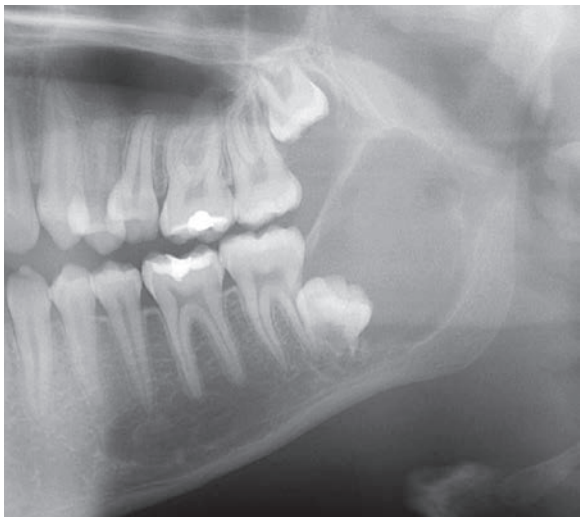


• **Figure 5-24** Posteroanterior skull film showing overpenetration of the bicortical screws used to stabilize the sagittal split osteotomies. This places the lingual nerve at risk for iatrogenic injury during orthognathic surgery. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

Maxillofacial Pathology

Several odontogenic and non-odontogenic cysts and tumors may be found in the nerve-bearing segment of the mandible in intimate relationship with the IAN. These can result in displacement or encompassment of the canal (Figure 5-25). This also applies to tumors of the maxilla in the vicinity of the IOC. Benign pathology usually is not associated with neurosensory disturbances with the exception of neural or vascular tumors originating from the involved neurovascular bundle (Figure 5-26). On the contrary, malignant lesions usually will be associated with sensory changes, as is the case with specific pathology (e.g., adenoid cystic carcinoma with neurotropism), in cases of tumors with aggressive behavior, when the IAC is invaded by the tumor, or the tumor has caused a pathologic mandible fracture (Figure 5-27). Infectious processes are similarly associated with neurosensory changes if they involve nerve-bearing areas of the jaws but usually spontaneously resolve with resolution of the infection (Figure 5-28).

Treatment of maxillomandibular pathology often involves extensive bone and soft tissue resection that may include the IAN, mental nerve (MN), or ION and result in permanent anesthesia in the distribution of the corresponding resected nerve. On occasion, nerve pull-through procedures or utilization of adjuncts such as enucleation and curettage with cryotherapy, have been advocated for some tumors in an effort to minimize morbidity associated with alternative treatments and associated permanent neurosensory disturbances. These approaches remain somewhat controversial with regard to the associated risk of recurrence and can be in conflict with the basic oncologic principles for management of these tumors.[170-178]



• **Figure 5-25** Panorex of a keratocystic odontogenic tumor causing displacement of the left inferior alveolar canal without paresthesia. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

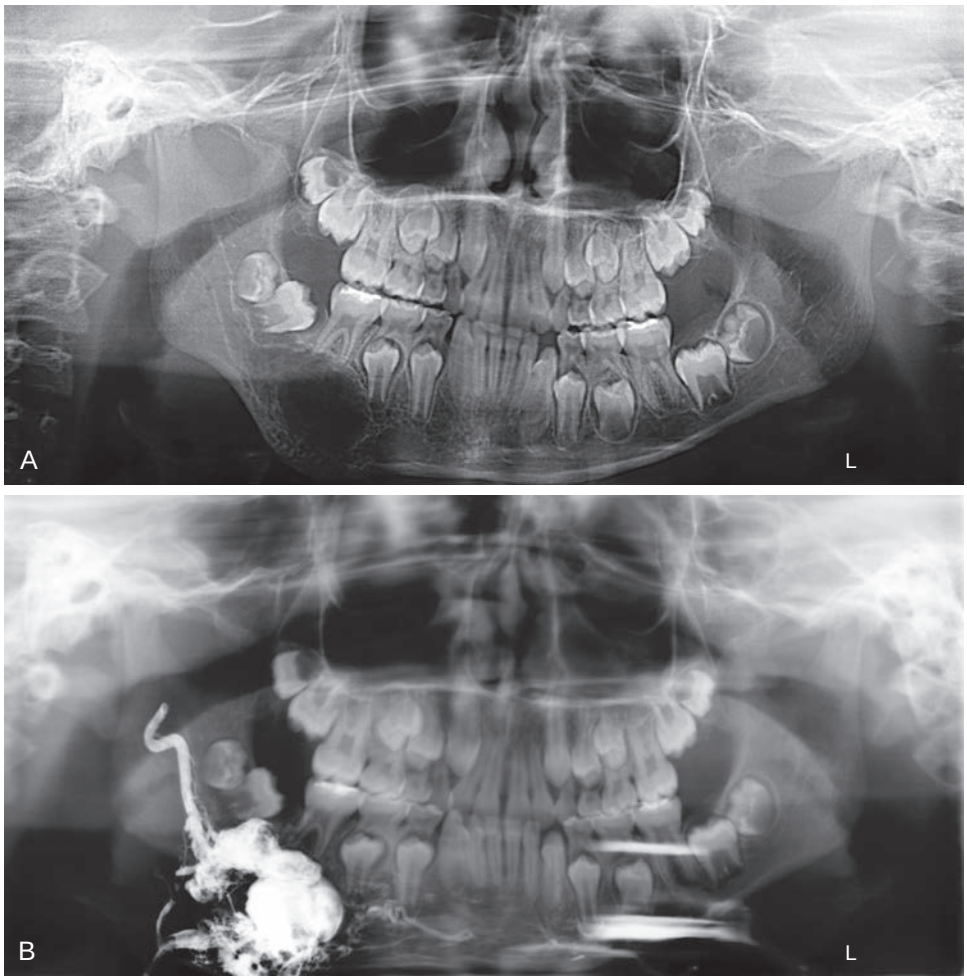
Endodontic and Chemical Injury

Endodontic therapy and periapical root surgery may place the IAN at risk for injury. The nerve may be injured by physical disruption with a file by overinstrumentation of the canal(s), by apicoectomy procedures, or by physical compression from extrusion of the filling materials used (Figure 5-29). The other mechanism of injury is that of chemical neurotoxicity, which may result from the use of certain root canal medicaments to treat the canal(s). These types of IAN injuries can be due to mechanical or chemical factors, or both, and can result in a foreign body reaction or granuloma formation in the canal that may impede spontaneous neurosensory recovery. Unfortunately, these injuries are difficult to manage, with variable success following microneurosurgery, and a large proportion of these injuries may manifest clinically as dysesthesia. For extrusion of potentially neurotoxic root canal filling materials into the IAC, prompt exploration, decompression, and debridement of the foreign material may be beneficial in preventing long-term sequelae.

In addition to root canal medicaments, many other chemical agents are potentially neurotoxic; these include tetracycline, Surgicel (oxidized cellulose), and prolonged exposure of the nerve to Carnoy's solution (a solution of ferric chloride, glacial acetic acid, chloroform, and ethanol).

Clinical Neurosensory Testing

The use of universally accepted terminology is crucial when discussing nerve injury, and it is imperative that the appropriate terms be used to describe and document each case for communication between clinicians, determination of management strategies, and medicolegal reasons (Box 5-2). In addition, a detailed description, including but not limited to nerve mapping and photographs of the region affected by

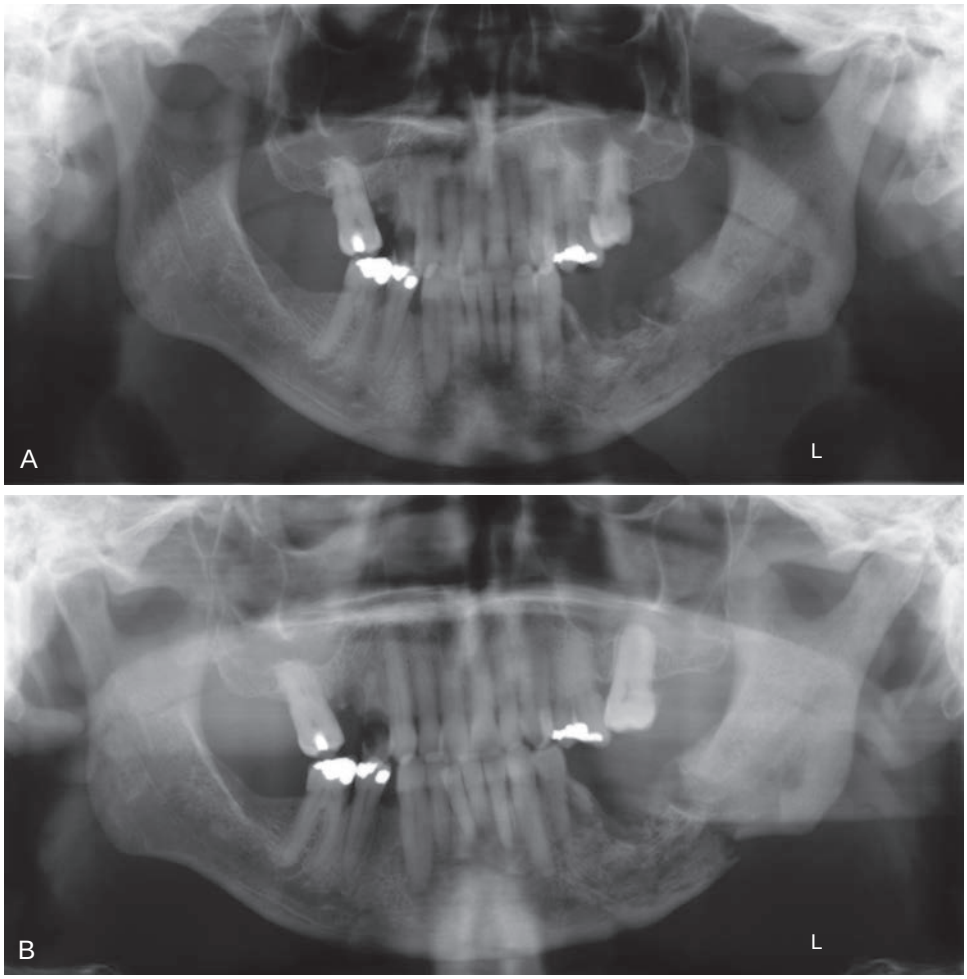


• **Figure 5-26** **A,** Panorex of an arteriovenous malformation of the right mandible involving the inferior alveolar canal. **B,** Panorex of the same patient following arteriography with embolization. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

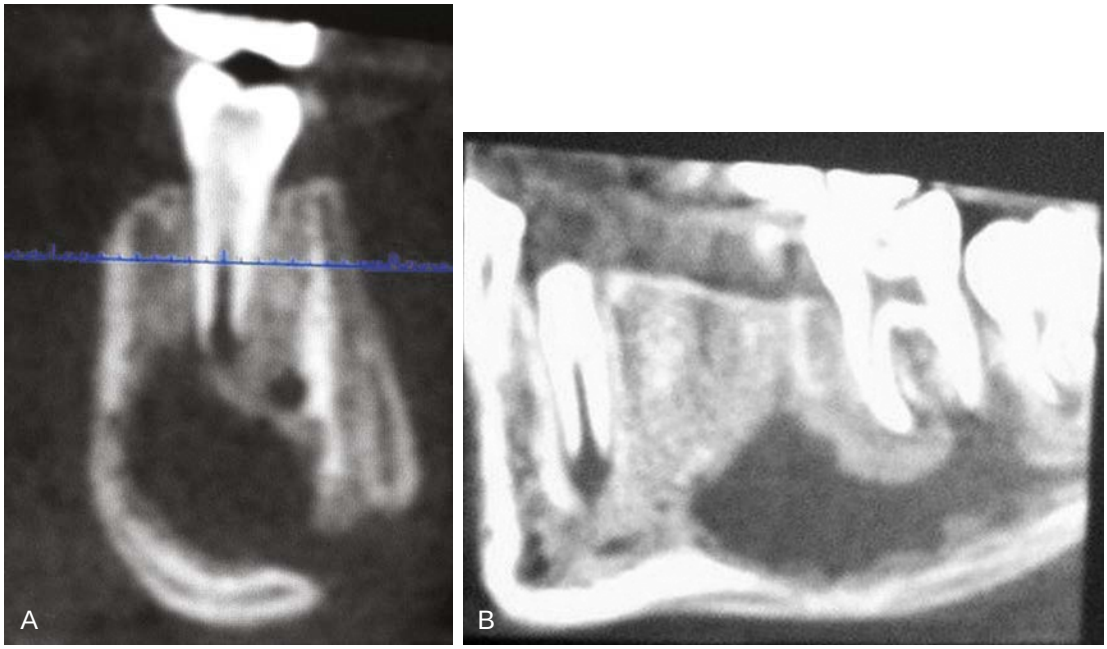
injury should be documented in each patient and used to quantify the initial presentation and, most importantly, to follow the progress of the area of involvement (Figure 5-30).

A detailed history and clinical examination along with objective testing that includes the use of specific neurosensory testing (NST), pain questionnaires, and visual analogue scales are crucial in the assessment of the patient who has sustained trauma to the trigeminal nerve. Attention to details regarding the onset of symptoms, events associated with the current complaints, and changes, including worsening or improvement, requires careful documentation and plays a critical role in the treatment decision-making process.[117,158,179,180] Descriptive terms used by the patient to qualify their symptoms need to be documented in the chart exactly as stated by the patient.

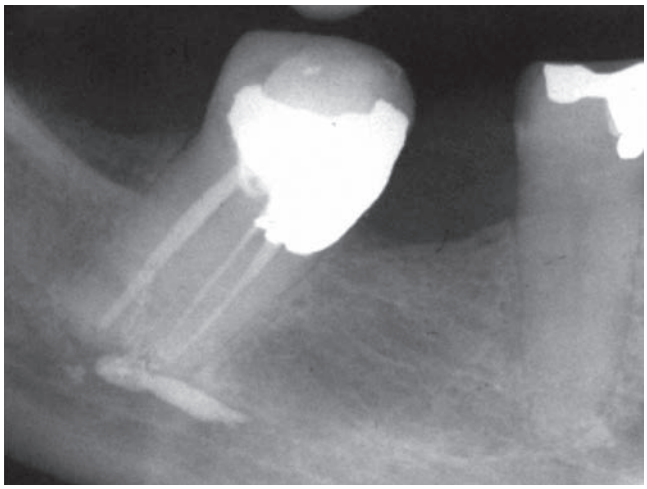
In a critical evaluation of the accuracy of NST to accurately diagnose trigeminal nerve injuries, Zuniga and co-workers demonstrated that for LN assessment, NST had superior sensitivity and specificity compared to examination of the IAN. In addition, IAN findings were associated with a high incidence of false-positive and false-negative results—23% and 40%, respectively.[181] This was subsequently supported in a recently published comparison between clinical NST and current perception thresholds.[182] NST should be performed in patients with neurosensory changes to determine the degree of sensory impairment, monitor recovery, and assist in decision making as to the need for surgical intervention. The clinical neurosensory testing protocol involves mechanoreceptive fiber testing performed first (two-point discrimination, static light touch, directional discrimination, and vibratory sense), followed by nociceptive fiber testing (pain stimuli and thermal discrimination). Testing should be performed in the same manner and sequence on each occasion, in a quiet, calm, comfortable environment with the patient in a semi-reclined position. It is important that the clinician explain in detail the tests that will be performed and assure the patient that there will be no pain involved. An uninvolved normal site should be used to establish a baseline control site and to demonstrate the tests about to be performed. Marking can be done directly on the patient's face with erasable markers, on photos obtained prior to testing, or on drawings on standard recording forms if available. If the marking is done directly on the face, the patient needs



• **Figure 5-27** **A,** Panorex of multiple myeloma involvement of the left mandibular body. **B,** Panorex of the same patient with progression of the disease with a displaced unfavorable pathologic fracture of the left mandibular body with resultant inferior alveolar nerve paresthesia. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)



• **Figure 5-28** **A,** Coronal cone-beam CT (CBCT) showing Garre' osteomyelitis of the mandible with buccal cortical perforation and proliferative periostitis in a young patient involving the inferior alveolar canal with paresthesia. **B,** Sagittal CBCT of the same patient showing the extent of involvement of the Garre osteomyelitis throughout the marrow involving the inferior alveolar canal. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)



• **Figure 5-29** Periapical film showing root canal filling material within the inferior alveolar canal in a patient with inferior alveolar nerve dysesthesia. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

• BOX 5-2 Select Terminology for Sensory Alterations

Allodynia: Pain due to a non-painful stimulus
Analgesia: Absence of pain from a painful stimulation
Anesthesia: Absence of any sensation from a painful or non-painful stimulation
Dysesthesia: Abnormal sensation, spontaneous or evoked, that is unpleasant
Hyperalgesia: Abnormal response to a painful stimulus
Hyperesthesia: Increased sensitivity to stimulation; excludes special senses
Hyperpathia: Increased reaction to a (repetitive) stimulus
Hypoalgesia: Diminished pain in response to a painful stimulus
Hypoesthesia: Decreased sensitivity to stimulation; excludes special senses
Neuralgia: Pain in the distribution of a nerve or nerves
Paresthesia: An abnormal sensation, spontaneous or evoked, that is not unpleasant

to be photographed, and all photos, drawings, and forms must be kept in the records for documentation purposes and for future reference and comparison.

The clinical neurosensory testing protocol (Figure 5-31) begins by outlining the area of sensory disturbance, using brush-stroke directional discrimination to differentiate between the normal and the affected area. Brush-stroke directional discrimination is performed with a camel-hair brush or a fine sable brush that is stroked across the affected area at a constant rate, and the patient is asked to indicate the direction of movement. The correct number of responses out of 10 is recorded. Static two-point discrimination is performed next using any device that allows for measurement between two points, and these tips should be blunt, not so sharp as to stimulate the nociceptive fibers. The closest distance at which the patient can discriminate two points versus one point at both the control and injured site is recorded. If the findings at this level of testing, brush stroke and two-point discrimination (Level A testing), are next level. Level B testing involves contact detection and is performed with von-Frey hairs or Semmes-Weinstein monofilaments of several diameters reflecting the stiffness of the filament and the force required to deflect it on contact. The narrowest filament consistently detected by the patient is recorded for the control site and the involved site. Level A and B testing examines the integrity of the large myelinated A-alpha and A-beta fiber types. If Level B testing is normal, no further testing is required, and the patient is considered mildly impaired, representing a Sunderland second-degree injury. If findings are abnormal at Level B, then testing proceeds to the next level. This involves pinprick nociception and thermal discrimination, and it evaluates smaller myelinated A-delta fibers and unmyelinated C fibers. A 30-gauge needle, in the absence of a pressure-sensitive device, can be used for pinprick testing, with care not to cause injury to the skin or mucosa, and an all-or-none response may be recorded. For thermal discrimination, there are specialized Minnesota thermal discs or simpler options such as ice or hot water on a cotton swab. Suprathreshold thermal testing has been shown to be valuable in the assessment of iatrogenic injuries to the IAN and LN.[183] Normal responses at Level C testing imply a moderate impairment (Sunderland third-degree injury), whereas abnormal findings may be consistent with either severe impairment with an increased thermal threshold or a decreased nociceptive response (Sunderland fourth-degree injury) or lack of response to pinprick or temperature with complete anesthesia (Sunderland fifth-degree injury).[117]

Pain as a result of nerve injury can be assessed with a simple visual analogue scale or with a more complex McGill pain questionnaire. This can also be used for evaluation of altered sensation and is a useful tool for continuous monitoring of progress. Direct or indirect injury to the LN may cause taste alteration that can be a significant component of the patient's subjective complaints. Taste requires special testing that may involve the entire mouth or be localized; however, it is generally difficult to assess taste alterations, and there is poor correlation between degree of injury, alteration in taste, and response to surgical intervention.[117,184-187] Taste can be evaluated with 5% saccharose (sweet), 5% saline (salt), 5% citric acid (sour), and 0.5% quinine hydrochloride (bitter).[186]

Indications for Microneurosurgery

Careful patient assessment and collection of information from neurosensory testing are crucial in the decision-making process for treatment recommendations and the need for



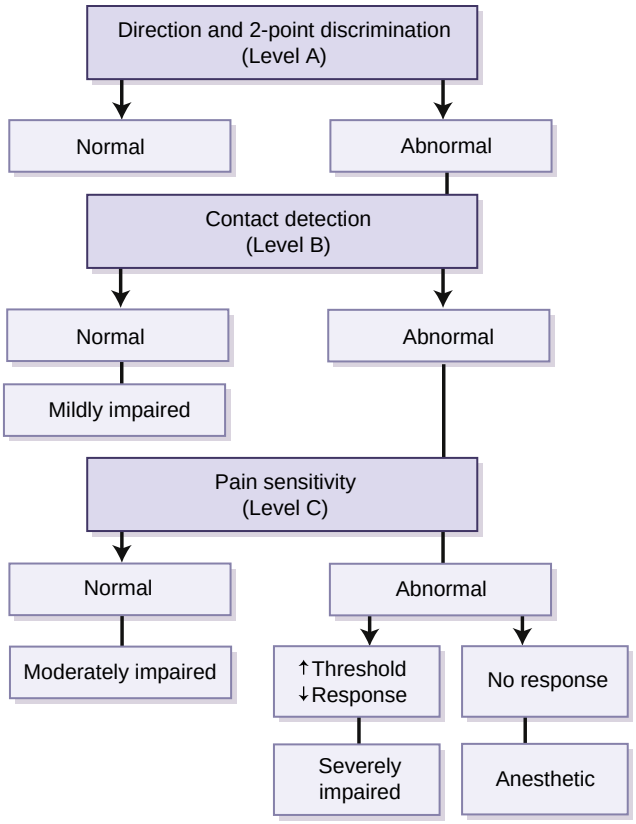
• **Figure 5-30** Facial photographs with the areas of involvement marked are useful for monitoring progression. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

surgical innervation (Table 5-4). With the exception of an observed nerve transection that requires immediate surgical repair, successful treatment of all other injuries requires a balance of timing to allow for potential spontaneous recovery without delaying timely microsurgical intervention. The complex events surrounding nerve injury with degeneration and regeneration distally, proximally, and centrally make timing of intervention critical when it is indicated.[188-191]

Clinical neurosensory testing, along with subjective findings, should guide and dictate appropriate treatment. When improvement is documented during periodic nerve testing, surgery is not yet indicated. Microneurosurgery is also not indicated in cases of central neuropathic pain, or most cases of dysesthesia or unpleasant sensations, and consideration should be given to pharmacologic management of these difficult clinical scenarios. If persistent paresthesia is documented in subsequent visits, then referral to a surgeon with expertise in microneurosurgery is prudent. Although several timing guidelines regarding surgical intervention exist, the scientific evidence to support them is limited.[192] It is generally accepted that prolonged delay may decrease the success of microneurosurgical repair. Regardless of the exact timing, indications for microneurosurgery include a witnessed nerve transection, no improvement of significant hypoesthesia (more than 50% compared to control site), the presence of a foreign body, neuroma formation, progressive worsening of hypoesthesia or dysesthesia, and intolerable subjective hypoesthesia.[193] Intervention for LN paresthesia should be considered earlier (1 to 3 months post injury) than for the IAN (3 to 6 months post injury), because the inferior alveolar canal provides a conduit to spontaneous nerve regeneration, whereas the LN lies in soft tissue. This may explain why IAN injuries have a higher rate of spontaneous recovery than LN injuries (Box 5-3). Some studies have indicated that no surgical intervention should be considered longer than 1 year post injury, because distal end organ neurotization is less likely, although others suggest that timing is less important and improvement can be achieved when microneurosurgery is performed after 12 months.[117,193]

Microneurosurgery for Trigeminal Nerve Injuries

Microneurosurgical procedures are best performed in the operating room under loop magnification or with use of an



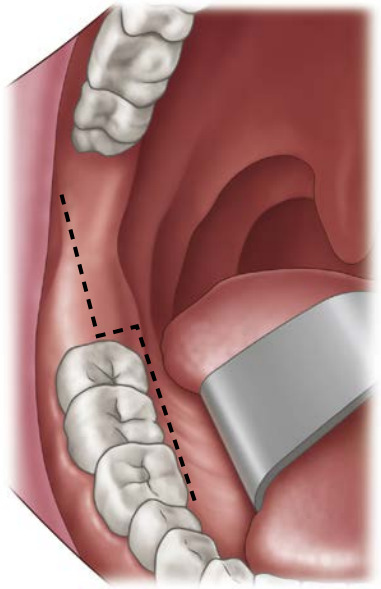
• **Figure 5-31** Clinical neurosensory testing algorithm. Level A testing (brush stroke direction and two-point discrimination) is done first, and if normal, the exam is normal (Sunderland 1st-degree injury). If Level A testing is abnormal, Level B testing with contact detection is performed, and if normal, the exam is mild impairment (Sunderland 2nd degree injury). If abnormal, Level C testing (pinprick and thermal discrimination) is done, and if normal, the exam is moderate impairment (Sunderland 3rd degree). If Level C is abnormal, then the patient is either severely impaired (Sunderland 4th degree) or, with no response to testing, is considered anesthetic (Sunderland 5th degree). (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

TABLE 5-4 Indications of and Contraindications for Microneurosurgery

Indications
Complete anesthesia
Less than 50% residual sensation (Sunderland III, IV, V)
No improvement within 3 months after injury
Observed nerve transection
Early dysesthesia (neuroma formation)
Intolerable subjective paresthesia
Contraindications
Continuing improvement in sensation
Late dysesthesia (especially IAN)
Central neuropathic pain
Complex regional pain syndrome
Trigeminal neuralgia
Atypical facial pain
Anesthesia dolorosa

• BOX 5-3 Recommended Time Frame for Microneurosurgery, When Indicated

Lingual nerve: 1-3 months after injury
Inferior alveolar nerve: 3-6 months after injury



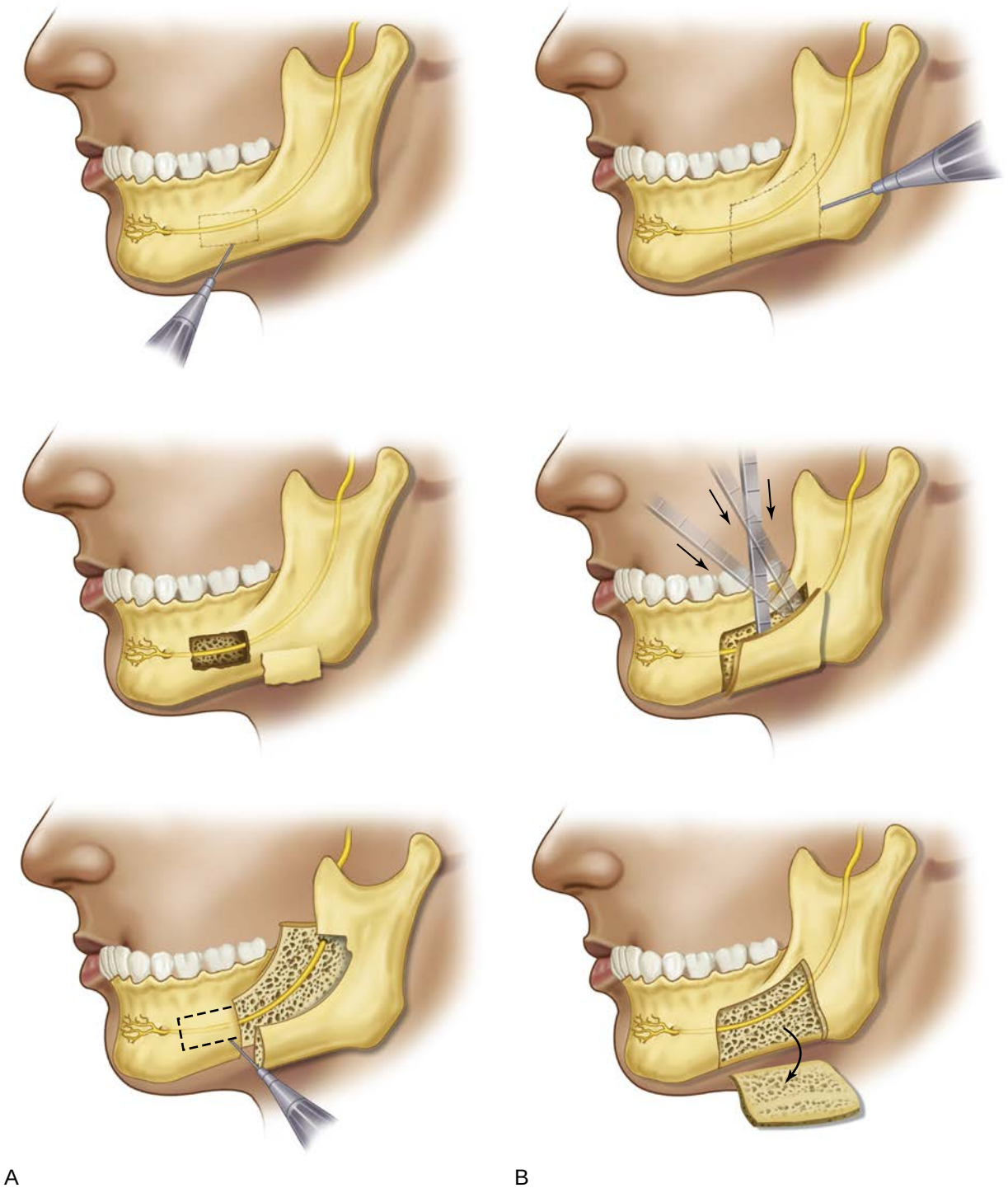
• **Figure 5-32** Diagram showing surgical access for lingual nerve repair using a lingual gingival sulcus approach with posterolateral extension. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

operative microscope. Surgical exposure to assess the IAN, LN, MN, and ION can be easily performed via intraoral approaches, and in these cases surgical loop magnification maybe more practical than a microscope. There is a clear esthetic benefit from intraoral approaches, but these may be more challenging based on the site of the injury.[117] The more proximal the injury, the more challenging the access is; for example, a LN injury at the third molar region is more challenging to repair than an IAN in the mental foramen area. The individual patient anatomy, surgeon experience, mechanism of injury, and location of the injury are further considerations when deciding the most appropriate surgical approach.

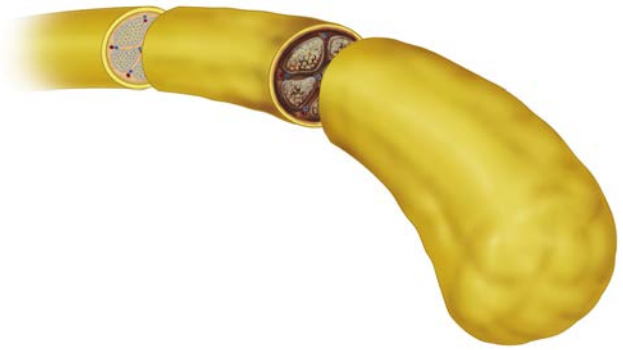
The LN is approached intraorally via a paralingual or lingual gingival sulcus incision (Figure 5-32). The paralingual incision allows for small incision and direct visualization of the nerve, but it may be more challenging to identify the nerve stumps after transection because of retraction into the soft tissues. The latter approach involves a longer incision with anterior and posterior releases, but there is less risk of retraction of the nerve endings during dissection.[194] For the IAN (and MN), a vestibular incision with identification of the mental nerve and lateral decortication to expose a portion of the IAN is usually adequate to mobilize the mental nerve for repair. In cases of restricted mouth opening, an extraoral approach may be required. Once the mandible is accessed, the IAN is approached via lateral decortication

techniques (Figure 5-33).[195] Access to the ION can be accomplished transorally via a maxillary vestibular incision at the time of maxillary or zygomaticomaxillary complex fracture repair. Alternatively, a lower lid, transconjunctival, or subciliary incision may be more suitable and an osteotomy around the infraorbital canal may be required for nerve isolation.[76,194]

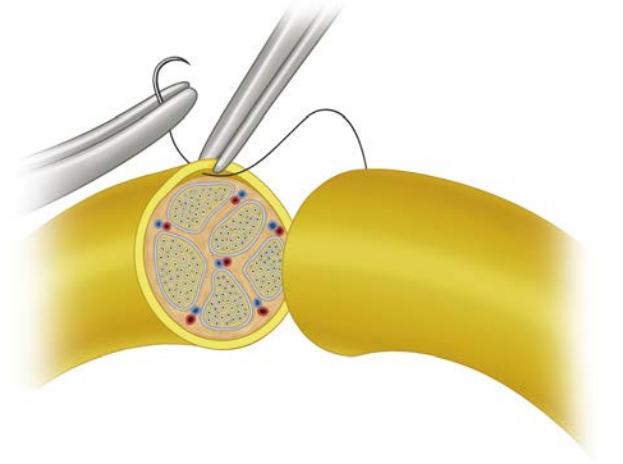
Dissection of the nerve from the surrounding tissue bed for inspection and further manipulation is the next step and is termed external neurolysis (EN). For the LN this may involve microdissection of the neurovascular bundle from surrounding scar tissue, whereas for the IAN it may imply the need for decortication of the IAC and lateralization of the IAN. Separation of the nerve from scar tissue that may be responsible for



• **Figure 5-33** **A,** Diagram of techniques for inferior alveolar nerve access, including isolated decortication, or a sagittal split osteotomy, with extension to the mental foramen if necessary. **B,** Diagram of technique described by Miloro (see Ref. 195) for wide access to the inferior alveolar nerve via a complete lateral decortication window that may be replaced to protect the nerve repair site.



• **Figure 5-34** Diagram showing preparation of the nerve stump with serial 1.0 mm resections to remove scar tissue (neuroma) and ensure that normal healthy neural tissue is encountered prior to the neurorrhaphy procedure. Failure to debride the nerve stumps adequately will result in failure of neurosensory recovery. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

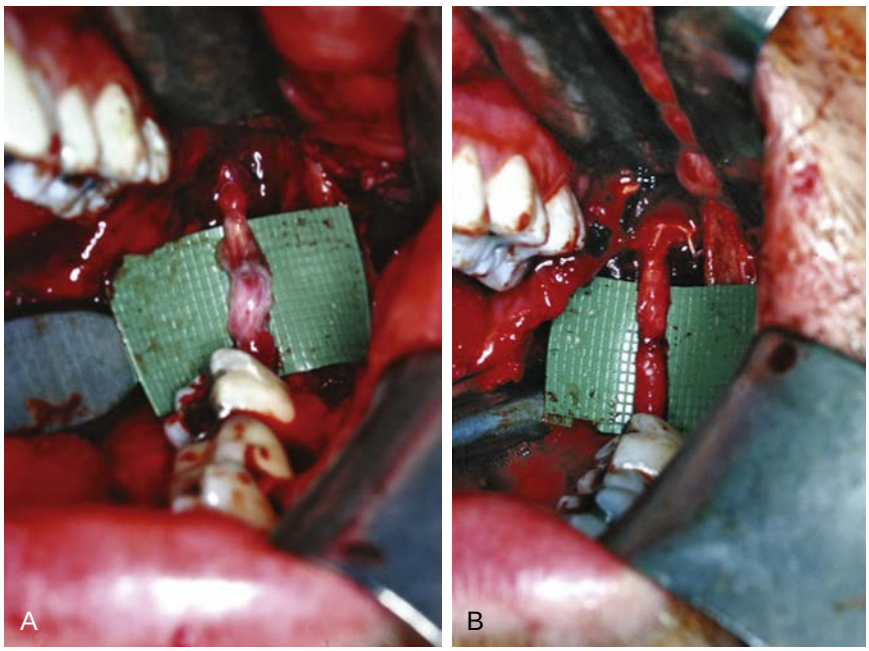


• **Figure 5-35** Diagram showing direct neurorrhaphy with epineurial sutures. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

restriction or compression leading to a conduction block and prevention of spontaneous recovery may be all that is required. In cases of short duration of symptoms (less than 6 months) or if nerve compression from scarring is less than 25% of the nerve diameter without neuroma formation, EN may provide definitive treatment.[117,193,196,197] EN is performed under loop magnification; once completed, an examination of the nerve is performed and the need for additional intervention is determined. If foreign material or bone or tooth fragments are identified, they should be removed at this stage.

Several injuries may cause intraneural scarring that results[198] of the sparse amount of epineurium in the trigeminal nerve branches, this may lead to further fibrosis and iatrogenic scarring. Caution should be exercised when making the decision to proceed with IN, since it may cause worsening of the condition.[117] Several types of IN are described based on the exact tissue manipulation performed: epifascicular epineurotomy, epifascicular epineurectomy, and intrafascicular epineurectomy that are of progressive complexity, involve tissue removal, and are of questionable benefit for the trigeminal nerve system.[117,192,193]

In cases of neuroma formation, excision followed by restoration of nerve continuity is required. Careful examination of the nerve stumps to be anastomosed is crucial so that healthy nerve tissues are repaired, and scarred and necrotic nerve stumps are completely removed at 1.0-mm resection increments until normal tissue is encountered (Figure 5-34). For a direct neurorrhaphy, epineurial suturing with three or four 7.0 or 8.0 nonreactive sutures (nylon) is adequate for the trigeminal nerve (Figure 5-35).[199] Coaptation is the alignment of individual fascicles during direct repair, and this is difficult if not impossible with a polyfascicular nerve such as the trigeminal.[200,201] Nerve mobilization for tension-free closure is critical and may require dissection in proximal and distal directions (Figure 5-36) or,

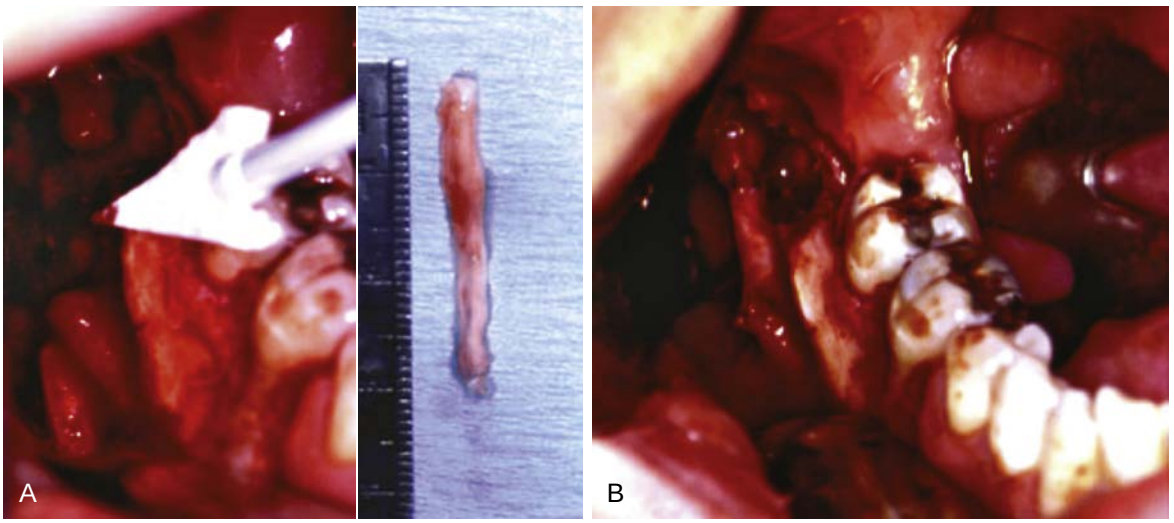


• **Figure 5-36** Clinical example of a left lingual nerve neuroma **(A),** and following resection of the neuroma and direct repair with epineurial sutures **(B)**. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

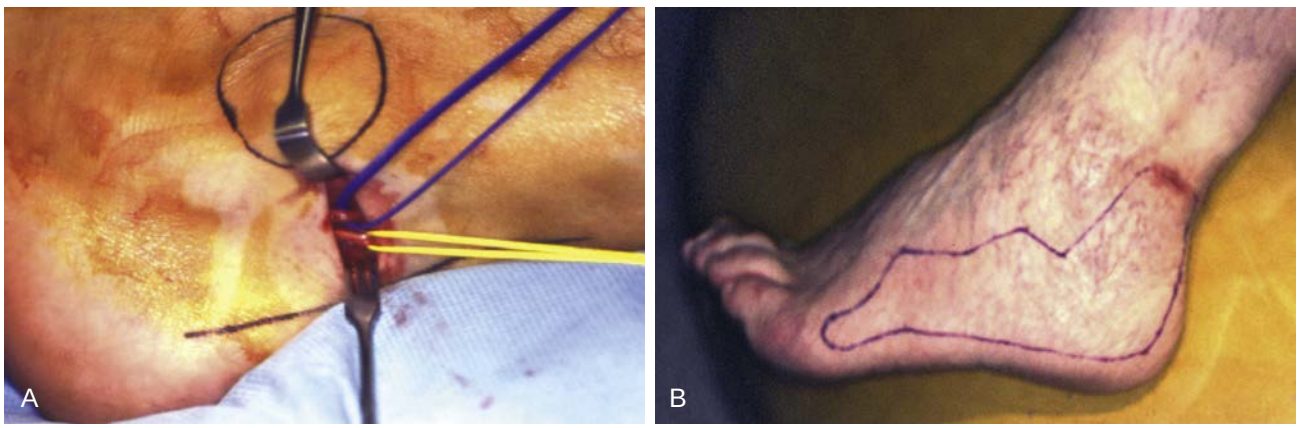
additionally, in the case of the IAN, sacrifice of the terminal incisive branch to allow further release and mobilization of the IAN.[200]

Cases of nerve injury that result in nerve continuity defects or prevent primary tension-free repair will require indirect repair with interpositional grafting (Figure 5-37). Traumatic avulsive injuries, pathologic conditions involving the nerve, or extensive neuroma resection at the time of nerve repair are common reasons for these continuity defects of the nerve. When nerve mobilization is not adequate to allow tension-free primary repair, then interpositional grafts may be required. The donor site selection for a nerve graft depends on several factors that include diameter and fascicular pattern, correlation of neural function, and donor site morbidity. Usual donor sites for trigeminal nerve repair include the greater auricular and sural nerves because of ease of access and relatively low donor site morbidity with relatively tolerable anesthetic areas.[79,117,193,194,201] In fact, the sural nerve may be the preferred autogenous nerve graft because it matches most closely with the diameter and fascicular pattern of the trigeminal nerve system and it results in an area of minor donor site paresthesia (Figure 5-38).[202] The greater auricular nerve diameter is approximately 50% of the trigeminal nerve diameter, and therefore its usefulness may be limited to cable grafting (multiple grafts) for the trigeminal nerve. Additionally, the harvest would result in a facial scar as well as an area of deficit in the facial region that is less tolerable to patients than the donor site deficit of the lateral foot that results from sural nerve harvest.

Alternatively, several other materials may be used for indirect neurorrhaphy via entubulation techniques, including alloplastic tubes (Silastic, expanded polytetrafluoroethylene,



• **Figure 5-37** **A,** Clinical example of a discontinuity of the right inferior alveolar nerve following resection of a neuroma due to a third molar injury (*arrowhead Weck-Cel sponge*) (*left*). Autogenous sural nerve graft, 3 cm (*right*). **B,** Indirect graft repair of the right inferior alveolar nerve continuity defect using the autogenous sural nerve graft with epineurial sutures. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)



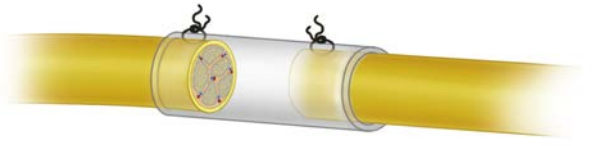
• **Figure 5-38** **A,** Clinical example of sural nerve harvest site posterior and superior to the lateral malleolus with identification of the lesser saphenous vein (anterior), and the sural nerve (posterior). **B,** Donor site deficit mapped with marker 1 week following sural nerve harvest. This area of paresthesia decreases significantly over time. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

polyester, polyglycolic acid polymer), vein grafts,[203] and allogeneic nerve grafts (Figure 5-39). The use of alloplastic tubes is attractive because it eliminates donor site morbidity. Unfortunately, there has been no consistency in the reported clinical outcomes with these entubulation techniques, and therefore, this is not a standard technique for management of trigeminal nerve injuries with continuity defects. Vein grafting, on the other hand, has been successfully used for this purpose with results comparable to primary repairs in small defects of less than 5 mm.[204-209] Following surgical intervention, periodic follow-up with repeat NST to evaluate response to treatment is required, and sensory reeducation exercises may be used to augment spontaneous neurosensory recovery.

Outcomes of Trigeminal Nerve Injury and Surgical Intervention

Injuries to the peripheral branches of the trigeminal nerve may be associated with impairment of speech, taste, or mastication and impact on quality of life. Long-term effects of these injuries are not very well documented in the literature. In a recent effort to elucidate this subject, Pogrel and colleagues attempted to obtain information from patients several years following nerve injury via a telephone survey. Despite the poor 20% response rate, patients did report long-term difficulties with jobs, relationships, depression issues, speech, and eating problems. It was reported, however, that patients noted general improvement over time, with 8% describing complete recovery. It is unclear from this study if this represents true neurosensory recovery or adaptation to the altered status of the nerve, yet the authors were in support of surgical intervention when indicated.[188]

Based on the literature in this area, the success of microneurosurgical reconstruction of trigeminal nerve injuries could be estimated to be between 30% and 50%, for all degrees of injury and types of reconstruction, with higher success rates achieved when primary repair is performed.[117,210-212] However, gap repair with an autogenous sural nerve graft may provide a better outcome because the graft itself provides a rich source of Schwann cells and neurotropic and neurotrophic factors to an area of injury that can assist in the degeneration and regeneration process of neural recovery.[202] Factors contributing to the variability of reported success rates relate to inconsistencies in documentation and standardization as well as heterogeneity with regard to etiology of the injury, specific medical or surgical intervention, experience of the surgeon, timing of intervention, length of follow-up, neurosensory testing methods used, method of reporting results, and criteria used to evaluate and define a successful outcome. In a retrospective review of outcomes in 51 patients who underwent microneurosurgical intervention, the following observations were reported: (1) repairs performed less than 10 weeks (early repairs) from the injury appeared to do better than late ones; (2) improved sensation for both IAN and LN can be achieved with microneurosurgery in select cases; and (3) carefully selected patients do benefit from trigeminal nerve microneurosurgery.[210] There is a consensus that a need exists for more data in this area in the form of a prospective, randomized, multicenter clinical trial with standardization in diagnosis and management of trigeminal nerve injuries.



• **Figure 5-39** Diagram showing the principle of entubulation using a conduit to guide neural regeneration in cases of nerve discontinuity. (From Fonseca RJ, Walker RV, Barber HD, et al: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

Facial Nerve Anatomy

Macroanatomy

The facial nerve contains approximately 10,000 fibers, of which 7000 are myelinated fibers innervating the facial musculature, with the remaining 3000 fibers providing sensation, taste, and parasympathetic secretomotor functions to the submandibular, sublingual, and lacrimal glands. The facial nerve is described as having three distinct segments: intracranial, intratemporal, and extratemporal. The intracranial segment contains both motor and sensory fibers. The motor fibers innervate the muscles of facial expression, the stapedius muscle, and the posterior belly of the digastric muscle. The sensory fibers include special sensory, preganglionic parasympathetic fibers, and special afferent sensory fibers. These two components join before becoming the intratemporal segment to form the common facial nerve. Within the caudal pons, motor fibers supplying the lower face cross to the contralateral motor nucleus. The majority of fibers supplying the musculature of the upper face also cross over to the contralateral motor nucleus; however, some fibers do not cross and continue to travel in the ipsilateral motor nucleus. The incomplete crossover of the fibers innervating the upper face results in forehead sparing, often indicative of a central etiology to facial paralysis. The nervus intermedius will provide sensation to the posterior concha and external auditory canal (EAC), taste sensation to the anterior two thirds of the tongue, and secretomotor innervation of the minor salivary, submandibular, sublingual, and lacrimal glands. The intracranial segment of the facial nerve is approximately 24 mm in length.[213,214]

Intracranial Segment

The intratemporal segment begins at the porus acusticus of the IAC and is divided into four portions as it travels to exit the stylomastoid foramen and become the extracranial portion. The first of four intratemporal segments is the meatal portion. This segment is 8 to 10 mm in length and extends from the porus acusticus of the IAC to the meatal foramen of the IAC.[213,214] Traveling in the anterior superior portion of

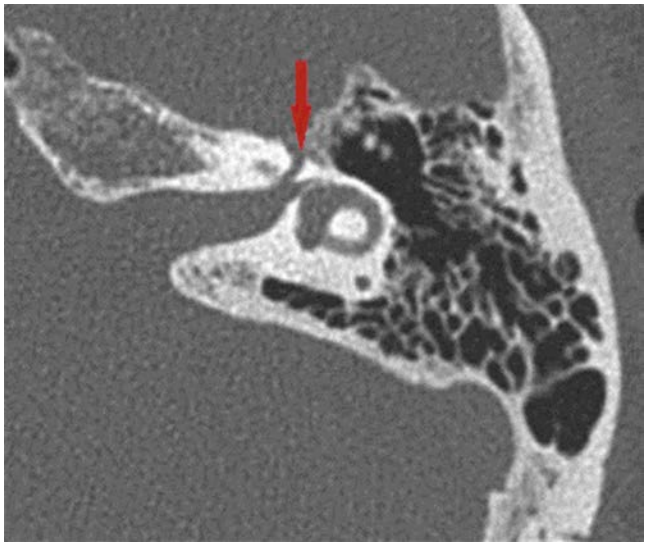
the IAC, the facial nerve is separated from the cochlear nerve anterior inferiorly by a horizontal segment of bone and the superior vestibular nerve posterior superiorly by a vertical segment of bone; it passes by the posterior inferiorly located inferior vestibular nerve. Running within the IAC is the anterior inferior cerebellar artery. A branch of this artery, the labyrinthine artery, supplies blood to this region of the facial nerve.[215]

Intratemporal Segment

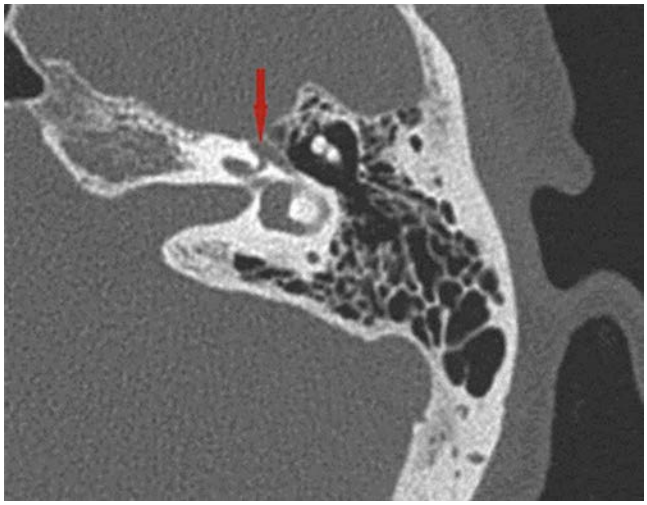
The bony canal of the facial nerve begins the second segment of the intratemporal portion, the labyrinthine segment, which is the shortest segment (3-5 mm) and extends from the fundus to the geniculate ganglion. It is within this portion that the facial never runs through the narrowest portion of the IAC (0.68 mm) (Figure 5-40).[213] It is hypothesized this narrow canal is the culprit in facial nerve compression due to Bell's palsy and other causes of facial nerve edema. As the labyrinthine segment ends at the geniculate ganglion the facial nerve gives off its first branch, the greater superficial petrosal nerve (GSPN) (Figure 5-41). The GSPN carries preganglionic parasympathetic fibers from the superior salivatory nucleus to the pterygopalatine ganglion, where it synapses and postganglionic fibers join the maxillary branch of the trigeminal nerve to innervate the lacrimal gland and minor salivary glands of the nose and palate.[215]

The third segment of the intratemporal portion of the facial nerve, the tympanic segment, extends from the geniculate ganglion to the second genu (Figure 5-42). It begins with a 75-degree bend at the geniculate ganglion (first genu). This 8- to 11-mm segment passes superior and lateral to the oval window, inferior to the lateral semicircular canal, and then makes a second turn at a 95- to 125-degree angle (second genu) to become the mastoid segment. The tympanic segment has the highest rate of bony dehiscence (40% to 75%).[215,216]

The fourth and final segment of the intratemporal portion of the facial nerve, the mastoid segment, exits the temporal bone at the stylomastoid foramen approximately 10 to 14 mm from its origin at the second genu (Figure 5-43).[213,215] It gives off two branches, chorda tympani and the nerve to the stapedius muscle. Chorda tympani passes



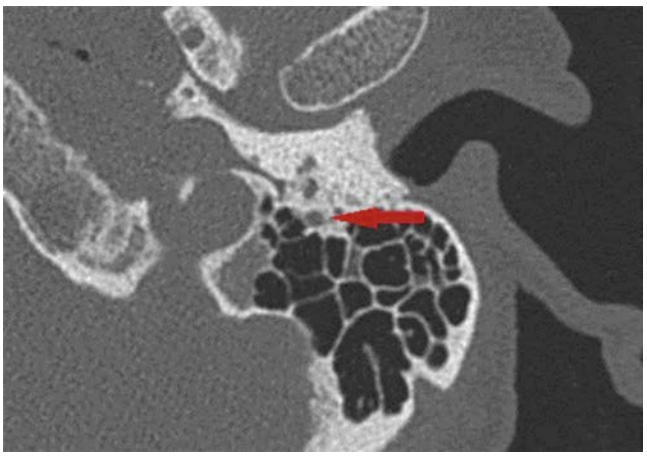
• **Figure 5-40** Labyrinthine segment (fallopian canal) of the intratemporal facial nerve segment (*red arrow*). Narrowest point in the course of the facial nerve canal.



• **Figure 5-41** Geniculate ganglion (*red arrow*).



• **Figure 5-42** Tympanic segment of the intratemporal facial nerve segment (*red arrow*).



• **Figure 5-43** Mastoid segment of the intratemporal facial nerve segment (*red arrow*).

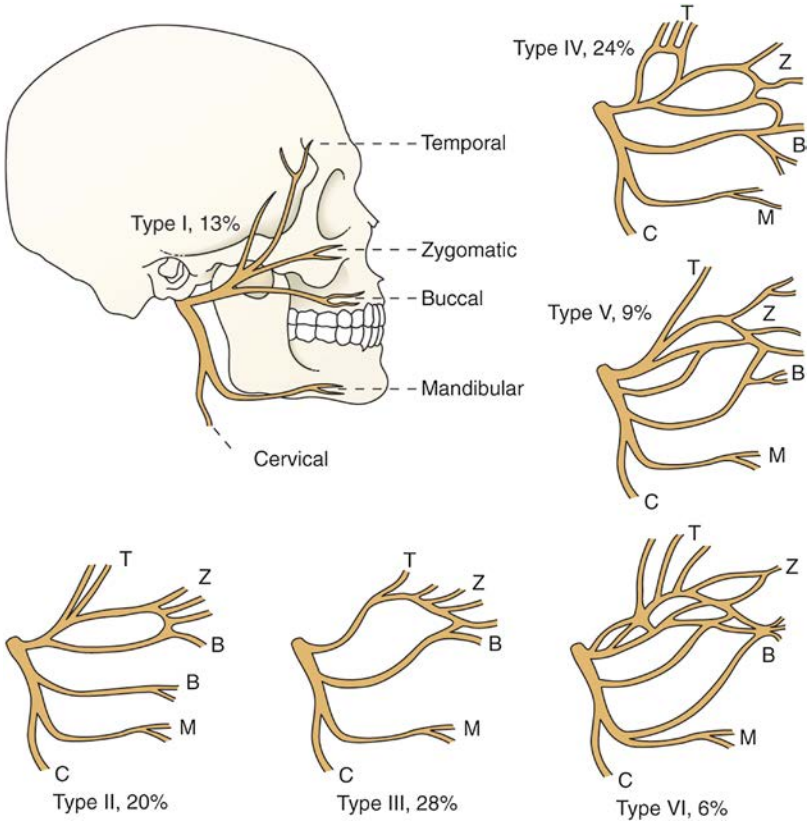
through the petrotympanic fissure and into the infratemporal fossa, where it joins the lingual branch of the trigeminal nerve before reaching the submandibular ganglion. Postganglionic fibers innervate the submandibular and sublingual glands as well as providing taste sensation to the anterior two thirds of the tongue.

Extratemporal Segment

The extratemporal segment of the facial nerve begins at the stylomastoid foramen, which is located posterolateral to the styloid process and anteromedial to the mastoid process. Before entering the substance of the parotid gland, the posterior auricular nerve and branches to the posterior belly of the digastric and stylohyoid muscle divide from the facial nerve. The posterior auricular branch divides into an auricular and occipital branch innervating the external auricular and occipital belly of the occipitofrontalis muscle, respectively. The facial nerve then travels between the digastric and stylohyoid muscles, superficial to the styloid process, and enters the substance of the parotid gland, dividing the parotid into a superficial and deep lobe. At an anatomic point located approximately 1.3 cm from the stylomastoid foramen, the pes anserinus (Latin: goose foot), the facial nerve divides into its two main branches, the temporofacial and cervicofacial.[217]

Various surgical landmarks are available to assist in locating the main trunk of the facial nerve. Prior to locating the nerve, exposure of several important anatomic landmarks should be completed. This includes exposure of the mastoid process, sternocleidomastoid, posterior belly of the digastric muscle, tympanic bone, and EAC. The main trunk of the facial nerve is located midway between the cartilaginous tragal pointer of the EAC and the posterior belly of the digastric muscle. It lies approximately 1.0 to 1.5 cm deep and slightly anterior and inferior to the tip of the external canal cartilage (tragal pointer). Additionally, the facial nerve is 1.0 cm deep to the medial attachment of the posterior belly of the digastric muscle to the mastoid. The tympanomastoid suture line is located approximately 6 to 8 mm lateral to the stylomastoid foramen. Additionally, as dissection proceeds, a branch from the occipital artery may be encountered. This artery lies in close proximity to the facial nerve trunk, and further dissection should be made with caution.[218,219] If the main trunk of the facial nerve cannot be located or its path traced proximally, retrograde dissection of one of the branches of the facial nerve may be necessary.

The temporofacial and cervicofacial trunks then divide into the final five branches of the facial nerve (temporal, zygomatic, buccal, marginal mandibular, and cervical) with various reported branching patterns and no predominant pattern (Figure 5-44).[220] The temporofacial trunk always gives rise to the temporal and zygomatic branches, whereas the cervicofacial trunk always gives rise to the marginal mandibular and cervical branches. The variation in branching patterns is due to the origin of the buccal branch as well as the presence of cross innervation. Cross innervation between the zygomatic and buccal branches is noted in



• **Figure 5-44** Variations in the branching pattern of the facial nerve. (From Townsend C, Beauchamp RD, Evers BM, et al: *Sabiston textbook of surgery*, ed 19, St Louis, 2013, Saunders.)

more than 70% of cases, whereas cross innervation between the temporal or marginal mandibular nerve to other facial nerve branches occurs in fewer than 15% of cases.[221]

The temporal branch of the facial nerve is described as crossing the zygomatic arch within or deep to the temporoparietal fascia approximately 0.8 to 3.5 cm anterior to the EAC and most commonly demonstrating two branches.[222] The course of the temporal branch has been noted to fall between two lines: a superior line connecting the upper tragus to the highest forehead crease, and an inferior line connecting the lower tragus to the lowest forehead crease.[223] In an axial high-resolution MRI study, Miloro and co-workers determined the mean distance from the most anterior aspect of the external acoustic meatus to the posterior ramus of the temporal branch was 2.12 ± 0.21 cm.[224] It innervates the frontalis, orbicularis oculi, corrugator supercilii and the anterior and superior auricular muscles. The temporal branch of the facial nerve also acts as the efferent limb of the corneal reflex.

The zygomatic branch of the facial nerve travels within the parotid gland until its exit approximately 30.71 mm (16.2-45.64 mm) anterior to the tragus and is located a mean vertical distance of 19.29 mm (5.7-28.72 mm) from a line connecting the lateral palpebral commissure and the tragus. It most commonly consists of two branches (69.7%) or three branches (25.8%). The nerve follows a path deep to the zygomaticus major and orbicularis oculi muscle and is located beneath the superficial fascia following its exit from the anterior border of the parotid. It innervates the medial head of the orbital portion of orbicularis oculi muscle, the depressor supercilii muscle, and the oblique head of the corrugator supercilii muscle.[225]

The buccal branch of the facial nerve exits at the anterior border of the parotid, generally noted to be 35 mm (21-53 mm) anterior to the tragus and along the transverse axis of the zygomatic arch, most often as a single branch located inferior and traveling parallel to the parotid duct. When multiple branches are noted exiting the parotid, the most common pattern is to have a branch superior and inferior to the parotid duct, with the superior portion crossing over the duct a variable distance from its emergence. In 100% of specimens, the entire course of the buccal branch of the facial nerve is below a line drawn from the tragus to ala nasi.[226,227] Innervation of the buccinator, levator labii superioris, risorius, levator labii superioris alaeque nasi, levator anguli oris, nasalis, orbicularis oris, depressor septi nasi, and procerus muscles is provided by the buccal branch of the facial nerve. For the majority of the paired facial muscles, innervation is from the deep aspect. The buccinator, levator anguli oris, and mentalis are the exceptions to this pattern.

The marginal mandibular branch of the facial nerve is located within or deep to the superficial layer of deep cervical fascia as it courses anteriorly and innervates the depressor labii inferioris, depressor anguli oris, and mentalis muscles. The location of this nerve in relation to adjacent structures has been extensively studied.[228-230] The marginal mandibular nerve is located above the inferior border of the mandible anterior to the facial artery in 100% of cases. Posterior to the facial artery, it is located above the inferior border in 81% of cases, and in the remaining 19% the marginal mandibular nerve is located up to 1.75 cm below the angle of the mandible with a reported average distance of 1.2 to,1.5 cm below the mandibular angle.[228-230] In addition, the marginal mandibular nerve is located superficial to the facial artery in 100% of cases. Cross innervation with other facial nerves is rare, and therefore injury to the marginal mandibular nerve causes permanent paralysis of innervated structures. The most common branching pattern is two or more with only 28% to 32% demonstrating a single branch-up until arborization near its termination.[228-230]

The cervical branch of the facial nerve innervates the platysma muscle and branches below the angle of the mandible in all cases. It can be reliably located 1 cm below a line connecting the mentum to mastoid about the position of the angle of the mandible.[231]

Microanatomy

The microanatomy of the facial nerve is consistent with that previously described in this chapter for the trigeminal nerve with few exceptions. The facial nerve is considered to be a polyfascicular nerve, although it does not begin to demonstrate true fascicular organization until the geniculate ganglion. Distal to this point, the number of fascicles increases in a proximal to distal fashion. The temporofacial trunk demonstrates on average 13 fascicles (2-29) and the cervicofacial trunk demonstrates an average of 16 fascicles (2-23) with an average fascicle diameter of 300 μm.[232] Within the substance of the parotid gland, the average facial nerve diameter ranges from 0.3 mm to 1.6 mm.[233] Similar to the trigeminal nerve branches, the mean number of fascicles and the cross-sectional area for the facial nerve branches decrease proceeding from proximal to distal nerve.[232]

Chorda tympani most commonly demonstrates a monofascicular pattern before its fusion with the lingual nerve 1 to 2 cm below the base of the skull and just above the lower border of the lateral pterygoid muscle.[78,234] At this point, the lingual nerve has been described as having both a monofascicular and oligofascicular pattern. Shortly after joining the lingual nerve, the fibers of chorda tympani are no longer recognizable as separate entities; the fibers join the lingual nerve fascicles. This explains the lack of gustatory recovery following repair of lingual nerve injuries at the level of the third molar.[78]

Facial Nerve Imaging

The choice of imaging modality in the evaluation of the facial nerve should take into account the location and suspected cause of injury. For suspected intracranial segment pathology or when the location of pathology is unknown, contrast-enhanced MRI is the preferred preliminary imaging. When pathology of the intratemporal segment is suspected, CT with thin cuts through the temporal bone is

indicated along with the addition of MRI, depending on the type of pathology suspected. For evaluation of the extracranial segment of the facial nerve, MRI is again preferred.[215]

Computed Tomography

CT is the preferred imaging modality for pathology of the intratemporal segment of the facial nerve. As mentioned previously, this segment extends from the porus acusticus of the IAC to the stylomastoid foramen and includes four segments: meatal, labyrinthine, tympanic, and mastoid. Dedicated high-resolution CT of the temporal bone with thin cuts (0.6 mm), helical mode acquisition, and contrast when neoplastic or vascular pathology are suspected is the imaging of choice.[235] If a tumor of the facial nerve is suspected, MRI should be obtained in addition to CT, as pathology of the facial nerve within its bony canal can only be inferred based on adjacent bony erosion evident on CT. High-resolution CT of the temporal bone can detect early erosion and destruction of the facial nerve canal in addition to providing important information regarding relationships to normal anatomic landmarks such as the ossicles that are not seen on MRI.[216] This information is crucial to preoperative planning in otologic surgery and leads to a decreased rate of iatrogenic facial nerve trauma.[216]

Magnetic Resonance Imaging

MRI is the preferred imaging modality for suspected neoplastic pathology and for the intracranial and extratemporal segments of the facial nerve. Its superior visualization of the soft tissues can identify perineural spread from parotid malignancy and enlargement of the facial nerve that can be missed with high-resolution temporal bone CT scanning.[214] The normal labyrinthine, cisternal, intracanalicular, and parotid segments of the facial nerve normally do not enhance, whereas the normal facial nerve will faintly enhance in the geniculate ganglion, tympanic, and mastoid segments on gadolinium contrast MRI imaging. Increased enhancement or asymmetric enhancement of these regions should prompt consideration of inflammatory or neoplastic processes. Once the facial nerve exits the stylomastoid foramen, it is best visualized with axial high-resolution T1-weighted images using a microscopic coil.[214]

Ultrasound

Ultrasound is rarely used in routine imaging of the facial nerve. However, there are several studies that have used ultrasound to evaluate the normal size of the facial nerve or prognosis of Bell's palsy based on nerve diameter.[233,236] In a prospective controlled trial, Lo and colleagues noted that a normal ultrasound diameter of the facial nerve on the affected side in Bell's palsy had a positive predictive value of 100% for recovery of facial nerve function, whereas an abnormal value had a negative predictive value of 77% for House-Brackmann Grade II or worse facial nerve function at 3 months.[236]

Classification of Facial Nerve Injury

land classification of nerve injury. In addition, the axonal and cellular response to injury is consistent between these two cranial nerves. Please see the section on classification of nerve injuries. In regard to facial nerve injury, an additional classification system, the House-Brackmann facial nerve function grading scale, is used (Table 5-5).[237] This scale is the official scale of the Facial Nerve Disorders Committee of the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS. It consists of grades I through VI, with VI representing total paralysis. In patients with isolated injury to a single branch, the House-Brackmann scale is of limited use, and therefore more subjective notation of injury is utilized.

Mechanisms of Injury to the Facial Nerve

Bell's Palsy

Named for the Scottish anatomist who first described it, Charles Bell, facial paralysis due to Bell's palsy is an uncommon condition with an incidence ranging from 11.5 to 53.3 per 100,000 person years.[238] The condition can be found

TABLE 5-5 House-Brackmann Facial Nerve Grading Scale

Grade	Description
I	Normal facial function
II	Mild Dysfunction—Slight weakness, slight synkinesis on close inspection. Moderate to good forehead function. Complete eye closure with minimal effort. Slight smile asymmetry with maximum effort. Normal symmetry and tone at rest.
III	Moderate Dysfunction—Obvious but not disfiguring difference between sides. Noticeable but not severe synkinesis. Slight to moderate forehead movement. Complete eye closure with effort. Strong but asymmetric smile with maximum effort. Normal symmetry and tone at rest.
IV	Moderately Severe Dysfunction—Obvious weakness and/or disfiguring asymmetry. Severe synkinesis. No forehead movement. Incomplete eye closure. Asymmetric smile with maximum effort. Normal symmetry and tone at rest.
V	Severe Dysfunction—Barely perceptible motion. Synkinesis usually absent. No forehead movement. Incomplete eye closure. Slight movement at the corner of mouth. Asymmetry at rest.
VI	Total Paralysis—No movement.

From House JW, Brackmann DE: Facial nerve grading system, *Otolaryngol Head Neck Surg* 93:146-147, 1985.

There is an increased risk in pregnancy and in patients with diabetes mellitus, hypertension, obesity, and prior upper respiratory infection (URI), with 60% reporting recent URI.[238] Although a viral etiology is suspected, the diagnosis of Bell's palsy is one of exclusion. Other causes of facial paralysis should be excluded through careful history and physical examination (Table 5-6). Imaging and laboratory testing are not routinely recommended in the evaluation of patients with new-onset Bell's palsy.[238] Despite being the most common cause of facial paralysis, the true etiology of Bell's palsy is not yet fully understood. Paralysis is thought to occur due to facial nerve edema and possible resulting compression of the vascular supply to the nerve as it travels through its bony canal, specifically within the labyrinthine segment.

Bell's palsy is defined by acute, unilateral facial nerve paresis or paralysis with progression to maximum severity [238] ity weakness, and signs of ear or cerebellopontine angle disease, such as hearing loss, tinnitus, or vertigo, will be absent. Patients may complain of concurrent or prodromal ipsilateral pain about the face or ear as well as exposure eye keratopathy, xerostomia, taste disturbance, and hyperacusis.

Treatment of Bell's palsy is controversial.[239,240] Clinical practice guidelines from the AAO-HNS recommend treatment of all patients with suspected Bell's palsy with oral steroids within 72 hours of symptom onset.[26] Multiple studies including randomized, double-blind, placebo-controlled multicenter trials have been published.[241-243] The findings of these studies are in accordance with the clinical practice guidelines previously mentioned. Regardless of symptom severity, all patients benefited from early initiation of oral steroids. The evidence from these studies does not support the routine use of antivirals alone or in combination with prednisone; however, the AAO-HNS clinical practice guidelines leave the addition of oral antiviral therapy as an option due to low risk and weak data unable to exclude a small benefit.[238] Surgical decompression remains controversial, and no recommendation is provided by the AAO-HNS because of low-quality evidence and a small subset of patients with specific indications who may derive significant benefits from decompression surgery.[238,244-246] In a multicenter prospective trial, Gantz and associates demonstrated a benefit to early (within 2 weeks of symptom onset) surgical decompression of the facial nerve in a subset of patients demonstrated by electroneurography and electromyography to have a higher risk of poor return of facial function.[245] A Cochrane systematic review of available evidence published in 2013 concluded that there is only very low-quality evidence, and this is insufficient to decide whether surgical intervention is beneficial or harmful. However, they did state that further research is unlikely to be performed because of spontaneous recovery in most cases.[246] Regardless of treatment approach, patients should be referred to a facial nerve specialist if at any point during recovery they develop new or worsening neurologic findings, ocular symptoms, or have incomplete facial recovery at 3 months from onset of initial symptoms.[238]

Prognosis is best in those patients with incomplete paralysis; 94% will recover completely. Most patients will show some recovery without any intervention within 2 to 3 weeks of symptom onset and continue to improve until complete recovery at 3 to 4 months. However, without treatment, up to 30% will have incomplete recovery. If improvement is noted within 2 weeks, prognosis for complete recovery is best.[239,240] Of those who do not recover completely, sequelae are slight to mild in a large majority, with only 4% being described as having severe sequelae.[240] Possible sequelae include ageusia, facial spasm, facial pain, and corneal infection/abrasion. Additionally, patients can develop synkinesis, an involuntary muscular movement occurring simultaneously with voluntary movements. An example would be a patient who has movement of the corner of the mouth when attempting to close the ipsilateral eye.

TABLE 5-6 Etiology of Facial Paralysis

Congenital	Möbius syndrome, hemifacial microsomia, Goldenhar syndrome
Birth-Related	Trauma during delivery
Neurologic	Guillain-Barré, ischemic/hemorrhagic stroke, hypertension
Bell's Palsy	Herpes simplex virus, autoimmune reaction, ischemic neuropathy, microcirculatory failure of vasa nervorum, entrapment, idiopathic
Neoplasm	Central, parotid, and acoustic tumors
Hematologic	Leukemia, hemophilia
Infection	Otitis media, Lyme disease, Ramsay Hunt, herpes simplex, Epstein-Barr virus, mycoplasma, mastoiditis
Trauma	Temporal bone fracture, blunt or penetrating trauma to the extratemporal segment
Iatrogenic	Facial surgery, otologic surgery, brain surgery

Trauma

Traumatic injury to the facial nerve can occur at any point along its course from the brainstem to the muscles of facial expression or other target organs. Blunt and penetrating trauma can directly injure the facial nerve or cause injury to adjacent structures resulting in nerve transection, edema, vascular compromise, and ischemia. The second most common cause of facial nerve injury, traumatic injuries represent 15% of all cases of facial nerve paralysis, with the most common traumatic cause being temporal bone fracture. In total, 5% of trauma patients will sustain a temporal bone

fracture. There are two subtypes of temporal bone fracture, longitudinal and transverse, although in reality many fractures are a combination of the two. Longitudinal fractures are the most common, accounting for 70% to 90% of temporal bone fractures, which is also the path of least resistance to fracture propagation in the temporal bone.[247,248] It is generally caused by a direct blow to the temporoparietal region. Fortunately, longitudinal fractures are associated with facial nerve injury in only 10% to 20% of cases, with 94% returning to normal function. Transverse fractures are described as extending perpendicular to the long axis of the petrous bone, commonly from the jugular foramen or foramen magnum to the middle cranial fossa, and involving the bony labyrinth and/or geniculate ganglion. Because of labyrinth involvement, sensorineural hearing loss and vertigo are common. These fractures are associated with high-impact frontal or occipital trauma, and up to 50% of patients will have a facial nerve injury that does not return to normal function.[247,248] Prognosis is improved for patients who present with delayed-onset facial paralysis compared to those presenting with immediate-onset paralysis.

Physical exam should include a thorough head and neck exam, including otoscopy and tuning fork testing. Laboratory testing should include a complete blood count, coagulation studies, and for beta-2 transferrin testing. In addition to imaging with high-resolution dedicated CT of the temporal bones, facial nerve conduction testing with topographic and electrodiagnostic methods is advised. The specifics of these tests are discussed later.

Treatment of facial nerve injury due to temporal bone fracture is guided by clinical and facial nerve conduction examination. Surgical nerve decompression should be performed as soon as possible (within 1 month of injury) in patients with neural degeneration of the facial nerve that is >90% by facial nerve electrogram.[248-250] Complications of facial nerve decompression include dural tears, conductive and sensorineural hearing loss, loss of vestibular function, persistent CSF leak, meningitis, and injury to the anterior inferior cerebellar artery or its branches. The technique of nerve decompression and a complete discussion of its use is beyond the scope of this text; however, further information can be obtained from multiple sources.[248-253]

Facial nerve injury due to penetrating trauma and involving the extratemporal segment of the facial nerve requires prompt evaluation and management to avoid functional and cosmetic deficits. Injuries that are proximal to a line dropped from the lateral canthus are amenable to surgical repair. Injuries distal to this line are generally not repaired due to extensive nerve arborization and cross innervation. Additionally, individual facial muscle fibers can possess multiple motor endplates arising from different branches of the facial nerve. For these reasons, facial nerve dysfunction due to injury anterior to this perceived line is likely to recover spontaneously.[254] Repair of proximal injuries is discussed in detail in later sections of this chapter.

Infection

Facial nerve injury due to infection is the third most common cause of facial nerve injury, with the most common subset of patients presenting with herpes zoster oticus (Ramsay Hunt syndrome).[254] Other infectious causes of facial paralysis include Lyme disease, acute otitis media, chronic suppurative otitis media, malignant otitis externa, infected cholesteatoma, mastoiditis, tuberculous mastoiditis, human immunodeficiency virus, and parotitis.[255-262]

Herpes zoster oticus, also known as Ramsay Hunt syndrome, is due to reactivation of latent varicella zoster virus (VZV). It presents most often in patients over age 60, although it is an important cause of facial paralysis in children 6 to 15 years of age.[256] Patients describe a prodrome of symptoms similar to Bell's palsy, with pain in and around the ear followed by facial weakness. Those patients with Ramsay Hunt syndrome will then progress to develop facial paralysis, hearing loss, vertigo, and possibly facial numbness due to involvement of the trigeminal nerve. Seventy percent of patients will develop a rash around the ear with vesicle formation and crusting. Patients with Ramsay Hunt syndrome often have more severe paralysis at initial presentation, late neural denervation, and a less favorable recovery profile than Bell's palsy. Up to 50% of patients will have persistent facial weakness or other related symptoms despite adequate treatment with prednisone and antiviral medication.[256]

Iatrogenic

Iatrogenic injury of the facial nerve is a feared complication of many head and neck procedures. Facial nerve paralysis due to iatrogenic injury results in cosmetic and functional deficits, ocular complications, diminished quality of life, and, often, malpractice litigation.[263] Injury is most common following parotidectomy procedures due to frequent but necessary manipulation of the facial nerve during surgery. Often, these are neuropraxia-type injuries, and therefore recovery is expected within a few days to weeks of the inciting event. Temporary facial nerve dysfunction occurs in 20% to 40% of patients undergoing parotidectomy; however, the incidence of permanent injury is less than 4%.[264,265] To decrease the risk of facial nerve injury during parotidectomy, many surgeons use intraoperative nerve monitoring techniques, most commonly electromyography.[264] Studies have shown a reduced rate of temporary facial nerve paralysis and an unclear benefit regarding permanent injury when intraoperative nerve monitoring techniques are utilized. Because of the rarity of permanent paralysis, sufficiently large and statistically powered studies are lacking.[264] Injury of the facial nerve during otologic procedures is relatively uncommon, with an incidence of 0.6% to 3.7% in primary surgery and 4% to 10% in revision surgery. For otologic

surgery, data on intraoperative nerve monitoring techniques demonstrate a clear and cost-effective reduction in facial nerve injuries.[264,266,267] Another possible cause of iatrogenic facial nerve injury is during temporomandibular joint (TMJ) surgery. In a review of 102 patients evaluated for iatrogenic facial nerve injury at the Massachusetts Eye and Ear Infirmary Facial Nerve Center, oral and maxillofacial surgery procedures accounted for 40% of total injuries, with TMJ surgery responsible for 27% of total injuries. The temporal branch of the facial nerve was most likely to be injured during TMJ surgery.[267] Reports regarding the risk of facial nerve injury during temporomandibular joint surgery range from 2% to 25%.[268] Repair of mandibular trauma, especially when involving the condyle or subcondylar region, is associated with a risk of temporary facial nerve injury ranging from 8% to 48%, with the buccal branch or marginal mandibular branch most likely to be injured and permanent facial nerve injury an infrequent occurrence.[269-272] Risk factors for injury to the facial nerve included fracture location at the condylar neck, fracture dislocation, and operator inexperience (<3 years).[269] Recovery time ranged from 4 to 24 weeks, and in multiple case series, no permanent facial nerve injury has been reported.[269-272]

Clinical Evaluation of Facial Nerve Injury

The evaluation of facial nerve injury, as with trigeminal nerve injury, begins with a detailed history and physical examination. Patients presenting with facial paralysis should be questioned regarding timing of onset and associated symptoms such as pain, dizziness, changes in hearing, hyperacusis, tinnitus, changes in taste, extremity weakness, prior ear or facial surgery, tick bites or travel to endemic areas, dysphagia, dysarthria, and dry eyes. Patients with extremity weakness, forehead sparing, dysphagia, and dysarthria should be promptly evaluated for central lesions as a cause of their facial paralysis or weakness. The incomplete crossover of the fibers innervating the upper face results in forehead sparing, often indicative of a central etiology to facial paralysis. These patients will maintain the ability to wrinkle the forehead and raise the eyebrows. Additional evaluation and management of patients with central etiology to facial nerve injury is beyond the scope of this text. The clinical examination of patients with facial nerve injury should also include otoscopic examination, especially in cases of blunt traumatic injury, to evaluate for signs or symptoms of temporal bone fracture such as canal laceration, step-off, TM

sidered the standard by the AAO-HNS; however, it should be noted that when an extratemporal source of injury is suspected, such as with penetrating trauma to the face, this scale is of limited use, and a subjective description of facial function by the examining physician is appropriate.[237,238] If temporal bone fracture, or benign or malignant pathology is suspected, appropriate imaging should be ordered. For temporal bone fractures, high-resolution dedicated CT of the temporal bones is recommended. If pathology is suspected, MRI should be ordered to better evaluate soft tissues and perineural spread. Following the history and physical exam, facial nerve testing can be ordered when appropriate. Facial nerve testing can help to determine the site and severity of injury, as well as dictating treatment and prognosis.[273,274] In cases of penetrating injury to the extratemporal segment, and when the proximal and distal cut stumps of the facial nerve are identifiable and available for repair, immediate surgical repair by primary neurorrhaphy is advised and can proceed without additional facial nerve testing.[254] Dedicated facial nerve testing is divided into two categories, topographic testing and electrodiagnostic testing.

Topographic testing is used to determine the anatomic level of a peripheral lesion through a variety of tests. A Schirmer test is used to evaluate for lesions at or proximal to the geniculate ganglion. This test evaluates tear production; because the GSPN branches just prior to the geniculate ganglion, a lesion proximal to the geniculate ganglion would result in decreased tear production. In this test, filter paper is inserted into the eye and the degree of wetting of the paper after 5 minutes is recorded. A normal result is greater than 15 mm. Severe disease would be represented by less than 4 mm of wetting. When evaluating for facial nerve lesions, if the affected side shows less than half the amount of lacrimation seen on the unaffected side, the test is considered positive. An alternative, less invasive test involves the use of fluorescein eyedrops. Drops are placed into the eye, and drainage into the nose through the lacrimal duct is expected within 2 minutes. The utility of this test in evaluating for facial nerve injuries has not been explored, as most topographic testing is rarely used since the advent of high-resolution CT and MRI to localize lesions. Stapedius reflex testing can be utilized to evaluate for lesions proximal to the stapedius nerve. An audiologist uses impedance audiometry to record the presence or absence of stapedius muscle contraction to sound stimuli of 70 to 100 dB. An absence of this reflex or a reflex with less than half the amplitude indicates a nerve injury proximal to the branch point of the stapedius nerve within the mastoid segment of the intratemporal portion of the facial nerve. Finally, taste can be evaluated through electrogustometry. This test evaluates the function of chorda tympani and would also indicate presence of an injury within the mastoid segment.

Electrodiagnostic testing includes nerve excitability testing (NET), maximal stimulation testing (MST), electroneurography (ENoG), and electromyography (EMG). Electrodiagnostic testing provides more useful information regarding function and prognosis compared to topographic testing and is more commonly used in clinical practice. All of these tests except EMG require a normal contralateral facial nerve for comparison. In NET, a stimulating electrode is placed at the stylomastoid foramen. Current is applied and the face monitored by the operator for movement. The test is repeated on the opposite side, and a difference of 3.5 mA or greater is considered significant. In

contrast to NET, which measures the minimum current for contraction, MST uses a current that produces maximal contraction of the normal side. An electrode is placed over the stylomastoid foramen of the normal side, and the current that produces maximal contraction is measured. This current is then applied to the side of suspected injury, and the response is recorded as equal or decreased (mild, moderate, severe, absent). The MST has the advantage of a lower false-negative response rate, and patients with an absent response will have incomplete recovery of function in 100% of cases.[274] Although this test is subjective, an equal or mild decrease in response has been shown to have a favorable chance of recovery, whereas a severe decrease or absent response indicates advanced degeneration with a poor prognosis and suggests that surgical intervention with decompression may be indicated.[274-276] The most accurate diagnostic testing modality, ENoG, provides quantitative analysis of the extent of nerve degeneration and is most useful 3 to 21 days after injury.[275] It is performed by placing bipolar electrodes at the stylomastoid foramen and stimulating the facial nerve. The summation potential is then recorded by electrodes placed at the nasolabial groove. A percentage of the response on the normal side of the face is calculated, and the literature states a value greater than 90% degeneration as an indication for surgical decompression of the nerve. Values less than 90% indicated expected recovery of function in 80% to 100% of patients. Disadvantages to ENoG include patient discomfort, cost, and test-retest variability due to electrode positioning.[273,275,277,278] Last, electromyography can be used to assess muscle function. EMG is more useful 10 to 21 days or more following injury when fibrillations being to appear.[275] A needle electrode is inserted into the muscle and recordings are made during rest and voluntary contraction. Six to 12 weeks prior to the return of clinically evident facial nerve function, polyphasic reinnervation potentials can be measured.[273,275] Regarding extratemporal facial nerve trauma, these tests are most often used in the postoperative period to monitor for recovery or prior to surgery when nerve transection cannot be verified.

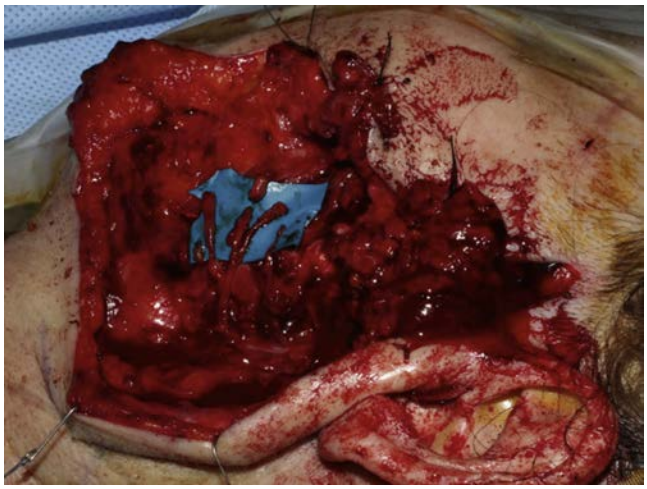
Treatment of Traumatic Extratemporal Facial Nerve Injuries

A discussion of the treatment of intratemporal facial nerve injuries is beyond the scope of this text; however, there are many injuries resources describing the indications, contraindications, and approaches for surgical treatment of intratemporal facial nerve injuries.[248-253]

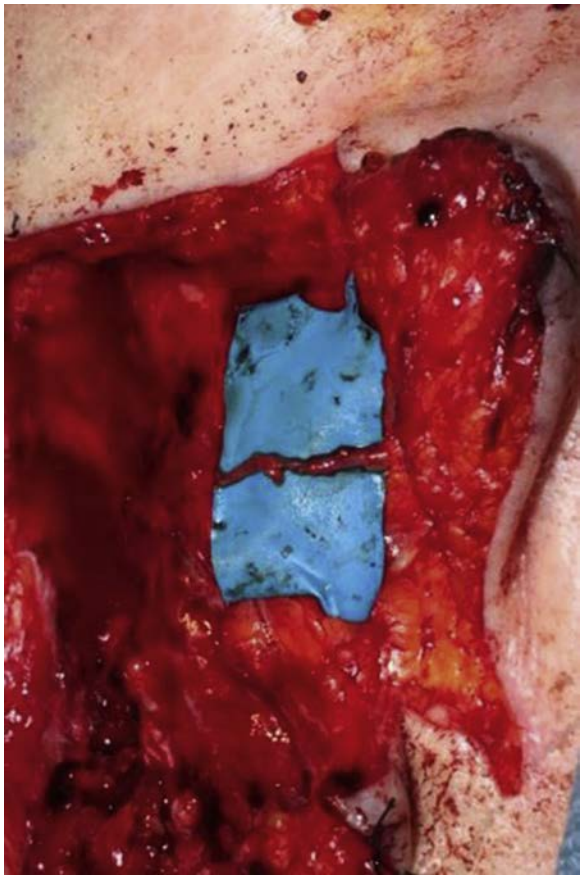
Extratemporal facial nerve injuries encountered by the oral and maxillofacial surgeon are most commonly due to penetrating trauma or iatrogenic injury. In both cases, prompt recognition of injury and surgical repair are required. Early repair within 72 hours allows for nerve stimulation to identify cut distal nerve endings. After 72 hours, motor endplate depolarization is not possible, as neurotransmitter stores are depleted in the absence of antegrade axoplasmic transport.[279,280] Repair within 30 days has been shown to improve recovery of facial function.[214,281] Loupe or microscope magnification is recommended to assist in locating branches of the facial nerve and in visualizing healthy fascicles. When immediate repair is possible, the surgeon should access the facial nerve through existing lacerations or incisions (Figure 5-45). If delayed repair is carried out, a modified Blair incision is recommended. Following skin incision, dissection just below the superficial musculoaponeurotic system is carried out to create an anterior skin flap. Next, the main trunk of the facial nerve should be located using the landmarks previously described in this chapter (tragal pointer, tympanomastoid suture, attachment of posterior belly of the digastric) and the course of the facial nerve followed from proximal to distal until the site of injury is encountered. The superficial lobe of the parotid will require mobilization to identify more proximal branches; alternatively, a superficial parotidectomy may be performed to assist in tension-free repair and ease of identification. Once the area of trauma is reached (if using an existing laceration, full dissection of the facial nerve and the facial nerve trunk may not be necessary if the proximal and distal ends can be located), the facial nerve should be freed from any adhesions. Damage to Stensen's duct should be ruled out, as a salivary leak or sialocele may compromise the repair. Next, a colored distally and electrical stimulation applied. A response with 0.05 mA indicates a good prognosis, and further exploration is not required. If a response is only obtained distally, further exposure is warranted prior to repair. A Victor-Meyer neurotomy instrument is then used to excise any neuroma or scarring until a normal-appearing fascicular pattern is noted. At this point, a determination should be made as to the need for any grafting or if primary neurorrhaphy can be completed. As a general rule, tension-free primary neurorrhaphy of the facial nerve can be performed if the defect is less than 17 mm.[214] The surgeon should always keep in mind that the most important



• **Figure 5-45** Severe facial soft tissue lacerations with injury to the facial nerve.



• **Figure 5-46** Proximal and distal ends of the facial nerve identified and isolated.



• **Figure 5-47** Repaired facial nerve.

prognostic factor for success is a tension-free coaptation of the nerve stumps.[214,282,283] If a tension-free repair cannot be completed, cable grafting, cross-facial nerve grafting, or crossover grafting should be considered. End-to-end anastomosis of the facial nerve is then performed with 8-0 or 9-0 nylon sutures as an epineural repair (see Figure 5-47). Most surgeons no longer perform perineural repair because of its increased technical difficulty and lack of demonstrated superiority over epineural techniques. Sutures should initially be placed 180 degrees to each other and should not be overtightened, as this can result in poor fascicle alignment and mushrooming. A loose approximation is preferred. Using the long ends to the already placed sutures, the nerve can be manipulated and rotated to allow placement of additional sutures as needed. Four sutures are typically all that is necessary to ensure alignment. The sutures are trimmed, and the wound is irrigated and closed in a layered fashion. In cases with significant gaps between the proximal and distal facial nerve stumps, superficial parotidectomy and mobilization of the branches of the parotid plexus can improve nerve mobility. Additional mobility can be obtained by decompression of the nerve from the mastoid and temporal portions of the intratemporal segment of the facial nerve by a neurotologist.[284]

When a tension-free repair is not possible, a cable (interposition) graft may be considered. Sources of allograft nerve include the greater auricular, sural, medial antebrachial, or lateral antebrachial cutaneous nerves. The greater auricular nerve is preferred because of its similar size to the facial nerve branches and location within the operative field in select cases. If more than 8 to 10 cm of graft is required, an alternative source such as the sural nerve will be necessary.[214] Facial nerve repair with a cable graft is similar to a direct repair, except that two sites of epineural suturing will be required.

If the proximal facial nerve stump is unavailable for repair, a cross-facial graft can be considered, using a contralateral facial nerve branch and nerve graft. This technique has the benefit of borrowing nerves with similar functions and can allow spontaneous and emotional facial expression without dyskinesis.[214,280] When smile reconstruction is desired, a buccal or zygomatic branch is identified and then stimulated to determine function. Multiple nerves are stimulated and mapped until a suitable donor with redundant functions is found. Use of a donor nerve that produces similar function as the injured side may decrease risk of synkinesis. A subcutaneous tunnel through the upper lip is then created to pass the graft from the normal donor side to the injured side, and tensionless epineural repair is performed on each side.[280]

An alternative technique is the nerve crossover or nerve transfer. This is most useful in cases where the contralateral facial nerve is unavailable or in the intermediate period following nerve injury, 3 weeks to 2 years. It requires an intact proximal donor nerve, intact distal facial nerve, and intact muscles of facial expression.[214,280] Possible donor nerves include the ipsilateral masseter branch of the trigeminal nerve and partial hypoglossal nerve. The ipsilateral masseter branch is advantageous because it can be used without the need for an intervening nerve graft and therefore will only have a single anastomosis. In addition, it has been noted that due to the close proximity between the facial and trigeminal nuclei in the pons, motor reeducation after this procedure is rapid. The ability to smile without active clenching has been reported in 66% to 82% of patients.[280] A partial hypoglossal donor is preferred over complete transection of the hypoglossal due to decreased morbidity. Patients with partial

transection have as little as 8% permanent tongue deficits, whereas the complete transection is associated with 100% deficit.[214,284] Patients who undergo this procedure will need significant biofeedback and motor sensory rehabilitation to learn voluntary control of movement, decrease synkinesis, and limit facial grimacing when chewing.[214]

Outcomes of Facial Nerve Injury and Surgical Intervention

Injury to the extratemporal branches of the facial nerve may be associated with impairment in facial expressions, eye protection, and oral competence, with additional effects on a patient's psychological, social, and economic well-being. The long-term effects of facial nerve injury are muscle denervation and atrophy. Immediate, primary repair of facial nerves has up to an 85% chance of acceptable recovery (House-Brackmann Grade I-III).[214,280-285] Cable grafting is associated with success rates of 54% to 80% (House-Brackmann Grade I-III), and recovery of function is first noticeable approximately 6 months after repair, with full recovery expected around 12 to 18 months following repair.[214,286-289] Cross-facial and crossover grafts are associated with success rates ranging from 25% to 82%, depending on the specific procedure performed and the definition of success, which is not standard across all studies.[214,280] In cross-facial grafting, noticeable facial movement is not evident until 9 to 12 months after surgery.[214] Factors that affect long-term results in facial nerve repair are patient age, chemotherapy or radiation treatment, nutrition status, time to repair, and underlying comorbidities such as diabetes mellitus.[214,284] When facial nerve repair and/or grafting techniques fail, static and dynamic reconstructive surgeries can be performed using static slings, regional muscle transfer, or free functional muscle transfer.[214,280]

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6

Diagnosis and Management of Dentoalveolar Injuries

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Introduction

Injuries secondary to trauma are common in the facial region, and about 20% of these include injuries involving the dentoalveolar complex.[1,2] In the United States, traumatic dental injuries have been evidenced in approximately 1 of 4 adults and 1 of 6 adolescents.[3] These injuries could involve the tooth, surrounding soft tissues, and alveolar bone. In many of these patients, comprehensive management will require multidisciplinary care from various dental specialties including oral and maxillofacial surgery, restorative dentistry, prosthodontics, and orthodontics.

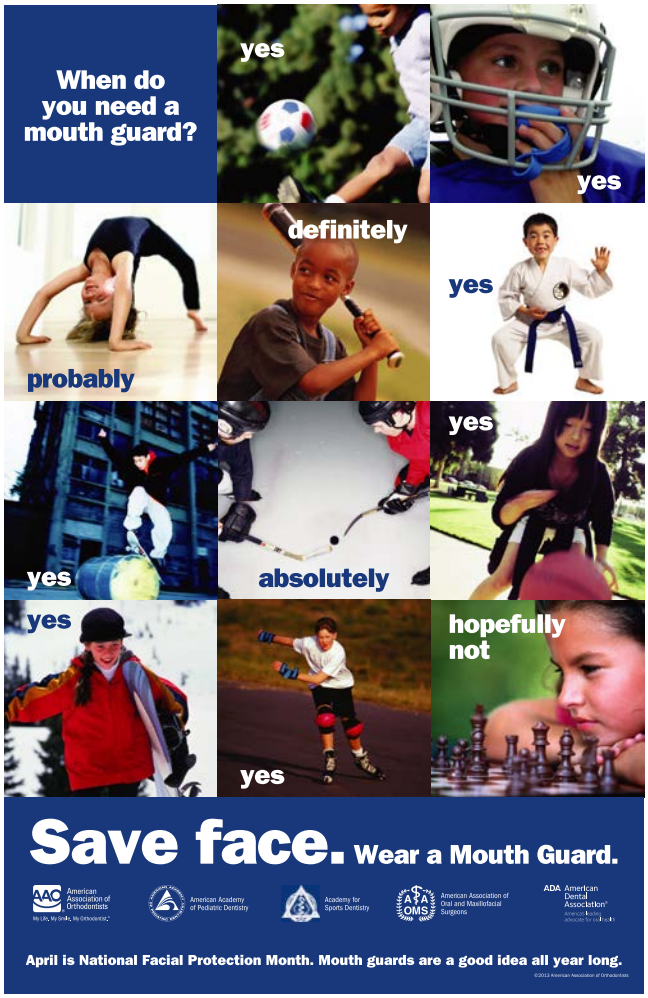
Isolated dentoalveolar injuries are common among children and adolescents, whereas those occurring concomitantly with other facial fractures are more common among young adults.[3-6] The reported prevalence of dentoalveolar injuries varies widely depending on factors such as age, cause of injury, country, environment, and gender. These injuries may be caused by motor vehicle accidents, motorcycles, bicycles, assaults, falls, sports, iatrogenic causes from intraoral procedures, and industrial accidents. Among preschool children and toddlers, dentoalveolar injuries are most often caused by falls, especially during the first year of life.[3,6,7] Boys have dental injury more commonly than girls.[6] A recent 12-year review estimated that across multiple studies spanning many countries, 71% to 92% of all dental trauma sustained in a lifetime occurs before the age of 19 years with a decrease in incidence after the age of 24 to 30 years.[3,7] Overall, the prevalence of dentoalveolar injuries among children with primary dentition is 11% to 30%, and among children with permanent dentition it is 5% to 20%. Boys also are affected almost twice as often as girls, with peak incidence at 2 to 4 years and 8 to 10 years.[7]

Many of these dentoalveolar injuries are underreported in trauma literature, as they are treated in an outpatient setting, in contrast to common pediatric facial fractures. The general prevalence of oral injury among pediatric patients is reported to be 5% of all facial fractures.[6]

Another cause of dentoalveolar and surrounding soft tissue injuries among children can be child abuse.[8-13] All 50 U.S. states have mandates for dentists and health care professionals to be able to identify and report child abuse and neglect.[8] When no obvious cause of the trauma is identifiable, child abuse may be suspected. In fact, roughly 50% of all physical injury associated with child abuse occurs in the head and neck region.[13] Finally, certain medical conditions may predispose a patient to dentoalveolar trauma, such as a history of uncontrolled seizures. Among children of school age, dentoalveolar injuries occur mostly on playgrounds and in bicycle accidents. In the teenage years, these injuries are most often caused by contact sports, motor vehicle accidents, and interpersonal violence. It has been stated that 33% of all traumatic dental injuries and up to 19% of injuries to the head and face are sports related.[14-16] Among adolescents with sports-related trauma, the incidence of dentoalveolar injuries is reported to be 36%.[16] Use of mouthguards has been strongly supported by the American Dental Association.[17] Extensive effort is spent on the fabrication of mouthguards, but there is no strong evidence in the literature to show their efficacy.[18] More recently the focus has been on preventive education and awareness among schools, sports authorities, and others. In addition, National Facial Protection Month, which occurs every April, has been successful in bringing attention to the prevention of sports-related injuries. This campaign has been promoted by the Ameri-

(Figure 6-1).

Injuries to the dentoalveolar structures can present as an isolated injury or in association with multisystem injury as seen in motor vehicle accident victims. Dentoalveolar injuries



• **Figure 6-1** National Facial Protection Month in April annually has been a great way to educate patients about importance of prevention of sports-related orofacial injury.

can also result from direct trauma to the teeth or from indirect trauma from mandibular dentition forcibly closing against the maxillary dentition. If the injury is caused by direct trauma, the most likely teeth to sustain injury in both the primary and permanent dentition are the maxillary central incisors, because of their relatively exposed position**.** Large overjet, proclined incisors, and short upper lip predispose to increased incidence of dental trauma.[19] This occurs most commonly when these teeth are protruding, as in patients with Class II Division I malocclusion, an overjet greater than 5 mm, or in patients with insufficient lip closure.[20] These are followed in incidence by the upper and lower lateral incisors and the upper canines. Depending on the force of the impacted trauma, direct injury mechanisms can affect the upper or lower lip, occasionally causing laceration of the lip as well as dental or osseous alveolar fracture (Figure 6-2). Dentoalveolar injury from indirect trauma usually results from force applied to the chin, forcing the mandibular teeth against the maxillary dentition. The impact of this force often results in crown or crown-root fracture as well as condylar and/or mandibular symphysis fracture and anterior intraoral soft tissue and submental laceration (Figures 6-3 and 6-4).



• **Figure 6-2** Direct trauma to the lower lip causing a laceration in a child.

The nature of dentoalveolar injuries also varies with age, possibly because of the anatomic differences between the teeth and supporting structures of adults and pediatric patients. The lack of sinus pneumatization and higher ratio of cancellous to cortical bone, as well as the developing dentition within the facial skeleton, tend to increase the elasticity of the pediatric facial bones, making them less vulnerable to fractures. Trauma to the primary dentition most often affects the supporting structure (luxation and exarticulation), whereas trauma to the permanent dentition mostly affects the teeth themselves (causes crown fractures).[21] Only 10% of injuries to the primary dentition are crown or crown-root fractures. Seventy-five percent involve luxation or exarticulation of the tooth, compared to the incidence of mostly crown or crown-root fracture involvement in the permanent dentition.

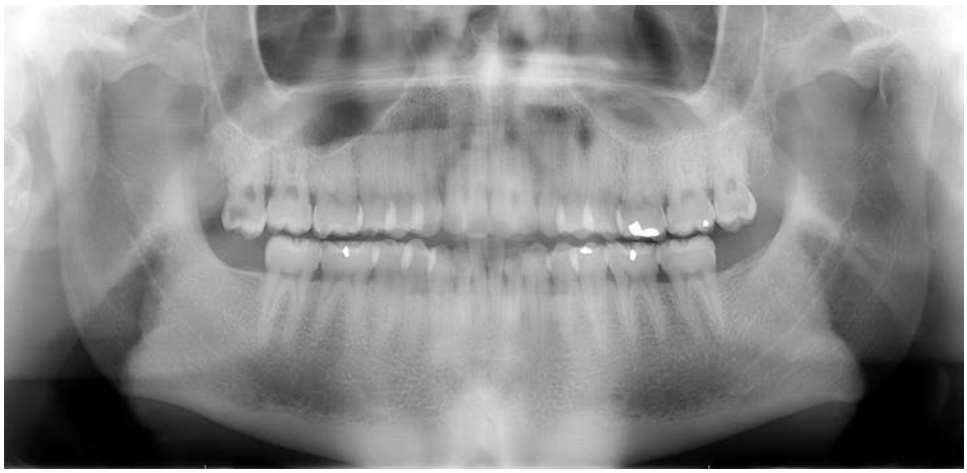
The oral and maxillofacial surgeon (OMS) is often called to the emergency department to evaluate patients who sustain orofacial trauma. The first-aid treatment is regularly performed by an OMS, and subsequent dental and restorative management is performed in outpatient setting by other dental colleagues.

Evaluation of the Dentoalveolar Injury Patient

As with any other trauma patient, the evaluation process of a dentoalveolar trauma patient should include a thorough history and comprehensive physical examination, along with any necessary radiographic examination or other diagnostic procedures.

History and Physical Examination

A thorough and systematic evaluation and diagnosis must precede management of traumatic dental injuries. In general, primary evaluation of any trauma patient must be carried out based on Advanced Trauma Life Support (ATLS) guidelines.[22] Once the systemic stability of the patient is



• **Figure 6-3** Mandibular anterior teeth luxated along with a concomitant subcondylar fracture. Dentoalveolar injuries can occur along with other facial bone fractures.

established, secondary evaluation is performed in a system wise fashion. Although dentoalveolar injuries, especially avulsive ones, are considered emergent, definitive repair of the dentoalveolar injury could be delayed until patient has been stabilized from a systemic standpoint. Results of the history and physical examination will dictate the need for diagnostic radiographs and/or special diagnostic tests such as pulp testing. Once a diagnosis is established based on clinical and radiographic evaluation, a treatment plan can be formulated. Because the length of time from injury until treatment is an important factor in determining the prognosis and outcome of dentoalveolar injury, the process of management should commence as soon as possible.[23]

History

Obtaining detailed history can provide invaluable information for the diagnosis and subsequent management of dentoalveolar injuries. However, the practitioner must keep in mind that children, in particular, do not often offer a reliable and detailed history, especially after a traumatic event. In this situation, one must depend on the accompanying adult or other eyewitnesses. The history obtained from patients with dentoalveolar injury should include the following information[24]:

1. Biographic and demographic data of the patient, including name, age, sex, race, address, and phone number.
2. The time interval between the injury and presentation. This is critical in ultimate prognosis of the teeth, especially in cases of avulsion or of tooth fracture with pulp exposure. The location of the incident or accident will help determine the degree of contamination of the wound and the indication for tetanus prophylaxis.
3. The mechanism of injury. This provides clues regarding the possibility of other injuries to suspect and evaluate via various imaging modalities. For example, a fall can cause injury to the maxillary anterior dentition, whereas a blow to the chin will often cause crown-root fractures of the premolar region with or without symphysis or condylar fractures. In children and women, if the reported mechanism of the injury does not correspond to the clinical presentation, the potential for abuse could be considered. In instances of abuse it is important that the clinician carefully document the clinical findings and the discussion with the patient and caregivers. Mechanism of injury also guides the clinician to suspect any occult injuries that may need further radiographic evaluation.
4. Information related to the event and its surroundings. This should also be recorded—for example, if any avulsed teeth, tissue, or fragments of teeth were noted at the site of the accident. Radiographic examination of the periapical tissues, chest, abdominal region, and perioral soft tissue is indicated when the preinjury dentition has



• **Figure 6-4** Gingival lacerations could be indicative of dentoalveolar fractures as well as underlying mandibular fractures.

changed in form or number. Management of partially or completely avulsed teeth by the patient should also be charted, including whether the teeth were replanted, or the storage medium used before presentation to the dentist or the emergency room. Medical events at the site of the accident are critical to note. Loss of consciousness, confusion, nausea, vomiting, or visual disturbances will indicate possible intracranial injury, which warrants neurologic evaluation. Patients who report persistence of these symptoms should be referred for emergent evaluation, and treatment of the dentoalveolar injury should be delayed until it is completed.

5. Subjective changes regarding dental occlusion as a result of the injury, which may indicate tooth displacement or dentoalveolar or jaw fractures.
6. A short medical and dental history to delineate any systemic or dental factors that can influence immediate and delayed treatment plans. Such factors include the presence of major systemic illness, especially those that may influence the treatment such as bleeding disorders and epilepsy. Also, knowledge of any previous oral and maxillofacial trauma may be helpful.

Physical Examination

An important aspect of the physical examination is the overall evaluation of the physical status of the patient. Historical findings will direct the examiner to anticipate injury patterns, thereby promoting a focused examination. As noted earlier, examination following the ATLS protocol will help identify or rule out systemic injuries in a systematic fashion. Abnormalities in vital signs may indicate intracranial injury, cervical spine injury, chest or abdominal injury, or even aspiration of an avulsed tooth. The mental status of the patient should also be assessed both by asking specific questions and by observing the patient's reaction and behavior during the history and examinations. Once a general examination is completed and a concomitant injury is ruled out, a thorough oral and maxillofacial examination is performed. Such examinations should include the following.[24]

Extraoral Soft Tissue Examinations

Lacerations, abrasions, and contusions of the face, chin, forehead, and scalp should be identified, and their depth, location, and proximity to vital structures should be established. The site of soft tissue trauma is a predictor of associated hard tissue injuries. Palpation of the temporomandibular joint and examination for range of jaw motion should be done to rule out condylar fracture.

Intraoral Soft Tissue Examination

Injuries of the oral mucosa, gingiva, lips, tongue, floor of the mouth, and cheek should be considered (see Figure 6-2). If present, such injuries should be carefully evaluated for the presence of foreign bodies, debris, and teeth or tooth fragments embedded within the tissue.[24,25] It may be necessary to debride the oral cavity of clots and debris and to stop active bleeding before completing a thorough examination.

Gingival lacerations (see Figure 6-4) are often indications of displacement of teeth, while bleeding from nonlacerated marginal gingiva often indicates periodontal ligament damage or mandibular fracture. It is important that all teeth be accounted for at this time. Missing teeth or pieces of teeth that have not been left at the scene of the accident should be considered to have been aspirated, swallowed, or displaced into the soft tissues, nasal cavity, or maxillary sinus (Figure 6-5).[24,26] Therefore, a radiographic examination of the head and neck, chest, and abdomen should be done to rule out presence of teeth or fragments into these tissues or organs.

Examination of the Jaws and Alveolar Bone

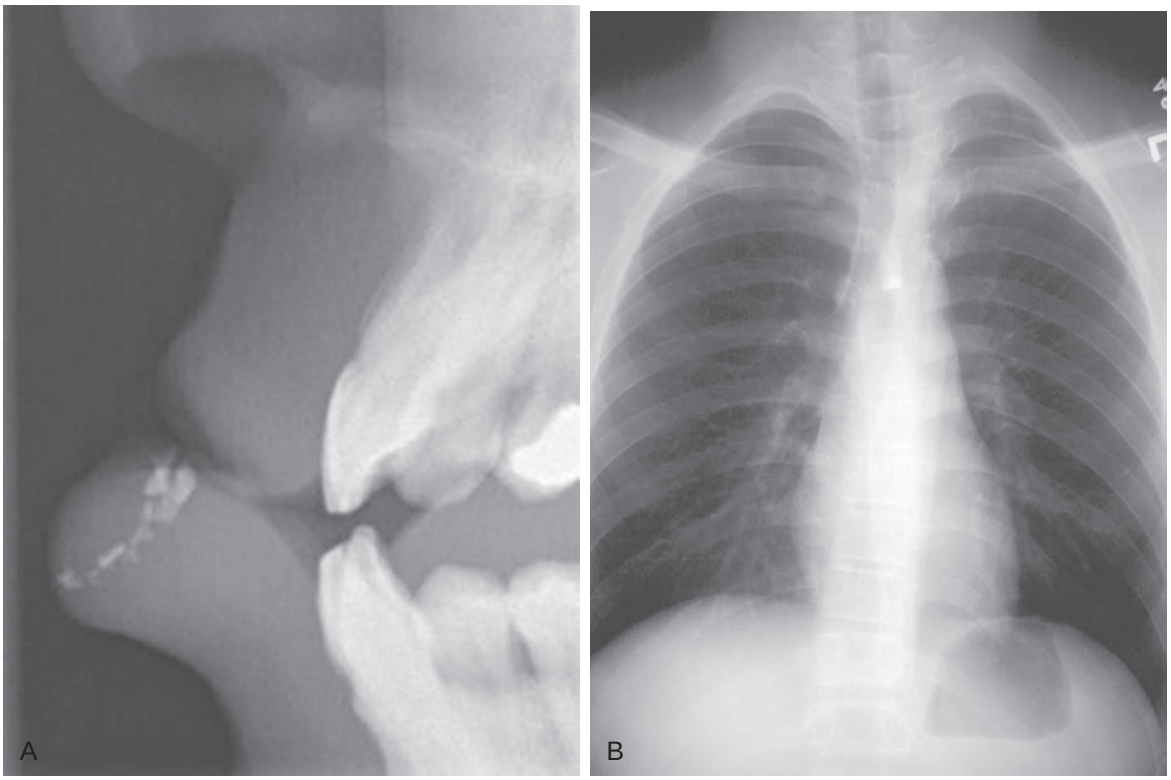
Fractures of the alveolar process protruding through the overlying mucosa are normally evident and readily detected by visual inspection. Mobility and crepitation of the palpated alveolar fracture segments confirms underlying bone injury when the overlying mucosa is not lacerated. Fractures of the jaw may be detected by presence of gross malocclusion, step-off deformities, pain, and mobility of the fractured segment to palpation. Bleeding from the gingival crevice of a tooth, vertical laceration of the attached mucosa, and submucosal ecchymosis of the floor of the mouth are other signs of jaw fracture.

Examination of the Teeth Structure

Direct examination of tooth structure is preceded by removing blood and debris from the teeth. Any infraction or fractures of the crowns should be noted. Infraction lines in the enamel can be detected by directing a light beam parallel to the long axis of the tooth. Crown fractures should be evaluated for extending into the dentin and the pulp. The size and location of pulp exposure should be recorded. Crown-root fractures in all quadrants should be evaluated as well. Changes in the color of a traumatized tooth and its translucency may indicate a pulp exposure. It is important to remember that indirect trauma leading to crown-root fractures in one quadrant is often accompanied by similar fractures in the ipsilateral opposing jaw.

Examination for Displacement of Teeth

Displacement of teeth as a result of dentoalveolar trauma can usually be readily detected by visual examination. Examination of the dental occlusion may also be helpful in detecting minor degrees of tooth movements. Although displacement of teeth as a result of dentoalveolar trauma can occur in any direction, the most common displacement is in a buccolingual direction (Figure 6-6). The direction and extent of displacement should be recorded. Lateral luxation and intrusion of teeth may present very minimal clinical symptoms because the teeth remain locked in this displaced



• **Figure 6-5 A,** Tooth fragments displaced into the lower lip. **B,** Chest radiograph showing aspirated tooth. Missing teeth or tooth fragments should be accounted for, and if they are not found, aspiration and displacement into surrounding tissues should be ruled out with imaging. (From Powers MP: Diagnosis and management of dentoalveolar injuries. In Fonseca JR, Walker RV, editors: *Oral and maxillofacial trauma*, ed 2, vol 1, Philadelphia, 1997, WB Saunders.)

position. Lingual and apical displacement of the apex of a primary tooth can interfere with its permanent successor.

Examination for Mobility of Teeth

All teeth should be tested for both horizontal and axial mobility by either manual palpation or use of a tongue blade. If a tooth does not appear to be displaced but is very mobile, a root fracture should be suspected. In such instances the location of the fracture usually determines the degree of mobility. When testing for mobility of one tooth, observing mobility of the adjacent teeth is suggestive of a dentoalveolar fracture.

Reaction to Percussion

Increased sensitivity to percussion in the absence of tooth displacement is indicative of injury to the periodontal ligament. This test can be performed by vertical and horizontal tapping of the tooth or gentle fingertip pressure when examining smaller children. A noninjured tooth should be used for control. Sound elicited by percussion, with the use of the handle of a mouth mirror, has been mentioned in the literature as providing diagnostic information.[24] An uninjured tooth will generally have a solid, metallic sound, whereas a luxated tooth will be dull. However, for this to be of any value, a quiet environment is required.



• **Figure 6-6** Buccal-palatal displacement of permanent maxillary central incisors is commonly seen.

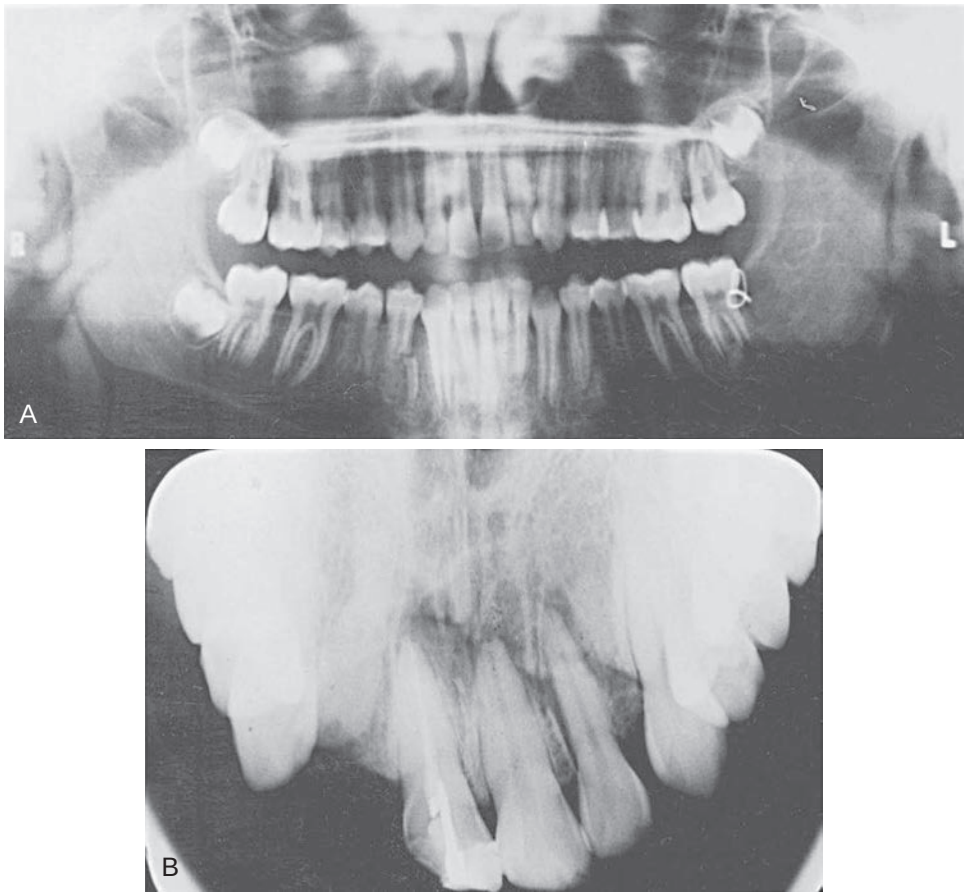
Pulp Testing

Traumatized teeth could have paresthesia and altered neurologic response, and neural recovery takes longer than vascular regeneration.[24] Currently used tooth vitality tests register the conduction of stimuli to the sensory receptors of the dental pulp. This type of vitality testing is subjective and may be difficult to perform or

relatively unreliable in the acute setting following traumatic injury. Lack of cooperation and unreliability, especially among children, and false-negative results, which are common in acute injury, diminish the usefulness of pulp testing in the acute setting. Nonetheless, pulp testing several weeks later, after revascularization and nerve repair of the pulp, may be more accurate and should be performed before endodontic therapy. It can also be beneficial and important for planning treatment. Some of the methods used in pulp testing include electric pulp testing, thermal test using treated gutta-percha, ice, ethyl chloride, carbon dioxide snow, and dichlorodifluoromethane. The low sensitivity of some of these techniques led some to search for new methods of pulp testing. Laser Doppler flowmetry has been used in recent years as a more reliable method of assessing pulpal flow and vitality. Although promising, it still remains a sensitive and time-consuming technique and is not widely used because of cost and availability.[27] Even if unreliable, pulp testing should be performed at the earliest possible time after trauma as a baseline recording and then at regular intervals of 2, 4, and 6 to 8 weeks and then 6 and 12 months.[27]

Radiographic Examination

Radiographic examination is an essential part of evaluation that helps identify injuries affecting the root portion of the tooth and the periodontal ligament, as well as status of the bone. Such information includes presence of root fracture, root infraction, and root dislocation (Figure 6-7). Concomitant jaw fractures, preexisting periapical or periodontal disease, degree of extrusion or intrusion, and teeth or tooth fragments or foreign bodies lodged in the soft tissue can also be identified.[25,26] In children and young adults, radiographic examination serves to provide information regarding the extent of root development, size of the pulp chamber and root canal, and proximity of succedaneous teeth to the injured primary tooth. Choice of radiographs should be based on history and physical examination. Radiographic imaging of dentoalveolar trauma usually consists of more than one radiograph, including intraoral periapical, occlusal, and panoramic radiographs.[28] Correctly positioned periapical radiographs (central beam of x-ray parallel to the line of fracture) provide the most detailed information to adequately evaluate root fracture and dislocation of teeth. Often multiple views (ideally three radiographs) with two



• **Figure 6-7** **A,** Panoramic radiographic examination for evaluation of dentoalveolar injury revealing a root fracture of the right mandibular first bicuspid. **B,** An occlusal radiograph showing a dentoalveolar fracture of the anterior maxilla. (From Abubaker AO, Papadopoulos H, Giglio JA: Diagnosis and management of dentoalveolar injuries. In Fonseca R, Marciani RD, Turvey TA, editors: *Oral and maxillofacial surgery*, ed 2, St Louis, 2009, Saunders.)

different vertical and three different horizontal angulations of the central beam may be necessary, especially to view root fractures. Periapical radiographs are also used postoperatively to confirm position of the root.

Occlusal radiographs are particularly useful to diagnose a root fracture, or lateral luxation with lingual displacement of the crown. Occlusal radiographs are also often made for patient comfort because they place minimal pressure on the traumatized area. They are also valuable in examining the floor of the mouth, tongue, cheek or lip lacerations for teeth or tooth fragments in the soft tissue. When occlusal radiographs or other x-ray exposure is used to examine soft tissue, a reduced radiographic exposure time is recommended.

Radiographically displaced teeth will appear as a widening of the periodontal ligament space or displacement of the lamina dura. Extruded teeth may appear as a periapical radiolucency compatible with the pattern and shape of the apical portion of the root. Lateral and extensive luxation of teeth will also appear as a widening of the periodontal ligaments. Intruded teeth often will show minimal radiographic findings or only a blurred or absent periodontal space.

If jaw fractures or fractures of the alveolar ridges are suspected, extraoral radiographs such as an orthopantomogram should be obtained. Although panoramic radiography can demonstrate fractures of the jaw, alveolar ridges, and teeth, it is best suited as a screening image for fractures of the condyle, subcondylar region, or angle or body of the mandible. The overlap of the vertebral column inhibits adequate visualization of maxillary and mandibular anterior dentition. Complex midface anatomy also limits the use of plain-film two-dimensional radiographs because of overlapping of structures. In these cases a three-dimensional (3D) imaging modality such as computed tomography (CT) or cone-beam CT (CBCT) is valuable in overcoming superimpositions while allowing a 3D evaluation. CT and CBCT both have good resolution, but CBCT have relatively less radiation exposure compared to a medical-grade CT scan. Imaging of soft tissue trauma may be better appreciated on a CT scan compared to a CBCT. Occasionally, access to or use of routine dental radiographs is limited, such as in a hospital setting and in children under the age of 2 years. CT scans have remained the gold standard for evaluation of facial bone fractures. With advent of CBCT and its availability and low cost in outpatient settings, it can be used a valuable tool in assigning both bony and dental structure injuries with higher definition and more accuracy to the nature of dentoalveolar injury.[30,31]

Classification of Dentoalveolar Fractures

Although historically there have been several classification systems in use for description of dentoalveolar trauma, each had its own advantages and disadvantages.[32-36] These systems are based on a variety of factors such as etiology, anatomy of injury, pathology, and therapy. The purpose of such classification is to provide a comprehensive and universal description of the injury for communication and treatment planning purposes. The most accepted and commonly used is Andreasen's modification of the WHO classification.[19,36,37]

Andreasen's classification[19] includes description of injuries to the teeth, supporting structures, gingiva, and oral mucosa, with some modifications to take into account anatomic, therapeutic, and prognostic considerations. This classification can be applied to both the permanent and primary dentition. In this classification system, dentoalveolar injuries are divided into four major categories: injuries to the dental tissues and pulp, to the periodontal tissues, to the supporting bone, and to the gingiva or oral mucosa. Descriptions and illustrations of the four categories are shown in Tables 6-1 through 6-4. Basic types of traumatic injuries to primary dentition are shown in Figure 6-8.[38]

Treatment of Dentoalveolar Injuries

General Considerations

An ideal outcome with treatment of dentoalveolar fractures would be to attain or preserve the premorbid functional state of teeth, bone, and gingiva; maintain esthetics; and optimize growth and development. Based on the Andreasen classification system and including the six luxation types and nine fracture types in both primary and permanent dentition, there could be 108 types or combinations of dental trauma entities. The complexity of diagnosis and management of dentoalveolar trauma has been perplexing to the clinician in making an evidence-based decision. The most recent IADT-recommended guidelines, updated in 2012, represent the best evidence based on the most current literature and expert opinion.[38] These guidelines are meant to help the clinician make acute management decisions with traumatic dental injury, but they do not substitute for comprehensive and detailed information on traumatic dental injury management as found in scientific literature and books.

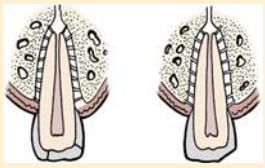
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nt planning include:

1. age of the patient;
2. cooperation of the patient;
3. primary, mixed or secondary dentition;
4. developmental state of the tooth;
5. classification and extent of the injury;
6. any concomitant bodily injuries or medical comorbidities;
7. restorability of the tooth based on decay and periodontal health; and
8. long-term restorative options.

Although every attempt should be made to preserve all of the dentoalveolar structures permanently, it is sometimes necessary to either sacrifice or only temporarily maintain teeth to facilitate future reconstruction, restoration, and rehabilitation. Therefore, deciding whether and when

TABLE 6-1 Injuries to Hard Dental Tissues and Pulp

Crown infraction	Incomplete fracture or crack of the enamel without loss of tooth substance	
Uncomplicated crown fracture	A fracture confined to the enamel or involving the enamel and dentin without exposing the pulp	
Complicated crown fracture	Involves enamel and dentin with exposure of the pulp	
Uncomplicated crown-root fracture	Involves enamel, dentin, and cementum without exposure of the pulp	
Complicated crown-root fracture	Involves enamel, dentin, and cementum with exposure of the pulp	
Root fracture	Involves dentin, cementum, and the pulp	

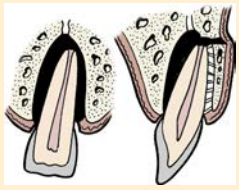
Modified from Powers MP: Diagnosis and management of dentoalveolar injuries. In Fonseca JR, Walker RV, editors: *Oral and maxillofacial trauma*, ed 2, vol 1, Philadelphia, 1997, WB Saunders, p 333.

to remove teeth or bony segments at the initial phase of treatment should be done cautiously. Heroic attempts to maintain teeth that are otherwise unsalvageable for decay or periodontal reasons should be avoided unless they are being retained temporarily to preserve at-risk alveolar bone. Being able to maintain proper alveolar contour and bulk will often allow for a more satisfactory dental rehabilitation. Likewise, avulsed teeth that have an extremely poor prognosis when associated with alveolar fractures may be replanted for a period of time as both a means of properly reducing the fracture and as physiologic space maintainers. Such a tooth can always be removed at a later date. If root fractures are evident, clinically concomitant with alveolar fractures, the teeth are removed if it can be accomplished without compromising the alveolar segment. Otherwise, they are left in place for removal at a later date after the segment is healed. Root fractures, particularly apical third fractures, are often only discovered on postreduction radiographs taken in the dental office. These are managed in the same manner as if they had occurred without an alveolar fracture.

When dealing with alveolar fractures, debridement of bone should be conservative. The alveolar bones are highly vascular, and vitality may often be maintained by even a very small soft tissue pedicle. Therefore, an attempt should always be made to retain fragments that have soft tissue attachments. The avulsed tooth associated with an alveolar fracture may have to be rigidly splinted for 3 to 4 weeks instead of physiologically splinted for 7 to 10 days.

Use of antibiotics in dentoalveolar trauma is controversial, with limited evidence in the literature about its efficacy. Use should be at the discretion of the provider, who should

TABLE 6-2 Injuries to the Periodontal Tissues

Concussion	An injury to the tooth-supporting structures without abnormal loosening or displacement of the tooth, but with marked reaction to percussion	
Subluxation (loosening)	An injury to the tooth-supporting structures with abnormal loosening, but without displacement of the tooth	
Intrusive luxation (central dislocation)	Displacement of the tooth into the alveolar bone with comminution or fracture of the alveolar socket	
Extrusive luxation (peripheral dislocation, partial avulsion)	Partial displacement of the tooth out of the alveolar socket	
Lateral luxation	Displacement of the tooth in a direction other than axially, accompanied by a comminution or fracture of the alveolar socket	
Retained root fracture	A fracture with retention of the root segment, but loss of the crown segment out of the socket	
Exarticulation (complete avulsion)	Complete displacement of a tooth out of the alveolar socket	

Modified from Powers MP: Diagnosis and management of dentoalveolar injuries. In Fonseca JR, Walker RV, editors: *Oral and maxillofacial trauma*, ed 2, vol 1, Philadelphia, 1997, WB Saunders, p 333.

consider other indications such as wound contamination, soft tissue trauma, and general medical status.[39]

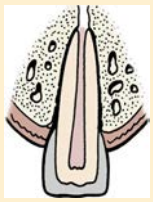
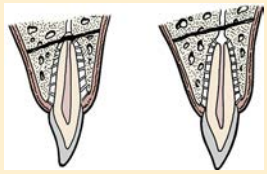
The sequence of treatment of dentoalveolar fractures is an inside-to-outside approach that includes bone, teeth, and then soft tissue. Accordingly, underlying alveolar bone injuries are treated first, followed by placement or reduction of the teeth as they relate to the underlying bone, and then the soft tissues are repaired. Prioritizing treatment sequence in the presence of other more critical bodily injuries, especially in a hospital setting, may sometimes preclude optimal treatment of the dental injury. Compromises are often unavoidable for the overall good of the patient.

Treatment of Specific Types of Injuries to the Hard Dental Tissues and Pulp

Crown Infraction

An infraction is an incomplete crack in the enamel without any loss of tooth structure. These are asymptomatic; if tenderness is present, other injuries such as luxations or fractures should be suspected. The infraction can be sealed with composite resin to avoid discoloration, but otherwise no treatment is indicated. These injuries may be easily missed and may require direct transillumination to diagnose. Pulp

TABLE 6-3 Injuries to Supporting Bone

Comminution of the alveolar socket	Crushing and comminution of the alveolar socket occur, together with intrusive and lateral luxation	
Fracture of the alveolar socket wall	Confined to the facial or lingual socket wall	
Fracture of the alveolar process	May or may not involve the alveolar socket	
Fractures of the mandible or maxilla	Involves the base of the mandible or maxilla and often the alveolar process; may or may not involve the alveolar socket	

Modified from Powers MP: Diagnosis and management of dentoalveolar injuries. In Fonseca JR, Walker RV, editors: *Oral and maxillofacial trauma*, ed 2, vol 1, Philadelphia, 1997, WB Saunders, p 333.

TABLE 6-4 Injuries to the Gingiva or Oral Mucosa

Mucosal or gingival contusion	A bruise that is submucosal hemorrhage without mucosal break and usually produced by a blunt object
Mucosal or gingival abrasion	A superficial wound resulting in a raw, bleeding surface usually produced by rubbing or scraping of the mucosa
Mucosal or gingival laceration	Shallow or deep mucosal wound from a tear and usually produced by a sharp object

Modified from Powers MP: Diagnosis and management of dentoalveolar injuries. In Fonseca JR, Walker RV, editors: *Oral and maxillofacial trauma*, ed 2, vol 1, Philadelphia, 1997, WB Saunders, p 333.

vitality tests are not reliable at the time of injury. However, teeth with crown infraction should be evaluated periodically to monitor the status of the pulp to determine the need for or the nature of treatment at a later time. Prognosis for pulpal health is good except in cases of combination injuries with concomitant subluxation, intrusion, or concussion, which could be often overlooked in an acute setting.[39,40]

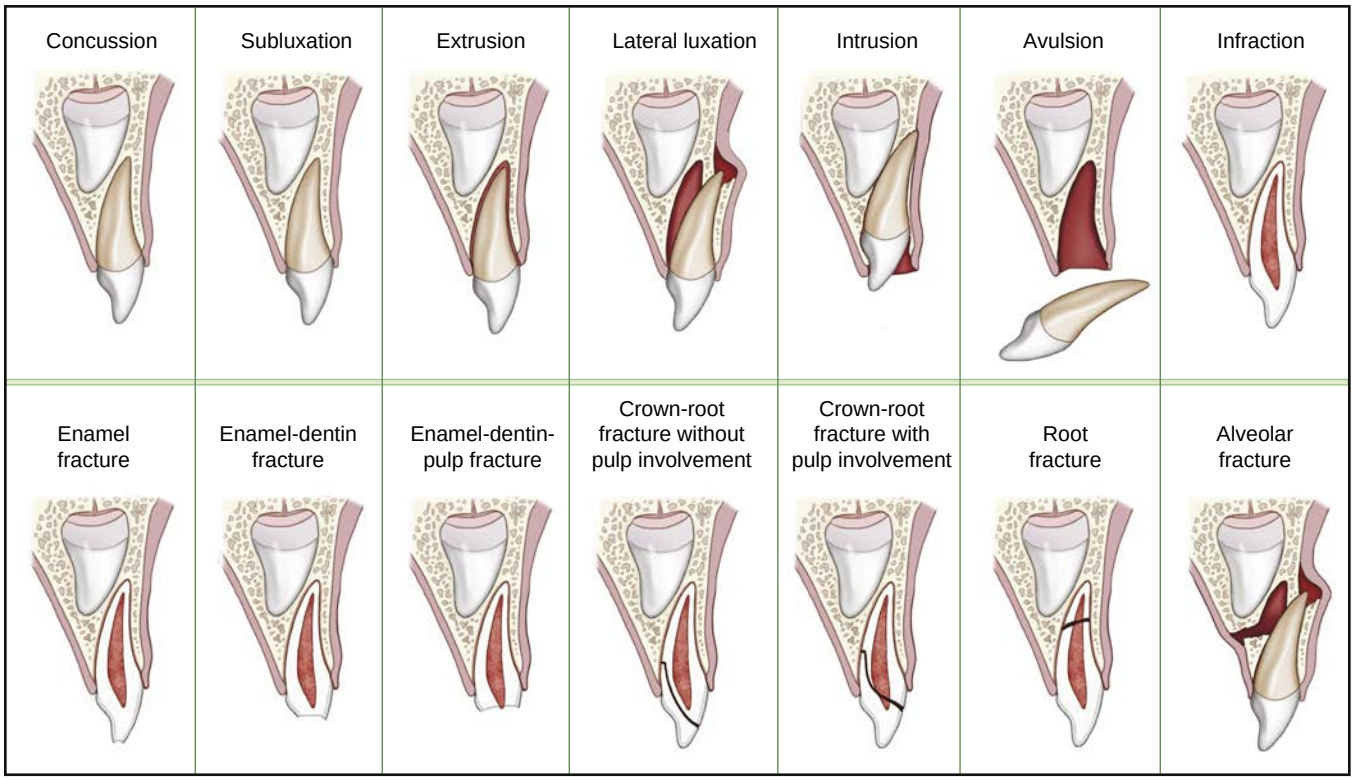
Crown Fractures

Enamel Fractures

The usual treatment for an enamel fracture is to smooth the sharp edges of the enamel or restore with composite and observe the tooth. The tooth fragment, if available, can also be bonded to the tooth. The accident impact force is not always proportional to the size of the fracture, and the pulp could later become necrotic; hence the need for periodic follow-up.

Enamel and Dentin Fractures

In permanent dentition, crown fractures account for 26% to 76% of all traumatic injuries seen in the dental office.[19] Radiographic and clinical examination is important to rule out tooth debris or fragments lodged in the soft tissue. Emergency treatment of enamel and dentin fractures is designed to reduce hyperemia and protect the pulp against any thermal stimuli or bacterial contamination. The tooth fragment, if available, can be bonded with bonding agents. A calcium hydroxide base should be placed on the exposed



• **Figure 6-8** Injuries to primary teeth. (Modified from the *Dental trauma guide 2010*. International Association for Dental Traumatology.)

dentin, followed by an immediate temporary protective acid-etch resin restoration, especially if the remaining dentin is in close proximity to the pulp. Acid-etch resin restorations should hold the calcium hydroxide in place for a sufficient length of time ideally (6-8 weeks) to allow secondary dentin formation. A light cured glass ionomer liner/base, such as Vitrebond (3M Dental Products, St Paul, MN), can be used in place of calcium hydroxide. Resin restorations should restore the contact area, prevent movement of adjacent teeth into the fractured area, and provide sufficient incisal length to prevent the tooth from moving lingually.

Concurrently, restoring crown contour will prevent overeruption of the opposing tooth. Intermediate resin restorations also allow the tooth to be pulp-tested. After allowing for secondary dentin buildup, the final acid-etch resin restoration can be placed.

Enamel, Dentin, and Pulp

The aim of treatment in cases of pulp exposure should be to preserve a vital noninflamed pulp along with formation of a biologic hard-tissue barrier.[19] Factors to be considered in treatment planning include (1) age of the patient, (2) length of time elapsed since the injury occurred, (3) size of the pulp exposure, (4) condition of the pulp (vital or nonvital), and (5) the stage of root development.

Pulp Exposure with Vital Pulp

The prognosis is best for teeth with a vital pulp exposure if the fracture is treated as soon as possible.[41] A combination injury such as luxation and root fracture increases the chance of pulpal necrosis. In young patients with immature root apices as well as with completely formed root apices, pulp capping or pulpotomy is the treatment of choice. Pulp capping is indicated in cases where there has been a small area of pulp exposure, both in roots with immature and in those with mature apices, if the patient is seen within 24 hours after the injury. Calcium hydroxide (CH) or mineral trioxide aggregate (MTA) can be used in cervical pulpotomies or partial (Cvek) pulpotomies after removal of the superficial area of inflamed and hyperemic pulp. The direct pulp cap or pulpotomy is designed to allow a tooth with an open apex or recently formed apex to complete root development (apexogenesis) and physiologic dentin apposition. An intermediate protective restoration should be placed. A tooth with a vital pulp and incomplete root formation has the best recovery prognosis. Usually teeth that have cervical pulpotomies will ultimately need root canal therapy along with a post-and-core plus a crown.[41]

If the pulp exposure is large and/or if it has been present longer than 24 hours, root canal therapy is favored. Recent studies have shown MTA to be able to form a calcific bridge without inflammation in the pulp, whereas CH showed lesser calcification and presence of inflammation in the pulps capped. MTA is growing in popularity among clinicians for apexogenesis and apexification.[41]

Pulp Exposure with Nonvital Pulp

Root canal therapy should be performed if the pulp is necrotic and there is a mature apex. Apexification procedures

should be performed if there is a necrotic pulp with an immature apex.[41] The purpose of this procedure is to provide a calcific seal at the apex prior to condensing the gutta percha. This differs from apexogenesis in which completion of the root occurs. In the apexification technique, the canal is cleansed and a calcium hydroxide paste is placed in the canal (Figure 6-9). In 3 to 6 months, the tooth should be evaluated radiographically for a calcific bridge. If bridging has occurred, a root canal with gutta percha can be done. On occasion the apexification technique might take up to 18 months and the calcium hydroxide might have to be replaced every 3 to 6 months. In successful apexification treatment, teeth do not undergo physiologic dentin apposition and they are left with thin dentinal walls. If a tooth with a successful apexification technique is injured again, the tooth would be more susceptible to a cervical-third root fracture due to the thin dentinal walls.

Crown-Root Fracture

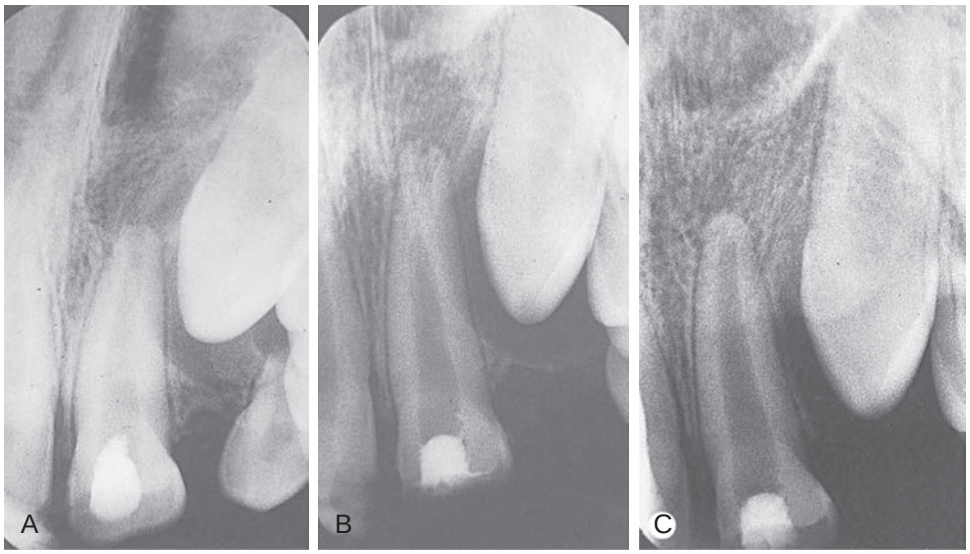
The treatment of crown-root fractures depends on several factors including the location of the fracture, the apical extent of the fracture, and whether the pulp is involved or not. Generally, emergency treatments for this type of fracture include temporary stabilization of the coronal fragment to the adjacent teeth and removal of these loose fragments before definitive treatment can be started sooner than later.[42] In fractures that are longitudinal and follow the long axis of the tooth or if the coronal fragment makes up more than one third of the clinical root, extraction is generally recommended. If the fracture line is above or slightly below the cervical margin, appropriate forms of conservative therapy can usually be employed to restore the tooth (Figure 6-10). Such therapies usually include crown-lengthening procedures or orthodontic elevation of the fracture site to provide for access for restorative margins. In young patients, treatment of this type of fracture is also influenced by whether the apex of the tooth is mature or immature. If the tooth is mature and restorable, endodontic treatment is indicated prior to restoration, whereas if the tooth is immature and the apex is open, a pulpotomy should be performed with a calcium hydroxide base and the tooth followed radiographically for closure of the apex. After such closure, definitive root canal therapy and permanent restoration can be completed.[40,42]

Root Fractures

Root fractures are relatively uncommon, with an incidence of 2.5% to 8% varying with age. They are found more commonly in adults, and they generally occur in teeth with complete root development, with the maxillary central incisor being the most common tooth.[44] Clinically, a root fracture is usually seen as an extruded tooth displaced lingually, making it difficult to differentiate from luxation injuries. Most root fractures occur in the apical and middle third and only rarely in the cervical third. Location of the root fracture plays a significant role in the prognosis of the tooth and hence in the treatment planning.[44]

Occlusal radiographs are useful for identifying the apical-third root fractures; periapical radiographs can identify root fractures at the middle and cervical thirds.

Radiographs taken immediately after an injury may not show a horizontal or diagonal root fracture. Intraoral periapical 90-degree film with central beam through the tooth can show a horizontal fracture more commonly in the cervical third of the root. In root fractures, separation of the

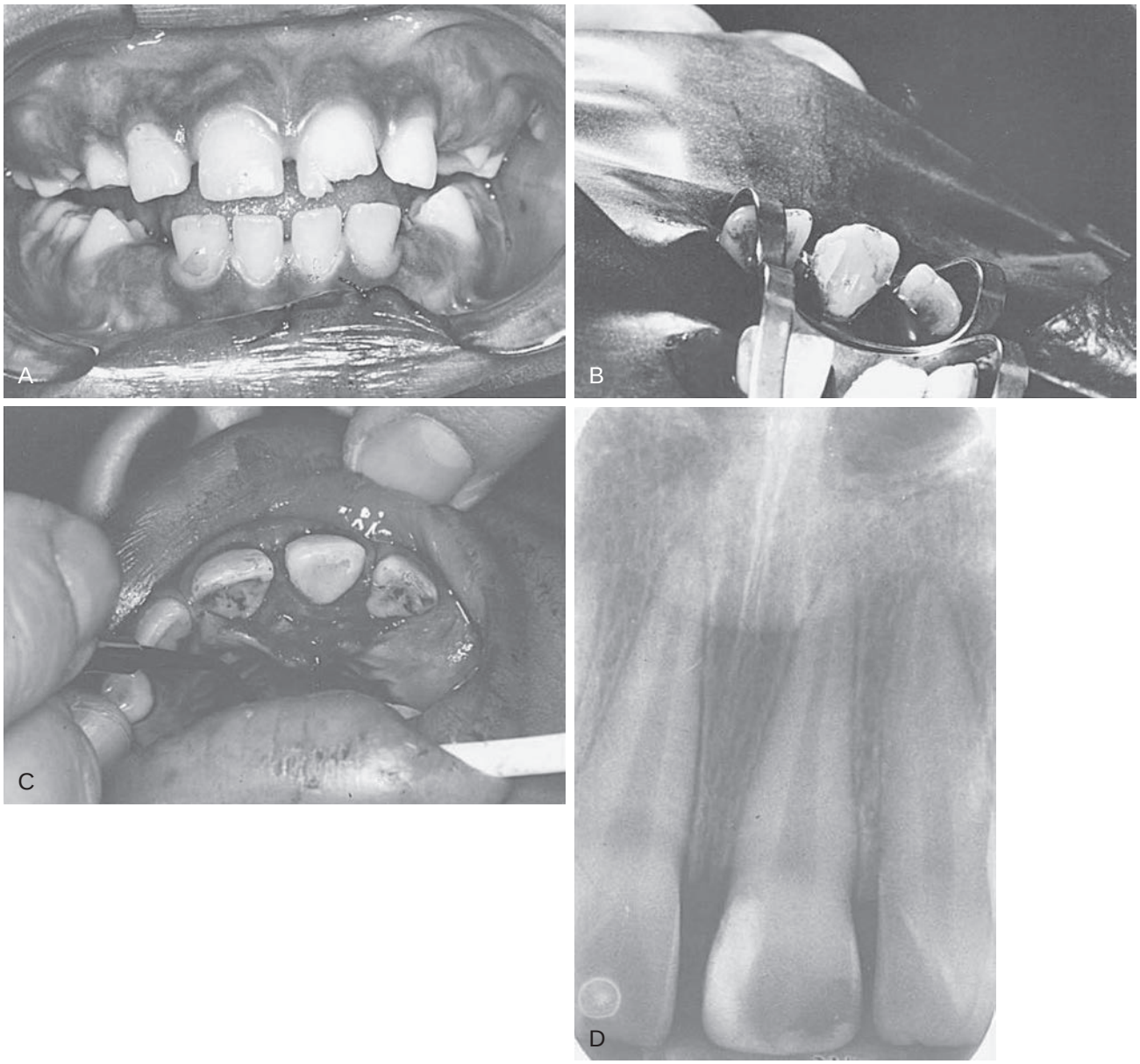


• **Figure 6-9** Periapical radiographs showing the results of the apexification procedure. **A,** A left central incisor necrotic tooth with an immature apex. **B,** The same incisor seen in Figure 6-8a after the placement of calcium hydroxide paste in the apex of the canal. **C,** Four months following treatment, note the radiopaque barrier that has formed at the apex. (From Abubaker AO, Papadopoulos H, Giglio JA: Diagnosis and management of dentoalveolar injuries. In Fonseca R, Marciani RD, Turvey TA, editors: *Oral and maxillofacial surgery*, ed 2, St Louis, 2009, Saunders.)

fragments must be substantial to appear on a radiograph. Only after a week or two, when hemorrhage, inflammation, and resorption have caused the fragments to separate, will the radiograph show the damage more conclusively. Diagonal root fractures are the most difficult to diagnose and are missed on intraoral periapical films. In suspected diagonal root fractures, a foreshortened (45-degree angulation) and an elongated (110-degree angulation) periapical film should be taken in addition to the standard 90-degree angulation.[40] Vertical root fractures in a labiolingual but not in a mesiodistal direction are easily discernible on a radiograph. Extraction is the treatment of choice in vertical root fractures because of nonrestorability.

Root fractures in the apical third without mobility require minimal treatment to avoid further trauma and improve the prognosis. The basic principle of treatment of root fractures with mobility consists of apposition of the fractured segments with flexible splinting for 4 weeks to 4 months for cervical-level root fractures. Splinting for 4 months is necessary because the repair of root fractures is similar to the repair of bone fractures, except slower.[41]

The treatment philosophy for cervical-third root fractures has changed significantly over the past decade. Extraction of the coronal part of the fracture followed by endodontic treatment was favored. Recent data have shown that—except for cervical-half root fractures, which are very close



• **Figure 6-10** **A,** A fracture of the maxillary left permanent central incisor. **B,** Isolation of the tooth after flap surgery was done to see the extent of the fracture. **C,** The fracture restored with an acid-etch resin system. **D,** A periapical radiograph 1 year following treatment. (From Abubaker AO, Papadopoulos H, Giglio JA: Diagnosis and management of dentoalveolar injuries. In Fonseca R, Marciani RD, Turvey TA, editors: *Oral and maxillofacial surgery*, ed 2, St Louis, 2009, Saunders.)

to the gingival crevice—splinting and follow-up has helped the fractures heal with formation of hard tissues.[46] If pulp in the coronal segment undergoes necrosis, then orthodontic treatment of a cervical-third root fracture with removal of the coronal segment is considered.[47]

Root fractures can heal by four different modalities: (1) calcified tissue, (2) connective tissue, (3) bone and connective tissue, and (4) granulation tissue.[45] Healing by calcified tissue is usually seen in teeth with immature roots or in teeth with little or no fragment separation.[46] Radiographically, the segments are not rounded at the edges. In connective tissue healing, radiographically the segment edges are rounded, with partial or complete pulpal obliteration.[45] In healing with bone and connective tissue, each segment has its own periodontal ligament, and total calcific metamorphosis of both segments is a usual occurrence. In healing with granulation tissue, the teeth are usually loose, slightly extruded, and sensitive to percussion. The pulp in the coronal segment usually undergoes necrosis, whereas in the apical segment it is vital.

Monitoring is recommended for at least 1 year prior to determining the final pupal status in absence of other signs and symptoms.[40] Root canal therapy is withheld for apical and middle-third root fractures, until there is evidence of pulpal necrosis. Pulpal necrosis is usually seen only in the coronal segment. Increased separations of the segments with an adjacent radiolucency and tenderness to percussion are indications of pulpal necrosis. Endodontic treatment for root fractures consists of (1) pulpectomy of the coronal segment only, (2) pulpectomy of both segments, or (3) pulpectomy of the coronal segment with surgical removal of the apical segment.[48]

Treatment of Injuries to the Periodontal Tissues

Concussion

A concussed tooth is one that has received a traumatic insult but exhibits no evidence of mobility, displacement, or fracture. The tooth may be sensitive to percussion and/or exhibit symptoms of hyperemia. No treatment is recommended other than palliative therapy. If there are excessive masticatory forces on the injured tooth, taking the tooth out of function by relieving the occlusion may help. Concussed teeth may later develop a reaction to the trauma. The patient must be advised that additional treatment may be required and that the prognosis is guarded; however, the incidence of pulpal necrosis is low.[40,49]

Displacements

extrusions (partial avulsions).

Subluxation

The tooth demonstrates tenderness to palpation with slight mobility but without evidence of displacement clinically and radiographically. No active treatment is usually necessary, but a flexible splint can be placed for up to 2 weeks for patient comfort. Patients have masticatory discomfort, which can be managed with a soft non-chew diet and relieving the occlusion. Continued observation of the tooth radiographically and by vitality testing during the follow-up period is essential. False-negative vitality tests are possible for up to 3 months, after which root canal therapy is usually necessary. This type of displacement injury has the best chance of the tooth remaining vital since the apical vessels are not displaced.

Extrusive Luxation

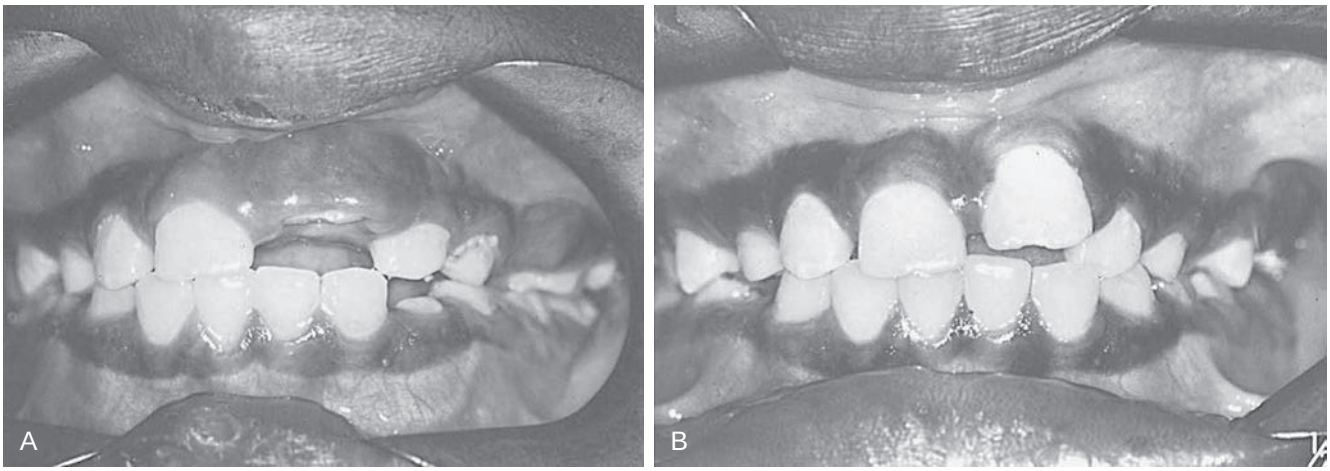
In extrusion injuries, the tooth is partially displaced from the socket, resulting in excessive mobility. Radiographic examination shows increased periodontal ligament space in the apical region. It should be repositioned in its original position using digital pressure and splinted with a flexible splint for 2 weeks. Continued clinical and radiographic observation is essential to identify pulpal necrosis and perform endodontic treatment. False-negative vitality tests are possible for up to 3 months.

Lateral Luxation

Lateral luxation is a complex injury that includes rupture or compression of the periodontal ligament (PDL), severance of the neurovascular bundle, and fracture of the alveolar walls around the tooth.[50] This causes lingual (most common), buccal, mesial, or distal displacement of the crown of the tooth. Such displacement is often painful, associated with large gingival laceration, and places the tooth in a "locked" position. The initial treatment of lateral luxation of the tooth is aimed at relieving the pain associated with this injury by repositioning and stabilizing the displaced tooth. This can usually be done by digitally manipulating the tooth to release the displaced root apex and repositioning the tooth into the proper alignment along with a flexible splint placement for 4 weeks. Repositioning of the tooth may require pressure application in the incisal direction to release the lock and return the root apex to its original location. These displacements should be followed closely to determine vitality. Such teeth may not respond normally to electric pulp testing for about 3 months. Follow-up examinations are therefore necessary, and depending on the stage of root development at the time of injury, endodontic therapy may be needed.

Intrusive Luxation

This results from apical displacement of the tooth into the alveolar bone. Intruded teeth are immobile with an ankylotic sound on percussion with minimal sensitivity. Stage of root development is a critical factor in treatment planning. In intruded permanent teeth with incomplete root development, spontaneous re-eruption is the first line of treatment (Figure 6-11). If there are no signs of re-eruption after a



• **Figure 6-11 A,** Intrusion of a maxillary left permanent central incisor with an immature apex. **B,** Six months later the tooth has partially re-erupted. (From Abubaker AO, Papadopoulos H, Giglio JA: Diagnosis and management of dentoalveolar injuries. In Fonseca R, Marciani RD, Turvey TA, editors: *Oral and maxillofacial surgery*, ed 2, St Louis, 2009, Saunders.)

month, orthodontic repositioning may be required. If the intrusion is greater than 7 mm to begin with, orthodontic or surgical repositioning or a combination should be performed. Repositioning is followed by flexible splinting for 4 to 8 weeks. Orthodontic repositioning has been shown to have better marginal bone levels compared to surgical repositioning. Root canal therapy for re-erupted intruded teeth with an immature apex should only be done if signs of pulpal necrosis develop. Time is allowed for apexification prior to definitive endodontic treatment. In general, intruded teeth with immature root formation have a better prognosis with regard to pulpal necrosis.[51]

If the tooth has completed root development, allow spontaneous eruption only if displacement is less than 3 mm.[40] If there is no sign of spontaneous eruption in 2 to 4 weeks, orthodontic extrusion is recommended. In cases of severe displacement (>7 mm), surgical repositioning to its original position either by finger pressure or with forceps is performed, followed by flexible splint for 4 to 8 weeks. The incidence of pulpal necrosis in this type of injury in general is 88%; therefore endodontic therapy is initiated 10 to 14 days after the injury.[51] Inflammatory and/or replacement resorption can occur in approximately 48% of these teeth. The depth of intrusion has been found to be a factor in the development of root resorption, with intrusions of 1 to 3 mm having the lowest frequency.[51] For intruded teeth with completed root development, there is high likelihood of pulp necrosis. Calcium hydroxide can be placed as a temporary filling, followed by definitive endodontic treatment within 2 to 3 weeks.[40]

Exarticulation (Complete Avulsion)

Avulsion involves complete displacement of the tooth out of its socket. It may occur by itself or in conjunction with alveolar fractures and/or gingival lacerations. Children between 7 and 9 years of age are more often subject to avulsion because of the unsettled condition of the periodontal ligament and low mineralization of the alveolar bone caused by continued eruption of the teeth. Usually avulsion involves a single tooth, and the most frequently avulsed tooth is the maxillary central incisor. The chances of survival of the pulp and periodontal cells in a replanted tooth are highly dependent on the extra-alveolar time and handling of the avulsed tooth, which affect the pulp and periodontal reactions.[53] Treatment must be aimed at maintaining cellular viability, which can increase the chances of successful reattachment and decrease the chances of root resorption. The tooth's pH, osmolality, and cell metabolites can be physiologically maintained by various storage media. The periodontal ligament is usually restored in 3 to 4 weeks after a prompt replantation. After an extraoral dry time longer than 60 minutes, the periodontal ligament cells become nonviable.[54] The viability of the PDL can be assessed based on the extraoral dry time, storage media, and time of replantation. The treatment plan for avulsed teeth relies on maturity of the root apex and condition of the PDL cells.

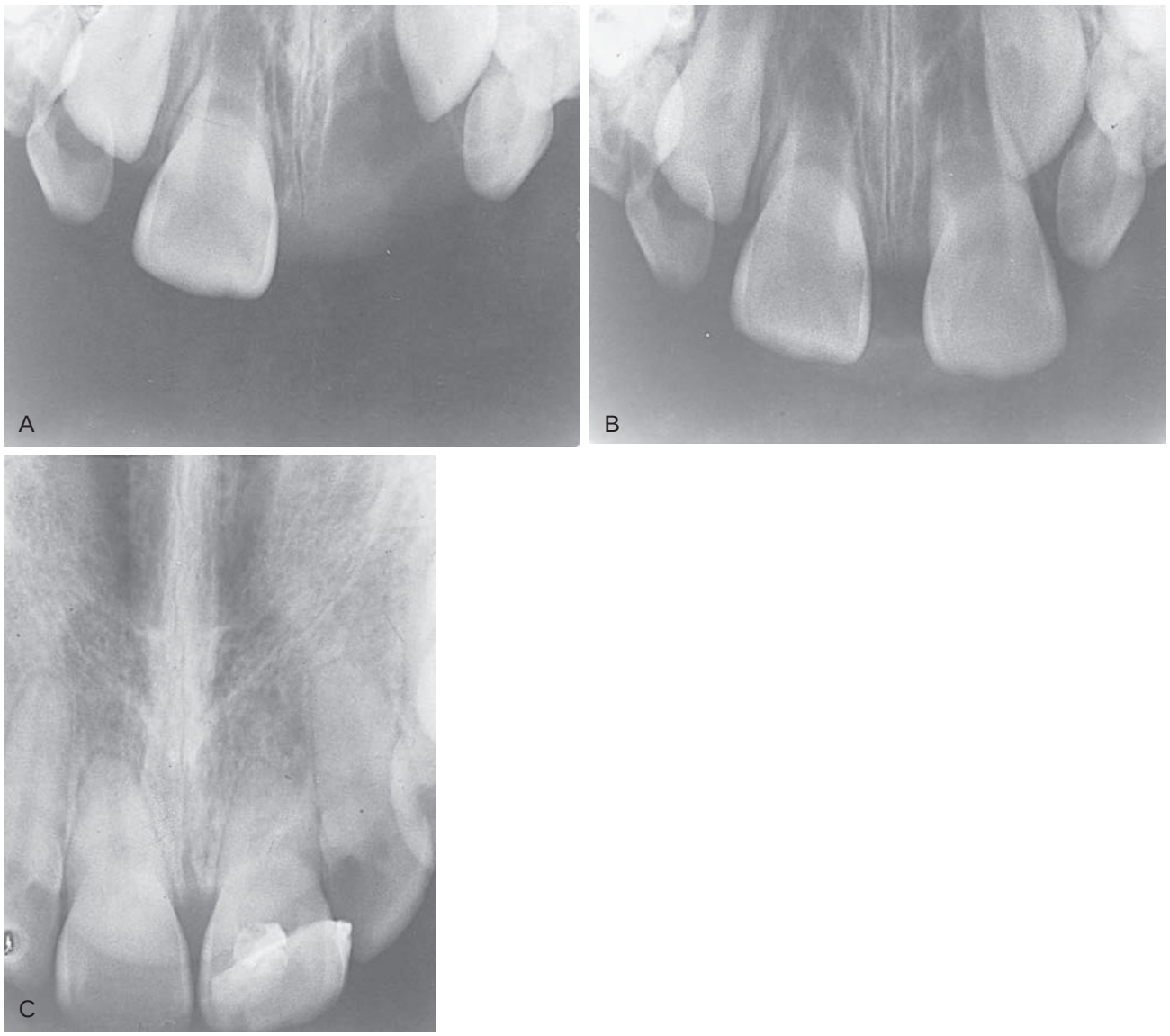
Teeth that are nonrestorable because of extensive caries or severe periodontal disease should not be replanted, except for the temporary purpose of maintaining alveolus or esthetics until a definitive replacement is planned. In teeth with a closed apex and pulp that have been replanted prior to arrival or have a extraoral dry time of less than 60 minutes and have been stored in an appropriate storage medium, replantation should be performed, with a flexible splint for up to 2 weeks. Endodontic treatment should be performed on these teeth within the first 7 to 10 days before splint removal.[54] In teeth with a closed apex that have had more than 60 minutes of extraoral dry time, the PDL is likely nonviable. Splinting can still be performed, but the patient should be informed of the poor prognosis and increased probability of eventual loss of the tooth, likely due to replacement resorption. Flexible splinting is recommended for 4 weeks. Endodontic treatment on these teeth can be

performed either prior to replantation or within 7 to 10 days after replantation. In children and adolescents, ankylosed teeth with infra-positioning can be managed with decoronation. Patients and parents should be informed about the possibility of ankylosis and indications for decoronation.

In avulsed permanent teeth with open apex that were replanted before the patient's arrival or have an extraoral dry time of less than 60 minutes, the goal of replantation is possible revascularization of the pulp. On the other hand, if the extraoral dry time was greater than 60 minutes, the long-term prognosis is poor and hence the goal is restoring the tooth for esthetic/psychosocial/functional purpose. The ultimate outcome in these teeth is ankylosis or resorption. The time period of flexible splinting is similar to that for teeth with a closed apex: 2 weeks for early replantation and 4 weeks for delayed replantation.

The overall prognosis for replanted permanent teeth in terms of continued pulp vitality is very poor. However, replanted teeth are useful during the mixed dentition stage in children even if the long-term prognosis is poor, because alveolar bone support is maintained during maxillary growth. These replanted teeth also serve as a good esthetic space maintainer, even if it is for only a few years. The central incisor also provides guidance for the eruption of the lateral incisor into its position in the arch (Figure 6-12), as would the lateral incisor for the canine.

In general, the avulsed tooth should be gently rinsed under tap water before replantation; it should not be



• **Figure 6-12** **A,** An occlusal radiograph of an avulsed immature maxillary left permanent central incisor prior to the eruption of the permanent lateral incisor. **B,** The tooth was replanted within 1 hour. The tooth has had the calcium hydroxide paste replaced every year. Seven years later the replanted tooth has served as guidance for the lateral incisor **(C).** (From Abubaker AO, Papadopoulos H, Giglio JA: Diagnosis and management of dentoalveolar injuries. In Fonseca R, Marciani RD, Turvey TA, editors: *Oral and maxillofacial surgery*, ed 2, St Louis, 2009, Saunders.)

scrubbed. If the tooth is maintained by soft tissue attachment, this attachment should not be removed. The objective is to maintain vital periodontal tissue and cementum. The tooth should be held in place either by finger pressure or by gently biting down on a handkerchief or washcloth until the patient is brought to the office or emergency room. If replantation is not possible, the tooth should be placed in the best transport medium available. The transport medium of choice is Hanks balanced salt solution (HBSS) or Viaspan.[55-57] Viaspan is used for transport organ storage. It has a pH of 7.4 with an osmolality of 320 mOsm, and vital cells were present at 7 days.[57] Hanks solution has a pH of 7.2 with an osmolality of 320 mOsm. Hanks can successfully preserve and reconstitute the periodontal ligament cells for at least 24 hours. Depleted cell metabolites can be replenished in Hanks solution.[58] Hanks solution is commercially available as Save-A-Tooth (3M Health Care) (Figure 6-13).

Milk, saliva, and saline are temporary storage media more readily available to the public; however, their effectiveness is very limited. Milk is a short-term storage medium (up to 6 hours) provided avulsed teeth are placed in it within 15 to 20 minutes. Milk only prevents cell death; it does not restore the cell's normal morphology and ability to differentiate and undergo mitosis. Milk has no ability to maintain viability after the cells have been dry stored for more than 20 minutes. Milk is a significantly better medium than saliva or water for preserving periodontal fibroblast viability and proliferative ability. If the tooth cannot be replanted immediately, it should be stored in milk if Hanks solution is not available. Storage of avulsed teeth in water or saliva should be avoided since they can damage the periodontal ligament cells and cause increased root resorption. Once teeth have been placed in Hanks solution, time is no longer as critical a factor.

Once the patient reaches the treatment facility, the tooth should be rinsed with saline. Any remaining periodontal ligament should not be removed. The alveolar socket should be debrided by saline irrigation without curettage. The blood clot should not be removed, because it will not interfere with positioning of the tooth or pulpal and periodontal healing. The tooth should be replanted and splinted as soon as possible. Manually compress the facial and lingual bony plate if spread apart. A radiograph should be taken to verify proper positioning of the replanted tooth. The need for tetanus prophylaxis should be evaluated. The value of antibiotic coverage for replanted teeth has not been clearly established by clinical studies, although experimental studies favor topical antibiotics. A 7- to 10-day course of amoxicillin is usually prescribed to prevent secondary infection from occurring and to promote wound healing.[53] The tooth should be taken out of occlusion, and the patient should not chew on it for the first month. When relieving the occlusion, reduction on the opposing teeth is preferable to avoid further pulpal injury. The patient should be instructed on gentle but thorough tooth brushing to prevent inflammation in the gingival crevice. Chlorhexidine rinses should be prescribed for gingival health, and analgesics for pain.



• **Figure 6-13** Save-A-Tooth containing Hanks balanced salt solution and a basket for placing the avulsed tooth.

Teeth with immature apices have a better prognosis than do teeth with mature apices. Immature teeth soaked in a doxycycline solution have a higher rate of pulpal revascularization than those not treated.[59] Tetracycline, in animal studies, has been also been shown to have antiresorptive properties.[60,61] If pathology is noted, thoroughly clean and fill the canal with calcium hydroxide (apexification procedure).

In 7 to 10 days the pulp should be removed and the canal filled with calcium hydroxide. The tooth can be obturated with gutta percha after 6 to 12 months of calcium hydroxide, provided there is no pathology present.

In teeth with an open or closed apex that have been extraoral for more than 60 minutes, endodontic treatment can be carried out prior to replantation or after. These teeth could be soaked in a 1% stannous fluoride solution for 5 minutes and in a 1 mg/20 mL doxycycline solution for 5 minutes. The antibiotic kills the bacteria that might remain on the root surface and has been shown in animal studies to synergize with the stannous fluoride to make the tooth more resistant to resorption.[62,63]

The two major reasons for failure of replanted teeth are inflammatory and replacement resorption (ankylosis). Inflammatory resorption is due to necrotic pulp, and replacement resorption is due to damage to the periodontal ligament. Andreasen and colleagues showed in a study on 400 replanted teeth that normal periodontal healing occurred in 24%, surface resorption in 5%, inflammatory resorption in 30%, and replacement resorption in 64% of cases.[64] Radiographically, the first signs of pulpal necrosis may be seen in 2 to 3 weeks, and inflammatory resorption could take 3 to 6 weeks up to 6 months. Inhibition of inflammatory resorption involves removal of necrotic tissue and filling the root canal with calcium hydroxide. Replacement resorption or ankylosis can be diagnosed clinically by percussion and immobility in 4-8 weeks, but radiographic evidence could take up to a year.[67] The extent of the injury, concomitant alveolar fractures, and age of the patient can affect the rate of progression of replacement resorption.[65,67] In younger patients, ankylosis alters the normal alveolar growth, resulting in infraocclusion of the replanted tooth.

There is no treatment for ankylosis as such, but to avoid extensive loss of alveolar bone from extraction of these teeth in younger children, decoronation, involving removal of the crown and the root canal filling so as to allow replacement of the remaining root with bone, has been the procedure of choice. This allows continued growth of alveolar bone coronal to the resorbing root.[68]

Radiographs should be taken in 2 weeks, 1, 2, 3, and 6 months, and then semiannually thereafter. The practitioner should also evaluate the unaffected adjacent teeth in displacement and avulsion injuries. Usually 50% of the supposedly unaffected adjacent teeth will undergo pulpal necrosis within 2 years from the time of injury. Finally, crown discol-[69]

Calcium Hydroxide Root Canal Fill

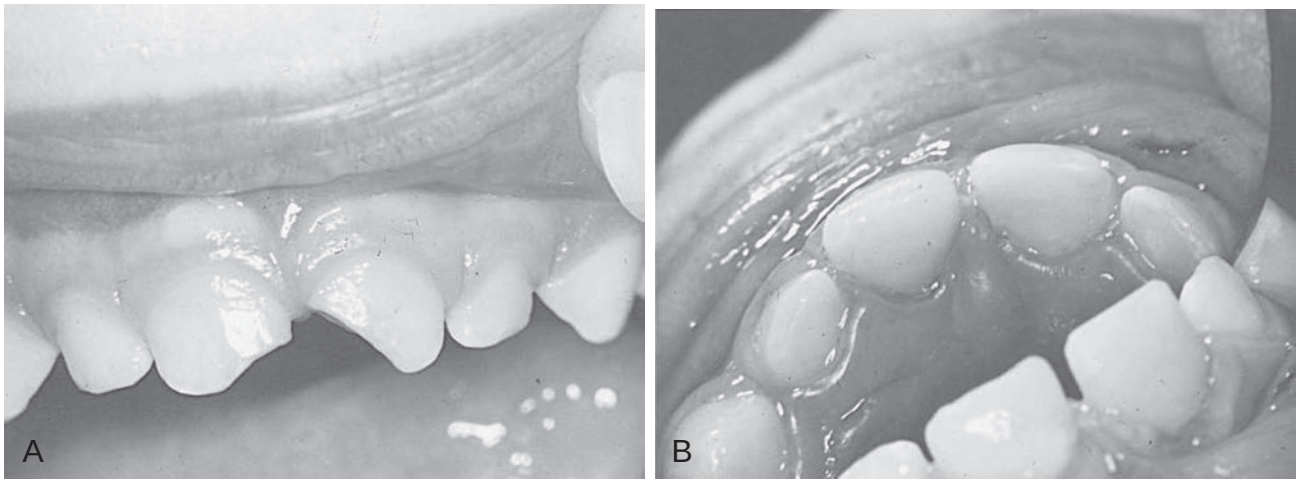
Inflammatory resorption usually occurs in teeth that have undergone severe displacement or avulsion. It appears to be related to pulpal necrosis. Removal of the necrotic pulp and the placement of calcium hydroxide in the canal appear to inhibit inflammatory resorption.[70-72] Calcium hydroxide should be used in avulsion and intrusion injuries and any luxation injury in which the tooth is displaced more than 3 to 5.0 mm. The procedure involves removal of the pulp and instrumenting the root canal thoroughly during the first or second week after the injury.[73] The canal should be filled with USP calcium hydroxide powder or Pulpdent (calcium hydroxide in aqueous methyl cellulose from Pulpdent Corp., Watertown, MA) (Figure 6-14). Filling the canal with calcium hydroxide at 1 to 2 weeks will allow initial repair of the periodontal ligament.[74] The powder may be inserted dry or made into a paste with either a local anesthetic solution, water, saline, camphorated monochlorophenol (CMCP). Because calcium hydroxide is a resorbable material, the canal should be recleansed and repacked with calcium hydroxide at 3-month intervals for a minimum of 1 year. There is no need to change the calcium hydroxide if it appears to occupy the root canal space adequately at the 3-month evaluation. If resorption is arrested or nonexistent, a gutta percha root canal can be done at the end of the year.

Treatment of Injuries to the Primary Teeth

Injuries involving primary dentition and injuries to children in general deserve special consideration. Difficulties with patient management due to lack of cooperation, as well as concern regarding underlying permanent dentition and the consequences, are some major factors affecting management. The treatment plan should aim at preventing or minimizing the injury to permanent dentition. Displacement injuries rather than fractures are more frequent in the primary dentition, in part because of the anatomic differences between a child and adult jaw in terms of bone mineralization and density. Most traumatic injuries to the primary teeth occur when the child is learning to walk, at 18 to 30 months old.[19,21,75]

Fractures of Primary Teeth

Fractures of primary teeth are less common than in the permanent dentition. Treatment of fractured primary teeth presents difficulties because of the small size of the tooth and the relatively large pulp chamber. In fractures involving enamel only, the sharp edges should be smoothed and the tooth observed. The same treatment can be provided for enamel and dentin (Class II) fracture. In severe or large fractures, calcium hydroxide/MTA and/or a light-cure glass ionomer liner/base (e.g., Vitrebond, 3M Dental Products) should be placed over the dentin followed by an acid-etch resin restoration[75,76] (see Figure 6-12). In primary teeth with fractures involving the pulp,



• **Figure 6-14** **A,** Mesioangular fractures of the maxillary primary central incisors. B, Acid-etch restorations placed using celluloid crown form. (From Abubaker AO, Papadopoulos H, Giglio JA: Diagnosis and management of dentoalveolar injuries. In Fonseca R, Marciani RD, Turvey TA, editors: *Oral and maxillofacial surgery*, ed 2, St Louis, 2009, Saunders.)

a calcium hydroxide partial pulpotomy should be performed, followed by a full-coverage restoration. Extraction of the involved tooth is the alternative option. Full coverage of all teeth that have pulpotomies or pulpectomies is necessary because the crown of the tooth is weak, usually unsupported, and is liable to fracture below the gingival attachment or crest of the alveolus.[75]

Root fractures are extremely rare. The most common root fracture occurs in the middle third of primary teeth (Figure 6-15). If the fracture is present in the apical third and the coronal segment exhibits no mobility, the tooth should be observed. If the fracture of the root occurs in the middle or cervical third, the coronal segment may be mobile and should be removed while the apical segment is left to resorb. The apical fragment should not be removed if injury to the developing permanent tooth is a possibility.[75]

If fistula, redness, or swelling appears, the tooth should be treated with pulpectomy or be removed. Teeth with zinc oxide and eugenol pulpectomies may not resorb normally and can cause displacement of underlying permanent teeth.[77] Pulpectomies should not be attempted on primary teeth with external resorption.

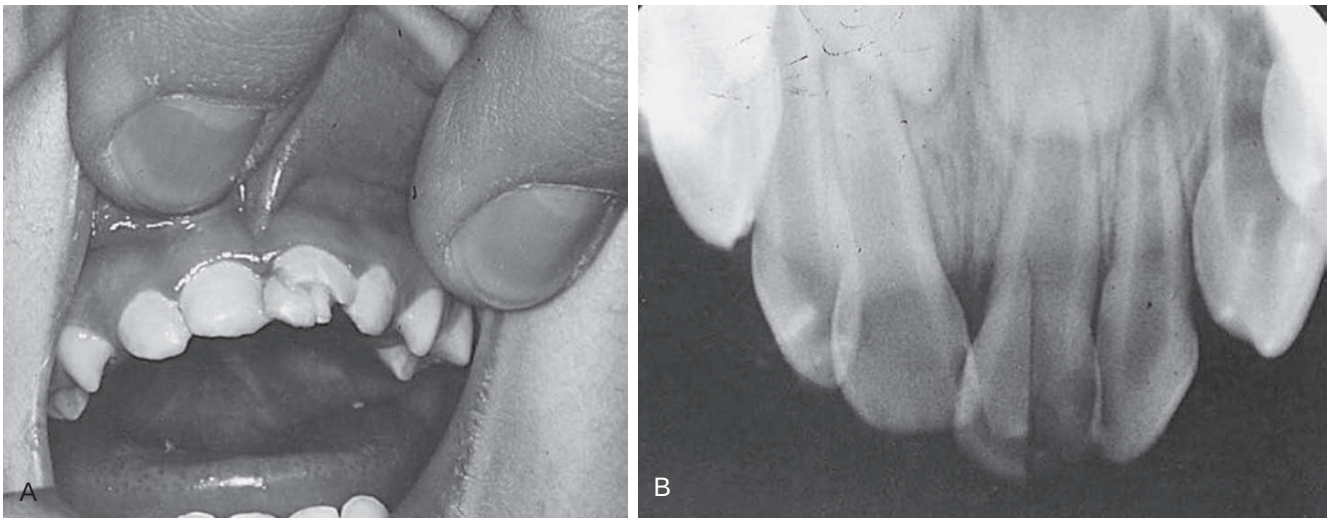
Displacements of Primary Teeth

Displacement injuries are more common in the primary dentition than in the permanent dentition. Primary teeth that have been subluxated do not need any acute treatment. They should be observed and the patient instructed about soft diet and oral hygiene measures. Treatment of displaced primary teeth depends on maturity of root formation, severity of displacement, and proximity or potential for injury to the permanent tooth bud. Laterally luxated teeth with the root apex displaced moderately in a labial direction with severe occlusal interference should be repositioned with digital pressure. Usually the tooth will snap back into position, and splinting may not be necessary. But depending on the patient's cooperation, a short period of splinting can be performed. Physiologic forces can be relied on to reposition the displaced tooth when the displacement is minimal and when there is no occlusal interference, as in the case of an anterior open bite. If the root apex is displaced into the permanent tooth, bud extraction is recommended. If a primary tooth is extruded, spontaneous realignment can happen in minimal extrusions (<3 mm) with immature root development. A tooth with a fully formed root with severe extrusion should be extracted.[75]

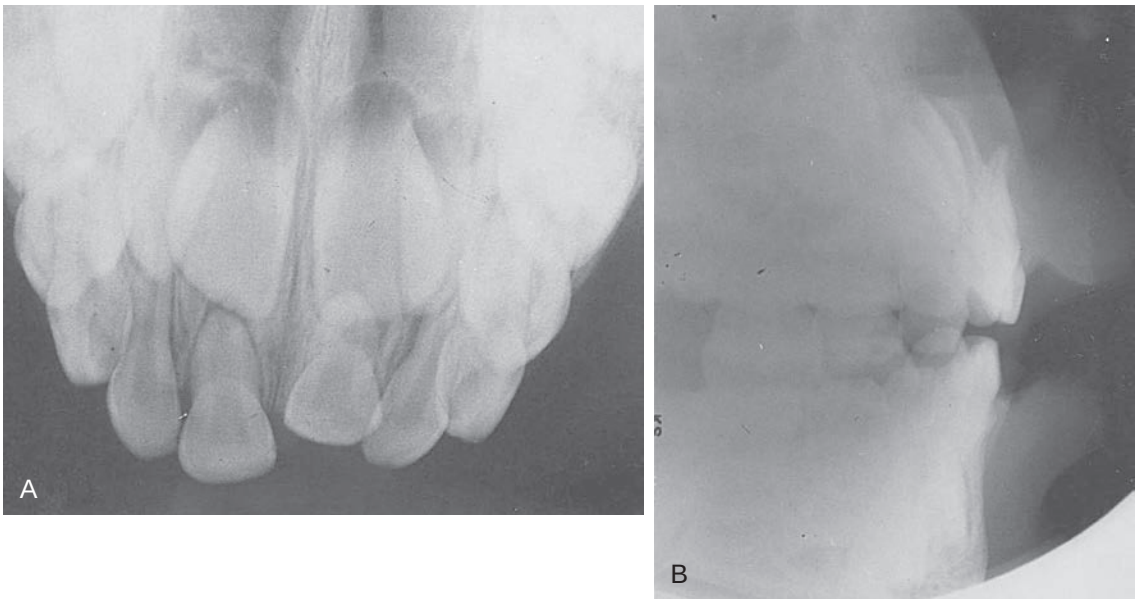
When a primary tooth is intruded, the practitioner should observe the tooth for re-eruption if the apex is displaced in a labial direction; otherwise, the tooth should be extracted (Figure 6-16). If the primary tooth has not started re-erupting within 4 to 8 weeks, it should be extracted. If acute inflammation and swelling, or inflammation of the gingiva and/or purulence from the gingival crevice, develop during the re-eruption phase, the tooth should be extracted. In primary teeth with alveolar fractures, the segment is repositioned and stabilized using a flexible splint for 4 weeks.

Replantation of primary teeth is not recommended. More importantly, the replacement of an avulsed primary of the permanent tooth.

Premature loss of a primary incisor before the eruption of the primary canines usually results in arch perimeter loss. Primary incisors lost after the eruption of the primary canines usually result in space loss in crowded or nonspaced arches but not usually in spaced arches. However, adjacent teeth in the anterior segment can drift, which could cause an esthetic problem.



• **Figure 6-15** **A,** A vertical fracture of a maxillary left primary central incisor. **B,** An occlusal radiograph showing that the vertical fracture extends to the middle of the tooth. The tooth was later extracted. (From Abubaker AO, Papadopoulos H, Giglio JA: Diagnosis and management of dentoalveolar injuries. In Fonseca R, Marciani RD, Turvey TA, editors: *Oral and maxillofacial surgery*, ed 2, St Louis, 2009, Saunders.)



• **Figure 6-16** **A,** An occlusal radiograph showing an intruded maxillary primary central incisor. **B,** A lateral radiographic view showing the tooth displaced in a vestibular direction. (From Abubaker AO, Papadopoulos H, Giglio JA: Diagnosis and management of dentoalveolar injuries. In Fonseca R, Marciani RD, Turvey TA, editors: *Oral and maxillofacial surgery*, ed 2, St Louis, 2009, Saunders.)

Premature loss of primary incisors will not cause a delay or disruption in speech.[79-81] Parents are usually more concerned with the esthetics of the child. If the child had normal speech prior to the premature loss of the incisors, adaptation to the new environment should occur. In some cases, there may be some lisping until the eruption of the permanent incisors. Replacing the teeth with a prosthetic appliance, though not necessary for speech, will create a more normal oral environment that will foster the maintenance of previously normal speech.

A primary incisor removed before the age of 3 generally causes a delay in the eruption of the permanent successor; a primary incisor removed 1 to 2 years before its normal exfoliation time generally causes an acceleration in the eruption of the permanent successor. The eruption of the permanent successor often occurs in a more facial direction.[82]

Treatment of Injuries (Fractures) to the Supporting Bone

Fractures of the supporting bone can be divided into four types.[83]

Comminution of the Alveolar Socket

This type of fracture is usually associated with dental injuries such as lateral or intrusive displacement of teeth. Digital manipulation and repositioning of the displaced tooth is often adequate to reduce these fractures. Monitoring the pulpal status of the tooth and evidence of root resorption and ankylosis by routine follow-up is recommended.

Fractures of the Socket Wall

Fractures of the socket wall are often associated with dislocation of teeth with mobility of the buccal osseous plate and mucosal contusion. Reduction of these fractures after administration of local anesthesia can be achieved using simultaneous digital pressure over the apical area and at the lingual aspect of the crown. In case of comminuted fractures, loose fragments not attached to the periosteum should be removed and attempts to preserve the tooth should be made. After completion of the reduction, any mucosal laceration should be sutured, the involved teeth should be relieved from forces of traumatic occlusion, and the segment should be splinted for 4 weeks to allow for osseointegration. The patient should be maintained on soft diet for 2 weeks and followed periodically to monitor pulp and tooth healing.

Fractures of the Alveolar Process

Alveolar process fractures may be isolated or may be seen in conjunction with other dental or facial injuries and with varying degrees of mucosal or gingival laceration. In most instances the fractured bony segment contains one or several teeth. Treatment consists of proper reduction and repositioning of the fractured segment using closed or open techniques followed by adequate stabilization to allow for osseous healing.[40] Closed reduction of dentoalveolar fractures may be accomplished with digital



• **Figure 6-17** **A,** Displaced dentoalveolar segment involving the maxillary anterior teeth. **B,** Closed reduction of dentoalveolar fractures using digital pressure on the alveolus and dental segment along with placement of a splint for stabilization.

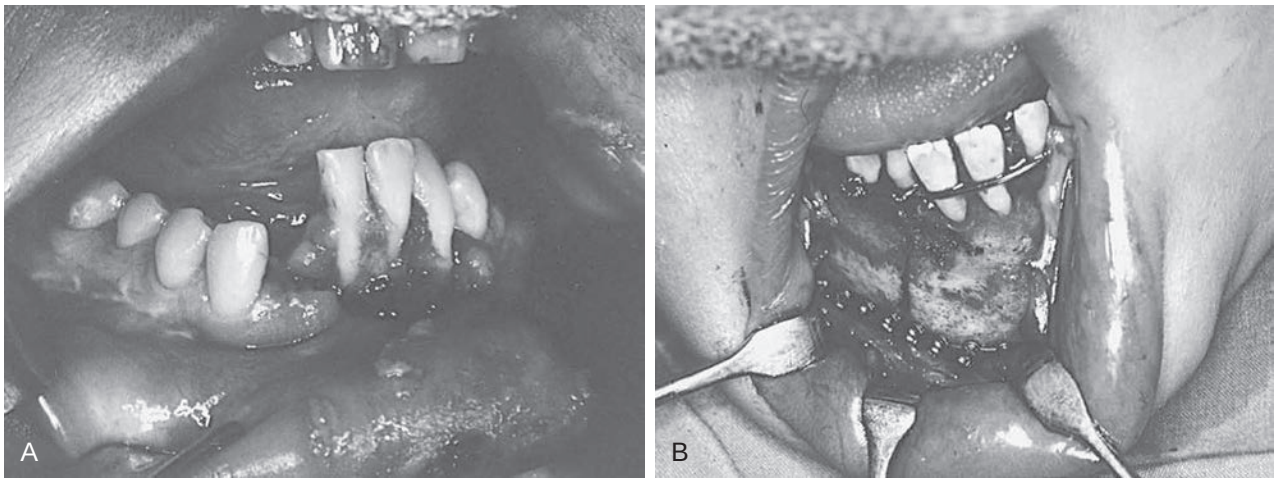
pressure on the alveolus and dental segments (Figure 6-17). The segments then should be stabilized in place using either rigid splinting of the involved teeth or other forms of splinting techniques for 4 weeks. In children this period can be reduced to 3 weeks because of rapid healing.

Although alveolar fractures can usually be reduced and stabilized in proper position using closed methods, occasionally, to reduce the segment properly and achieve adequate stabilization, it is necessary to resort to open surgical techniques. Once the fracture is reduced, it can be stabilized or fixed in a variety of ways. In most instances, one arch fixation is adequate to provide stable fixation of simple alveolar fractures. However, a splint of bonded brackets or composite resin that fixes a wire to the teeth on either side of the fracture is superior to other forms of fixation with regard to hygiene and periodontal effects—although it may be impossible in instances where a procedure needs to be done in an emergency room or at bedside, without the necessary armamentarium, facilities, or cooperation to cleanse, dry, acid-etch, and bond brackets to composite resin. In these instances, an arch bar or a Risdon or Essig wire, either alone or supplemented with autopolymerizing acrylic resin, may be the best method of fixation. If necessary, this fixation may be changed to a more optimal splint at a later date.

Processed or autopolymerizing acrylic resin splints on the palatal, lingual, or occlusal coverage are also effective methods of fixation. However, they require impressions and models to construct and thus introduce a delay in the treatment. Fixation should be maintained for 4 to 6 weeks. Patients should maintain a soft diet. Open reduction is occasionally required, especially when the alveolar segment is significantly displaced or the roots of teeth or the bone in the segment interferes with proper repositioning of the segment. A vestibular incision is made apical to the fracture line and the segment pried into position using a sharp instrument such as periosteal elevator. Occasionally, an irregular area of spongy bone may inhibit the reduction. Proper alignment of the alveolus may require removal or contouring of the obstructing segment. Once the segment is satisfactorily repositioned and the proper occlusion is verified, the segment is fixed in place using transosseous wire or a small bone plate (Figure 6-18). Condemned teeth in an alveolar fracture segment should only be considered for extraction in the acute phase if they are poorly supported or infected. In general such extractions should be delayed until bone healing is complete to prevent inadvertent removal of the entire alveolar segment with the teeth during the extraction. Antibiotic coverage with penicillin, erythromycin, or clindamycin and the use of chlorhexidine oral rinse are recommended, especially in delayed treatment and extensive associated soft tissue lacerations. Tetanus booster is usually only indicated in wounds with dirt and road debris contamination. Careful follow-up of the involved teeth should be done to monitor the vitality of the tooth.

When an alveolar fracture occurs in conjunction with a jaw fracture, the treatment should be accomplished as soon as the patient's condition is stable. Generally, reduction of the fractures and maxillomandibular fixation with appropriate wiring techniques (arch bars, Risdon wiring, etc.) are required. This should be done as soon as possible to improve the prognosis of the dental and alveolar components. Additional maneuvers, such as open reduction of the jaw fractures, may be done later, if necessary.

Avulsed injuries of the alveolus are occasionally seen in conjunction with major facial injuries. The treatment is often dependent on the anatomic location of the avulsion and its relationship to other injuries, particularly fractures. In these instances, advancement of mucosal flaps is often used to cover exposed bone, particularly areas where there are fractures. Avulsions that result in nasal or maxillary sinus openings should be closed, if flaps can be advanced, so as not to compromise treatment of other injuries or preclude a more predictable closure by conventional means at a later date. The



• **Figure 6-18** **A,** Open reduction of a displaced mandibular dentoalveolar fracture. **B,** A mucoperiosteal flap was elevated, the segment was satisfactorily reduced, the proper occlusion was verified, and the segment was fixed in place using arch wire and a small bone plate.

patient should be informed of the prognosis, especially as it applies to insurance coverage and possible litigation.

Splinting Techniques

Splinting is a form of fixation to stabilize the injured teeth in its normal anatomic position during the healing period. Importance of allowing physiologic mobility during this period of healing to avoid damage to the periodontal and pulpal healing is well known.[84-86] Requirements of an ideal splint would include:

1. Splint fabrication materials easily available in a dental office or emergency room,
2. Avoids or minimizes further trauma to the injured tooth or supporting structures,
3. Facilitates oral hygiene maintenance, avoids soft tissue irritation,
4. Stays passive and remains in its normal position throughout the immobilization period,
5. Allows physiologic movement of the tooth,
6. Does not interfere with the occlusion,
7. Allows easy access for endodontic treatment and pulp testing, and
8. Is easily removed in the dental office.

The splints that come closest to fulfilling these requirements are the acid-etch resin arch wire splint (Figure 6-19, *A*) and the orthodontic bracket arch wire splint (see Figure 6-17, *B*). These, of course, are difficult to apply when blood and saliva cannot be isolated from the field, such as in an emergency room.

A rigid splint increases the amount of external resorption and eventual early loss of the tooth.[87] For this reason, arch bars and other forms of interdental wiring are less than optimal. These types of splints also can cause orthodontic movement of the teeth, such as extrusion.

A splint should be left on for a minimal amount of time. Prolonged splinting will increase the risk of ankylosis. The optimal splinting period for a displaced or avulsed tooth is based on the type of dentoalveolar injury. Ideally, the splint should be maintained for 7 to 10 days because the gingival fibers are usually healed in 1 week, and this should provide adequate periodontal support. Alveolar bone fractures with replanted teeth may require a splint for 3 to 4 weeks, luxation may require a splint for 2 to 4 weeks, and root fractures require a splint for up to 12 weeks.

An acid-etch resin-only splint is easy to fabricate, but does not allow the teeth much mobility and is also fragile, resulting in fracture of the material. Newer multiphase resin materials (Protemp, Luxatemp) have been reported to provide semirigid splinting and retain the ease of application, oral hygiene, and patient acceptability. These do require the teeth to have fully erupted crowns with proper interproximal contact; otherwise the use of wire or fiber lines is unavoidable. A better splint is an acid-etch resin arch wire splint (see Figure 6-19, *A*).[86-88] This allows the tooth some mobility. Fiberglass instead of wires has been used in many cases, but the flexibility varies depending on the extension of the splint.[89] The wire is bent to conform to the facial surfaces of the teeth to be splinted. At least one tooth on either side of the displaced tooth or teeth must be included. The facial surfaces of all the teeth to be splinted are etched with phosphoric acid for 1 minute, after which they are washed and dried. The bonding agent is applied and a small amount of resin is placed in the middle of the facial surface over a small area. The arch wire is then passively placed in the resin. The resin material should not contact the gingiva because it will cause gingival inflammation. The practitioner must be sure that the displaced tooth is in its correct position. A radiograph should be taken to verify this after the splint is in place. The patient should be instructed in proper oral hygiene, stressing the importance of keeping the gingival crevice as well as the rest of the teeth clean.



• **Figure 6-19** **A,** An acid-etch resin arch wire splint. **B,** Luxation of maxillary permanent central incisors treated with an orthodontic bracket arch wire splint using ligature wires. **C,** Luxation of the maxillary permanent four incisors treated with an orthodontic bracket arch wire splint using AlastiK ligatures (3M) with banding of the permanent first molars for stabilization. (From Abubaker AO, Papadopoulos H, Giglio JA: Diagnosis and management of dentoalveolar injuries. In Fonseca R, Marciani RD, Turvey TA, editors: *Oral and maxillofacial surgery*, ed 2, St Louis, 2009, Saunders.)

When removing the splint, the wire can be cut between each tooth. The resin should not be removed because the replanted teeth are still loose and can be displaced. After the teeth are firmly attached in 2 to 3 months, the resin can be removed.

The orthodontic bracket arch wire splint is an excellent technique.[90,91] Acid-etch brackets are placed on the displaced tooth or teeth as well as on at least one sound tooth on either side of the displaced tooth. Sometimes it is necessary to extend this type of splint by banding the permanent first molars (see Figure 6-19, *C*). This can occur in the mixed dentition when permanent lateral incisors, canines, and/or premolars are absent or there is a deep overbite and additional teeth are necessary for stabilization. The arch wire can be either round or rectangular and is bent to conform to the facial surface of the teeth to be splinted. AlastiK (3M

Dental Products) ligatures are used to hold the arch wire to the brackets. The advantages of this splint over the acid-etch resin arch wire splint are that the practitioner can remove the elastic ligatures and the wire to check mobility of the displaced teeth. If there is excessive mobility, the splint can be replaced. New prefabricated splinting materials, such as the titanium trauma splint (TTS) with a rhomboid flat design, are being used because of ease of adaptability to the tooth (0.2-mm thickness) and increased patient comfort[92,93] (Figure 6-20).

It should be noted that a fairly high percentage of teeth endodontic intervention initiated at the appropriate time.

Treatment of Gingival and Mucosal Injuries

Injuries to the Gingiva and Mucosa

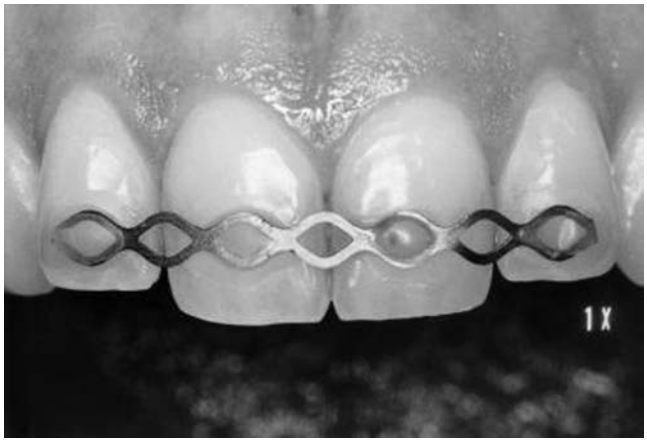
Intraoral soft tissue injuries to the gingiva and mucosa occur in the form of contusions, abrasions, lacerations, and avulsions. They are seen either alone or in conjunction with injuries to the teeth, facial bones, or alveolus.[94] Management in many instances depends on the presence or absence of injuries to these underlying structures as well as on periodontal considerations.

Contusions of the gingiva seldom require any active treatment other than appropriate oral hygiene to allow healing. These contusions are helpful in indicating possible underlying fractures of the bone and a need for further radiographic evaluation.[95] Underlying ecchymosis and/or hematoma will resolve with time without residual deformity.

Abrasions and lacerations of the oral soft tissue require thorough debridement and cleansing to remove all foreign bodies that could be potential sources of infection. Larger lacerations or avulsion injuries extending to the facial tissues should be considered for be treatment in the controlled setting of an operating room under general anesthesia. Careful oral hygiene and avoidance of thermally or chemically irritating food and drink allow for healing in a few days. Lacerations need to be repositioned without tension in correct anatomical position to avoid wound breakdown. Since the gingiva is highly vascular and necrosis is unusual, debridement when done should be extremely conservative. Antibiotic coverage and tetanus prophylaxis are considered on an individual basis depending on the extent of injury and degree of contamination of the wound. Evidence in the literature for routine use of antibiotics is limited, although most intraoral soft tissue wounds are considered contaminated by oral flora.[95] Hence the judgment for providing prophylactic antibiotics in absence of active infection is based on certain factors: degree of contamination of the wound, delay in debridement or repair, systemic indications due to immunocompromised status, and concomitant fractures. Current evidence shows benefit in use of preoperative and 24-hour postoperative antibiotics only. No benefit has been proven from prolonged use of postoperative antibiotics.[96,97]

Plain gut, chromic gut, or polyglycolic acid resorbable sutures in 3-0 or 4-0 sizes are commonly used to repair intraoral lacerations. Gut suture material is quite irritating, whereas polyglycolic acid suture is more difficult to tie and may take a long time to resorb. Less reactive nylon suture may annoy the patient by scratching the tongue, lip, or cheeks.

Avulsive wounds of the gingiva are infrequent and often are more apparent than real. After the wound is cleansed and the tissues are reassembled, presumed missing tissue may, in fact, be present. Management of an avulsive wound of the gingiva, in many respects, depends on the presence or absence of underlying injury to the alveolus or teeth. A gross alveolar fracture associated with a luxated or displaced tooth needs to be covered with soft tissue to promote healing of the fracture and/or retention of the tooth or teeth. Advancement soft tissue flaps to cover alveolar soft tissue defects will often be from non-keratinized alveolar mucosa rather than attached gingiva. Accordingly, small areas of avulsed attached gingiva, without underlying injuries, should be left to granulate and thus produce fixed gingiva, which is more periodontally desirable. Large areas of exposed bone should be covered whenever possible, even if it requires advancement of unattached gingiva.



• **Figure 6-20** Titanium trauma splint.

Prognosis of Dentoalveolar Trauma

Reactions of Teeth/Surrounding Tissues to Trauma

The multiple types of dentoalveolar trauma and their combinations give rise to highly complex and variable healing scenarios. Knowledge of the basic reactions of the teeth and surrounding tissues to trauma is essential in rendering appropriate acute and follow-up care. Traumatized teeth and surrounding tissues often have an unpredictable course of healing. Ability to determine the ultimate outcome would help in fabricating the treatment plan. Basic reactions of dentoalveolar structures to trauma include healing

events related to alveolar bone, periodontal ligament (PDL), and the pulp tissue within mature and immature teeth.[98]

There are several basic healing patterns after trauma, based on events related to the tissue type involved in the injury. Alveolar bone healing events include those subsequent to acute bone loss and those secondary to ischemia and crushing. The chance of bone regeneration is good, especially in younger patients, owing to induction of bone from cells in PDL. Necrosis or loss of bone, either transient or permanent, happens more often in teeth with intrusion injuries that have mature roots.

Events related to PDL reaction can be divided into PDL loss facing the alveolar bone, loss of PDL facing the cementum, and PDL ischemia or contusion. PDL has good regenerative capacity when it is lost on the surface facing the alveolar bone. PDL loss facing the cementum and ischemic reaction lead to repair-related resorption or could result in ankylosis. Cementum tissue, when lost in cases of root fracture, is regenerated from the adjacent cementoblasts.[98]

Pulpal injuries can vary from direct pulp exposure to the oral cavity, exposure to PDL in root fractures, bacterial contamination secondary to invasion through the dentinal tubules, to partial or total severance at the apex during luxation injuries. Irrespective of the injury, there is a resultant neurovascular disturbance in the pulp to which it reacts, of the dentin-pulp complex varies depending on the type of injury, presence or absence of infection, root apex maturation, and origin of progenitor cells involved.

After pulp exposure from trauma, untreated exposure even after 1 week leads to superficial inflammation up to a depth of 2 mm.[99] In cases where capping is performed with a suitable material (calcium hydroxide or MTA), a hard tissue barrier is established. Healing starts with hemostasis, inflammation, proliferation, and remodeling. MTA is a promising new material for pulp capping, with reduced inflammation compared to calcium hydroxide.[100]

Luxation injuries, as discussed previously in this chapter, involve partial or total severance of neurovascular supply, resulting in ischemia. Wound healing starts at the apex and moves coronally and is significantly affected by the size of the apex. The recovery from pulpal severance includes either pulp revascularization or necrosis depending on the presence or absence of bacteria in the wound. In general the risk of pulp necrosis increases with the increase in root development. Revitalization is frequent in apical foramens larger than 1.0 mm in size, but infrequent below 0.3 mm. In teeth with a completely formed apex, in the absence of bacteria this sterile necrosis can persist asymptomatically for long periods of time. Tissue can be revascularized by ingrowth of mesenchymal cells. For example, in the case of PDL-derived progenitor cells, PDL tissue will be formed with cementum deposition on root canal walls. Dentin formation after revascularization is extensive, leading to pulpal obliteration. resorption is characterized by an irregular radiolucency in the lumen of the canal. Histologically the replacement resorption is seen as a metaplasia of the pulp tissue into seen histologically as transformation of pulp into granulation tissue, with giant cells in the granulation tissue resorbing the dentinal walls. Progress of this condition depends on interaction between necrotic and vital pulp, and root canal treatment is helpful if the condition is diagnosed early enough.

External resorption of the root in luxated or avulsed-replanted teeth is often the most difficult to predict. It is categorized into three types: inflammatory, surface, and replacement. Inflammatory external root resorption is related to the necrosis of pulp and is thought to be related to migration of bacteria thought he dentinal tubules into the PDL, causing inflammation and resorption.[101,102] Progressive resorption of tooth substance along with adjacent persistent alveolar radiolucency is a typical finding in inflammatory resorption. In surface resorption, the root surface shows lacunae repaired with cementum tissue. Surface resorption is self-limiting. Replacement resorption leads to ankylosis, resulting in direct union between root and bone. Disappearance of PDL space and progressive root resorption are characteristic radiographic signs.

Response to treatment and long-term success of treatment for dentoalveolar injuries are dependent on internal and external factors surrounding the individual case. Although treatment modalities can be planned and standardized, individual patient response and circumstances surrounding the treatment cannot be controlled. Factors influencing outcomes can be divided into intrinsic patient factors and extrinsic environmental factors. Patient-related factors include age, physical status, oral health including condition of the teeth and periodontium, habits of oral hygiene, mental and emotional status, and motivation to follow through with long-term follow-up examinations and necessary care. Important extrinsic factors affecting prognosis and treatment outcomes include nature of the injury, extent and severity of the injury, presence of concomitant trauma, and length of time from injury to definitive care.

Prognosis of Injury to the Primary Dentition

Primary teeth also show reactive responses in pulpal and PDL tissues. Initial reaction to trauma is pulpitis, characterized by pain and sensitivity to percussion and occurring as a result of vascular congestion.[77] This can lead to reversible or irreversible changes. Diagnosis of pulpal necrosis in primary dentition is challenging owing to unreliable pulp vitality testing.[103] Schröder found the frequency of pulpal

necrosis following luxation injuries to be similar to that for permanent teeth.[104] Color of the crown and associated radiographic indications are used to arrive at the conclusion of necrotic pulp. Discoloration of the crown following injury to primary teeth is frequently reversible, so color change should not be the sole criterion for pulpal therapy or extirpation. Hence, unlike permanent teeth, primary teeth that become discolored or darkened are not necessarily nonvital or necrotic. If the discoloration of the crown does not lighten within 3 weeks after the injury, and if radiographic signs of nonvitality including periapical radiolucency, nonobliteration of pulp, and lack of root formation are seen, ally seen in traumatized primary anterior teeth that are visibly damaged. Radiographically, pulpal obliteration (calcific metamorphosis) is seen in primary teeth with a yellowish hue (Figure 6-21). The tooth usually remains vital. Primary teeth with calcific metamorphosis will usually resorb and exfoliate normally.[105]

A reversible grayish color will be seen in about 55% of the injuries to primary teeth. Studies have also shown that grayish discoloration was most often associated with pathology.[106,107] Periapical inflammation becomes evident 1 to 2 months after injury. Pulpectomy has been advocated in primary teeth with necrotic pulp.[108]

All displacement injuries to the primary teeth could potentially affect the associated developing permanent tooth buds, so careful follow-up evaluation for this sequela is required. Enamel hypoplasia in permanent dentition is the most common sequela after trauma to the primary dentition.[78] Pulp obliteration can happen in primary teeth as well, but no treatment is indicated, as these have been seen to resorb in a similar way to nontraumatized primary dentition. The crown of a tooth with pulp obliteration may show yellowish discoloration clinically, although this

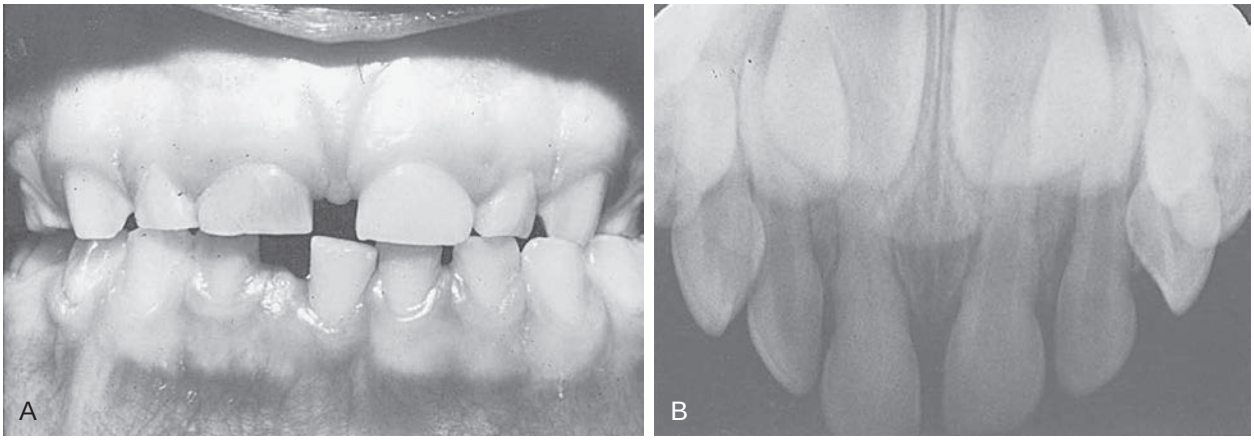
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buds. If any signs of resorption are noted, the teeth should be extracted.

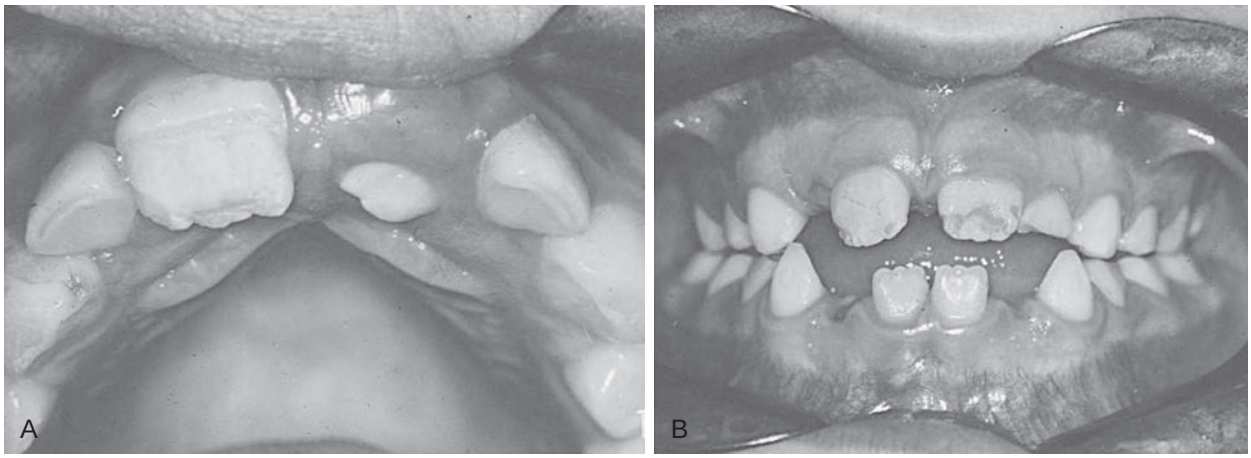
Prognosis of Injuries to the Permanent and Developing Dentition

Isolated crown fractures involving only enamel and without associated injury to the periodontal ligament have a very good prognosis, more so if the root apex is open. The incidence of pulp necrosis is directly related to the degree of concomitant injury to the periodontium from combination of injuries. The overall incidence of necrosis irrespective of type of fracture or management is reported to be 1% to 6%. Exposed dentin may complicate the prognosis, because bacterial contamination of exposed dentinal tubules can result in infection. Both the length of time the dentin is exposed to the oral environment and the degree of dentin exposed are directly related to pulp survival. In one study, treatment pulp capping and pulpotomy improve the chances of pulp survival. Pulpotomy had lower chances of resulting in pulp necrosis compared to pulp capping.[41]

The prognosis for pulpal healing after root fracture will depend on the extent of coronal fragment displacement and the stage of root development. Moreover, the location of a transverse root fracture does not affect pulp survival after injury. Repair of root fracture primarily depends on the degree of mobility and dislocation of the coronal segment and the stage of root development. Healing can occur regardless of fracture location, provided that proper reduction and fixation of the segment is accomplished.[110-113] The



• **Figure 6-21** **A,** A previously traumatized right primary maxillary central incisor. Note the discoloration of the tooth associated with pulpal obliteration. **B**, An occlusal radiograph showing partial pulpal obliteration of a maxillary right primary central incisor (calcific metamorphosis). (From Abubaker AO, Papadopoulos H, Giglio JA: Diagnosis and management of dentoalveolar injuries. In Fonseca R, Marciani RD, Turvey TA, editors: *Oral and maxillofacial surgery*, ed 2, St Louis, 2009, Saunders.)



• **Figure 6-22 A,** Hypoplasia of the maxillary permanent central incisors resulting from displacement injuries to the primary teeth. The maxillary left primary central incisor had been intruded and the maxillary right primary central incisor had been luxated. Note the crown dilaceration of tooth left permanent maxillary central incisor due to intrusion of the primary incisor **(B).** (From Abubaker AO, Papadopoulos H, Giglio JA: Diagnosis and management of dentoalveolar injuries. In Fonseca R, Marciani RD, Turvey TA, editors: *Oral and maxillofacial surgery*, ed 2, St Louis, 2009, Saunders.)

incidence of pulp necrosis among permanent teeth with root fractures in general ranges between 20% and 55%.[114]

Although injuries to developing permanent teeth could result from proximity of the root apices of the primary teeth to the permanent tooth buds, damage to the permanent tooth buds most commonly occurs before the age of 3 years, when the permanent teeth are calcifying.[105] Intrusive and avulsion injuries at 2 years of age, occurring when the permanent tooth crown is about half formed, can result in permanent crown dilaceration. These teeth can erupt spontaneously or require surgical intervention to assist eruption.

Studies have shown a 50% (12%-69%) incidence of damage to the permanent tooth bud from displacement and avulsion injuries in the primary dentition.[78] Displacement and avulsion injuries may affect the developing permanent successor in the following way:

1. A white or yellow-brown discoloration with or without enamel hypoplasia (Figure 6-22, *A*)
2. Dilaceration of the crown (Figure 6-22, *B*) or root
3. Cessation of root development
4. Odontoma-like malformation
5. Sequestration of permanent tooth germs
6. Disturbance in eruption

The effect on the permanent tooth is dependent on its stage of development, the nature and the extent of the injury to the primary tooth, and the length of time the injury is allowed to exist in proximity to the developing tooth.[115,116] A very high frequency of disturbance in the development of permanent teeth is seen in intrusion (69%) and avulsion (52%), whereas extrusion (34%) and subluxation (27%) represent lower risks.[117,118] Any resulting infection from trauma poses another threat to the permanent teeth. Whether the various treatment modalities of removal, repositioning, pulpal therapy, or antibiotic therapy influence the prognosis of the injured primary tooth or its successor is not known.

Frequency of pulp necrosis after luxation injuries has been found to be between 15% and 59%. Key factors in determining the prognosis of these injuries are the type of luxation injury and the stage of root development at the time of injury. Teeth with mature root formation are at greatest risk of pulpal necrosis. Diagnosis of pulpal necrosis in permanent teeth after luxation injuries can vary from 6 months to up to 2 years because of difficulty in assessing radiographic signs of necrosis. Tenderness to percussion is found to be significantly related to presence of infection; however, sterile necrosis can be asymptomatic, and diagnosis is based on clinical parameters such as crown color, radiographic features, and pulpal sensitivity tests.

The greatest frequency of pulp necrosis is after intrusions, followed by lateral luxation and extrusions. In intrusive injuries, teeth with immature roots may be expected to spontaneously re-erupt over a period of several months and require little or no intervention.[52] Mature teeth are likely to undergo ankylosis if left in the intruded position. Endodontic treatment will be necessary but can be postponed until the tooth is in position.

Since the replanted tooth must revascularize the periodontal ligament, form a new periodontal fiber and gingival attachment, and finally revascularize and re-innervate the pulp, successful healing depends directly on the time from injury to replantation and the handling of the tooth (storage medium) prior to the replantation.[64-66] Consequently, avulsed immature teeth maintained in a physiologic medium before replantation will have the optimal prognosis for healing for up to 3 hours. Revascularization in replanted teeth with mature root apex is rare and mostly if carried out immediately after the avulsion. Root resorption, however, is the most frequent sequela after replantation. Factors shown to affect root resorption include length and type of extra-alveolar storage, stage of root development, and contamination of root surface. Three forms of postavulsion

root resorption have been identified.[119] Surface resorption appears to be transitional and a precursor to more severe resorption. Inflammatory resorption includes both the root surface and adjacent alveolar bone. Careful timing of root canal treatment (2 weeks post-replantation) can best arrest inflammatory resorption. Replacement resorption, which includes bony ankylosis, is the most severe form of resorptive response to avulsion and can lead to eventual loss of the tooth. Ankylosis can be usually detected in 4 to 8 weeks with a percussion test, but radiographic evidence may take up to a year. Avulsed teeth that have been replanted more than 60 minutes after the injury can be expected to eventually undergo replacement resorption. Prolonged splinting has been related to an increase in replacement resorption.

Finally, many patients with injuries of the dentoalveolar region, especially those that are avulsive, will benefit from a multidisciplinary approach to oral rehabilitation. Advances made in our specialty over the past 20 years in the areas of bone grafting, soft tissue grafting, and implantology have made the restoration of preinjury form and function the gold standard of care.

Prevention of Traumatic Dental Injury

The consequences of traumatic dental injuries are not just physical and esthetic, but psychosocial and economic as well.[6] Traumatic dental injuries are irreversible, and loss of tooth or supporting tissues could have permanent effects on the individual. Although much emphasis has been placed on various modes of prevention, including the role of mouthguards and faceguards, not all traumatic dental injuries are practically preventable, as most of them occur unexpectedly during daily activities.[120] Sports-related, iatrogenic, and fall-related injuries could possibly be prevented or reduced in severity. Contact sports have a higher incidence of dental and oral trauma based on the population and demographics, varying between 7% and 30%.[120-122] Certain preventive strategies include use of mouthguards, patient education, and modifying risky behavior. During sports and other activities in which there is a risk of falling or being hit by an object, wearing a faceguard or mouthguard still seems to be the only way to prevent or at least significantly reduce the seriousness of dental injuries. It has been reported that before the mandate to wear faceguards and mouthguards in U.S. high school football, facial and oral injuries constituted up to 50% of all reported football injuries. Subsequent to the mandate, a significant decrease was noted in reported injuries.[121] Currently, the U.S. National Collegiate Athletic Association requires mouthguards for four sports (ice hockey, lacrosse, field hockey, and football). However, the American Dental Association recommends the use of mouthguards in 29 sports/exercise activities.[122,123] Despite efforts to reduce the number of traumatic dental injuries, most current studies indicate that the overall incidence of dental trauma remains unchanged and is at a relatively high level for children and young adults. Knapik and colleagues[124] concluded from a systematic review of literature on effectiveness of mouthguards that the risk of orofacial sports injury was 1.6 to 1.9 times higher when mouthguards were not used. However, a review of this systematic review and meta-analysis shows that the studies included were of low level of evidence.[125] Hence, although mouthguards and faceguards do help reduce the incidence of sports-related injuries and those from other preventable etiologies, emphasis should be placed on education related to dental trauma and its first aid among children, teenagers, adults, and their caregivers. Controlling risks such as increased overjet or previous history of trauma in children that have been known to increase the incidence of dental trauma should be given priority.

Most of the literature on mouthguards has been focused on their fabrication and material properties rather than on their effectiveness. Mouthguards can be divided into three basic types on the basis of how they are manufactured and used[126]:

1. Stock prefabricated
2. Mouth-formed
3. Custom-made

Stock mouthguards carry the advantage of being readily available and inexpensive, and replacement is easy in case of loss. But these are not properly adapted to the dentoalveolar structures of the wearer and have to be held by occluding into them. These stock mouthguards have been reported to provide the least protection and carry the risk of falling out of the oral cavity before the impact of trauma, although there are no clinical studies to substantiate this claim.

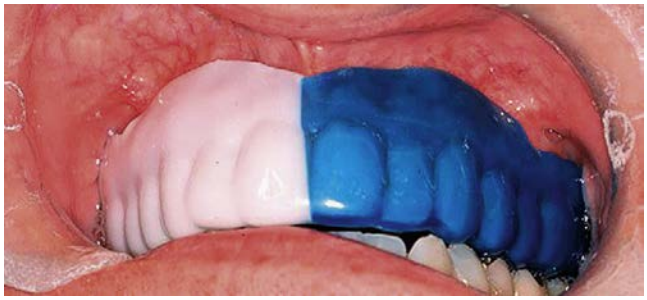
Mouth-formed or self-adapted mouthguards (Figure 6-23) are a readily available and inexpensive alternative to custom-made mouth guards. They are two-layered, with a thick non-moldable outer layer and an inner resilient soft lining that is adapted by the wearer before use. The outer shell is adjusted to relieve the frenal attachments and flange depth, while the inner material is a layer of self-curing methyl methacrylate or silicone rubber. The other type of mouth-formed mouth guards are made of thermoplastic material that is again adapted by the user after warming the material to a set temperature while in the mouth. If adapted well, they can give a better fit than a stock mouthguard, but they carry the risk of thermal injury and improper adaptation that could potentially cause soft tissue injury.

Custom-made mouthguards (Figure 6-24) are fabricated in the laboratory on dental models of the individual's dentoalveolar structures. Many studies have shown better acceptance and comfort levels with these custom-fit mouthguards as opposed to stock and mouth-formed ones. Very few studies, however, offer clinical outcome data on the relative effectiveness of the various types of mouthguard, and the distinction is not clear and substantiated.

Use of faceguards and helmets has significantly reduced the incidence of facial injuries in certain contact sports.[121] One fact that has been noted among these youths is that although the number of oculofacial injuries has been reduced by faceguards, the number of spinal injuries has increased. More studies on their effectiveness and use are needed.



• **Figure 6-23** **A,** Boil and bite mouth guard placed in hot water and then adapted to the teeth and the palate **(B).** (From Bourguignon C, Sigurdsson A: Preventive strategies for traumatic dental injuries, *Dent Clin North Am* 53:729-749, 2009.)



• **Figure 6-24** Custom-made mouth guards made from the dental models of a patient are more acceptable and comfortable. (From Bourguignon C, Sigurdsson A: Preventive strategies for traumatic dental injuries, *Dent Clin North Am* 53:729-749, 2009.)

Conclusions

Although dental traumatology has made significant advances, there still need for development of evidence-based practices. The lack of ethical basis for conducting large-scale, high-quality randomized controlled trials with dental trauma patients in distress is a significant obstacle to such studies. Although there have been a number of animal studies, which are a reasonable alternative, their application in humans is controversial. Most dental trauma occurs during everyday activities among children and adolescents, making them less likely to be prevented. More emphasis should be placed on educating patients, caregivers, and the general public about prompt management of dental trauma so as to reduce morbidity and long-term adverse consequences, which have physical, esthetic, emotional, psychosocial, and financial impact on the individual.

The successful launch of *Dental Trauma Guide* by the International Association for Dental Traumatology, based on the most recent literature evidence and expert opinion, is a substantial step in advancing the science. Ease of availability of information over the Internet and smartphones can help the clinician provide the best possible treatment option to the dental trauma patient. Large-scale clinical studies are needed on the effectiveness and long-term outcomes after successful management of dental trauma.

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7

Diagnosis and Management of Mandible Fractures

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Introduction

Mandible fractures constitute a significant proportion of facial trauma treated in both urban and rural hospitals. Treatment of facial fractures, specifically those involving the dentition, has been a core discipline for oral and maxillofacial surgeons around the world.

The evolution of mandible fracture treatment modalities has mirrored materials advancements with the development of rigid fixation and titanium metallurgy. Our specialty has moved away from the strict adaptation of commonly held orthopedic principles, instead modifying these ideas to better suit the unique demands of the maxillomandibular complex. The mandible is a complex bony structure involving unique cranial and dental articulations, a network of opposing and specialized muscles, and supporting functions of respiration, speech, deglutition, swallowing, and facial expression. Therefore, reconstructing the mandible and restoring function can have a significant impact for patients and can also present a challenge in the setting of high-velocity blunt or avulsive injury. With advancements in the treatment methods and armamentarium for fixation, we are able to piece together and stabilize fractures using a combination of rigid and semirigid fixation. Open reduction techniques allow early but graduated return to function without adding significant morbidity for the patient. Load-bearing titanium reconstruction plates are able to stabilize atrophic and comminuted mandible fractures, while endosseous dental implants are used to restore dental injuries.

The complexity of mandible fractures varies based on pattern, degree of comminution, displacement, and favorability. The AO/ASIF (Arbeitsgemeinschaft für Osteosynthesefragen/Association for the Study of Fixation) provides guidance and forms the basis for fracture fixation techniques to restore function and premorbid occlusion and avoid complications (such as nonunion, malunion, or infection). The principles assume an understanding of bony biology and wound healing that is critical to proper treatment planning.

History of Mandible Fractures

Mandible fracture treatment has been documented for thousands of years dating back to 1650 BC, as highlighted in ancient Egyptian scrolls.[1,2] Hippocrates was one of the first individuals to describe the concept of immobilization for mandible fractures, a problem that was previously considered a hopeless disease process.[3] Circumdental wires were successfully used to reduce and immobilize mandible fractures to aid in healing.

The 13th century brought about the concept of maxillomandibular fixation by using the stable jaw to reduce the fracture of the injured jaw. This added to the notion that recreating a proper occlusion should assist in reducing fractures to their appropriate anatomic position to heal.[4] The final publication of the use of occlusion and maxillomandibular fixation for stabilizing fractures was not to come for another 200 years.[5] Chopart subsequently designed a stabilization device mimicking a modern-day vise between which the mandibular occlusal surface and the external mandible border were placed in compression. Efforts toward more stable fixation took a leap forward at the turn of the 20th century as Gilmer described metal rods wired together that spanned the fractured site.[6] In 1846, Buck was the first surgeon of record to perform an open reduction.[7] He used an iron wire to fixate the fractured segments. Dr. Robert Ivy, a military oral and maxillofacial surgeon, built on Gilmer's lead to develop the "Ivy loop" technique, placing interproximal wires in the premolar regions of both arches to reduce the occlusion.[8] World Wars I and II brought further innovation and surgical progress to treatment of facial fractures. A distinct need for predictable and safe methods for fracture repair spawned surgical units on the front lines in Germany and France, but the mainstay of care was based on closed treatment.

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contamination of bone and hardware. There were few attempts to advance the management beyond bandages, maxillomandibular fixation, and Gunning-type splints until the 1960s, thanks to the research of two German surgeons, Luhr and Spiessl.[9,10] The concept of compression plates made of vitallium (cobalt-chrome-molybdenum) revolutionized the fixation concept and developed into the principles advocated by AO/ASIF. The field of orthopedics and orthopedic injuries guided the initiation of rigid fixation, but developments were hampered by bulky plates and significant morbidity (reoperation, nerve damage, large facial scars, etc.).

The introduction of miniplate fixation in the 1970s by Champy and Michelete[11,12] further reduced the morbidity of open reduction and recognized the mandible as a unique structure with dynamic musculature and movements that may help or hinder fracture healing. Based on lines of osteosynthesis, fractures without comminution, complex fragmentation, or comminution could be repaired using miniplates (Figure 7-1).

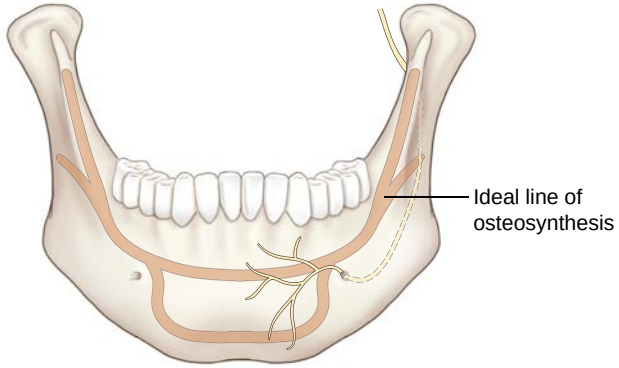
Intermaxillary fixation screws (IMFs) were introduced in the 1990s to further simplify the closed reduction technique and reduce the possibility of surgeon injuries because less wiring was now necessary (Figure 7-2).

Mandible fracture repair methods are continually evolving to optimize outcomes and minimize treatment. Recently a combination titanium arch bar with titanium bone screws introduced by Stryker allows multiple-vector, semirigid maxillomandibular fixation similar to Erich arch bars, but avoiding the tooth-borne forces. Resorbable plates using polymer materials are transitioning from cranial procedures to maxillofacial trauma, especially in the pediatric population. The biodegradable materials can maintain stability similar to miniplates in non—load-bearing areas (zygoma or midface fractures). Resorbable plates are also being used in nondisplaced angle fractures and pediatric mandible fractures as alternate means of fixation that eliminate the need for reoperative hardware removal.

Pathogenesis

In the United States, mandible fractures are largely the result of interpersonal violence, motor vehicle–related injuries, or accidents and falls.[13-15] Pathologic fractures and ballistic injuries are also seen, but with less frequency. Fortunately, with the advent of airbags and other traffic safety mandates, the incidence of motor vehicle–associated facial fractures has been reduced.[16] The populations most likely to be affected by facial fractures are male, younger than 35, in an urban setting, and of lower socioeconomic status.[17]

One of the largest retrospective studies, by Morris and colleagues in 2015, reviewed 4143 mandible fractures over a 17-year period.[18] The injury distribution by site was the angle (27.0%), symphysis (21.3%), condyle and subcondyle (18.4%), body (16.8%), multiple sites unspecified (7.1%),



• **Figure 7-1** Champy's lines of osteosynthesis. (From Ricardo Cienfuegos, Carl-Peter Cornelius, Edward Ellis III, George Kushner: *Mandible fractures*. AO Foundation Online Resource, 2015.)

ramus (5.4%), alveolar border (2.9%), and coronoid (1.0%) (Figure 7-3). Injuries were typically the result of low-velocity blunt trauma. July and the summer months resulted in the highest number of mandible fractures, and 49.6% were single-site fractures.

Anatomy

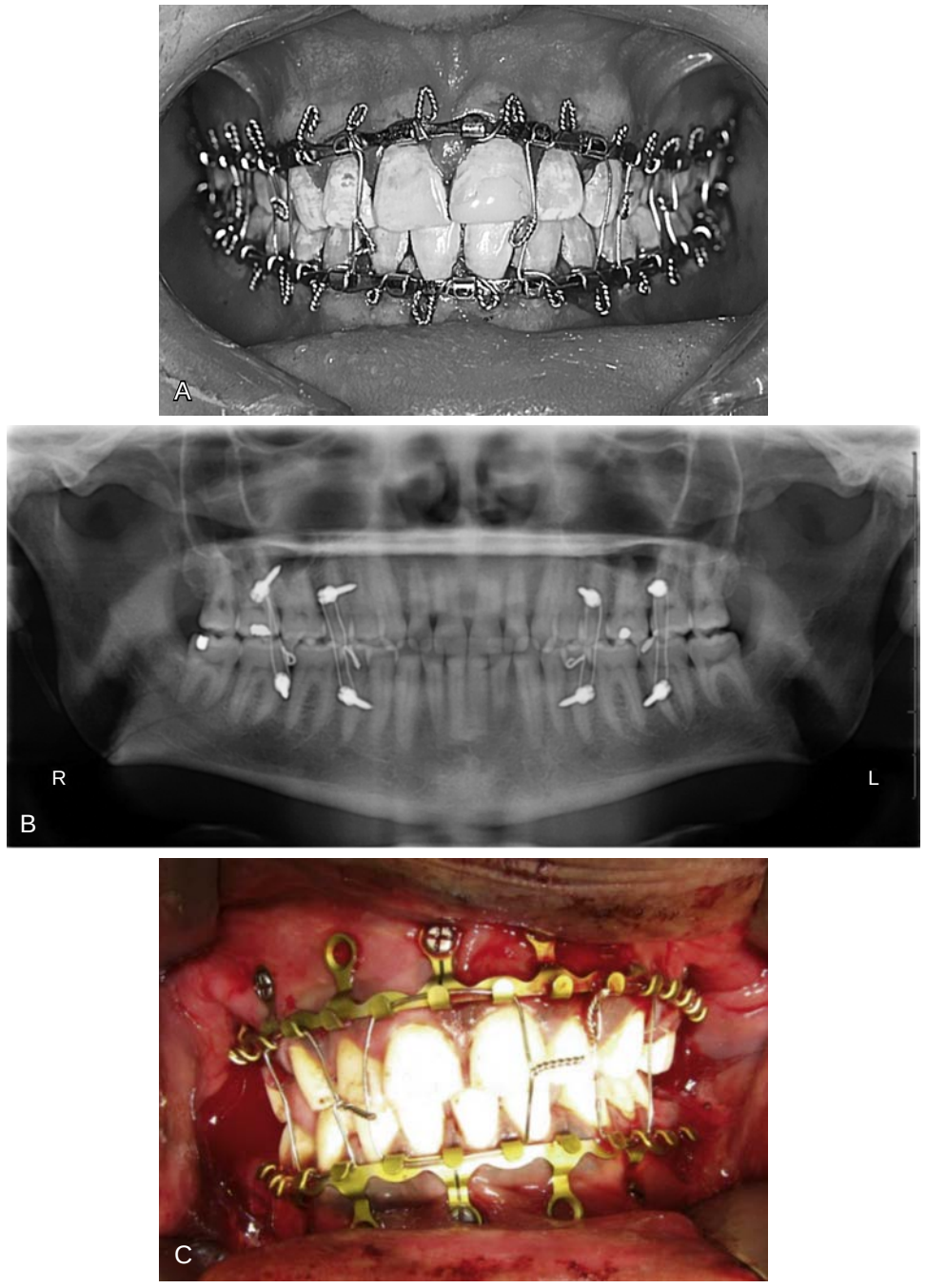
The mandible is one of the more complicated bones in the

(digastric, lateral pterygoid), and glottic attachments (genioglossus and geniohyoid). The remaining muscles, such as the buccinator, platsyma, mentalis, mylohyoid, depressor labii inferiorius, and depressor anguli oris, can influence bone remodeling and displacement in fractures.

The temporomandibular joint (TMJ), the mandible's primary articulation with the cranial base, is a specialized system that allows two types of movement, including translation along the articular eminence and rotation within the glenoid fossa. The capsule, TMJ disc, and lateral ligaments support most of the TMJ movements. Deviation in opening or preauricular swelling may clinically indicate a TMJ injury or condyle fracture that should be investigated.

The major blood supply to the mandible develops along the inferior alveolar artery but transitions to the surrounding periosteum and muscle attachment as the body ages.[19] In the case of comminuted or atrophic mandible fractures, careful consideration of hardware location should target the highly vascular areas of the mandible (ramus and symphysis) and avoid sites with poor blood supply (the body).

The inferior alveolar nerve innervates one half of the mandibular dentition and exits at the mental foramen to supply the chin and lip soft tissue. The lingual nerve runs just inferior to the alveolus and supraperiosteal in the area of the third molar in most cases. Even with displaced fractures, this nerve rarely is injured. Nerve injuries associated with mandible fractures are discussed later in this chapter.



• **Figure 7-2** Intermaxillary or maxillomandibular fixation using **(A)** Erich arch bars or **(B)** IMF screws. **C,** hybrid system (Stryker CMF).

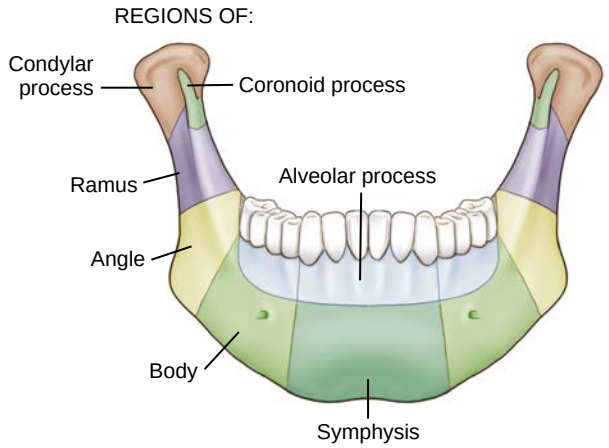
Fracture Classification

Fractures can be divided into several categories based on:
1. Location
2. Biomechanics
3. Fracture pattern

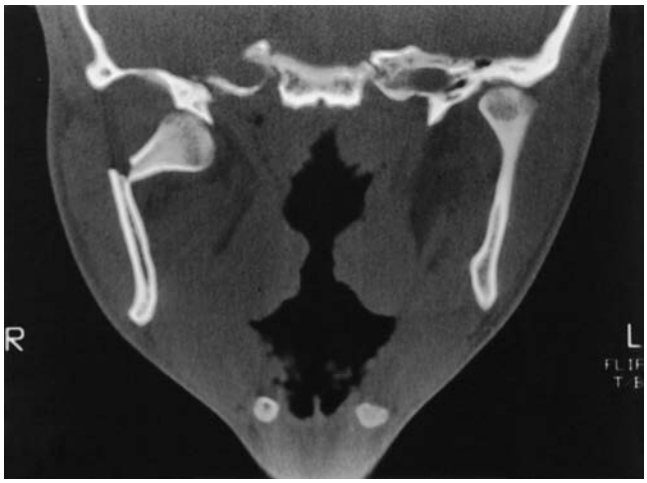
Location

The mandible is divided into anatomic subunits to better characterize the association of the dentition and associated muscle attachments with the injury.

- Symphysis: Occurring in the midline, between the central incisors.
- Parasymphysis: Area bound between vertical lines distal to the canines.
- Body: Area bound from the distal of the canine to the anterior border of the masseter muscle (the distal of the second molar).
- Angle: Area bound from the anterior border of the masseter (distal of second molar) to the posterior border of the masseter. Third molars, if present, are typically involved in angle fractures.



• **Figure 7-3** Fractures of the mandible according to anatomic region. (Adapted from Stevens M, Emam H: Mandibular body fractures. In Kademani D, Tiwana P, editors: *Atlas of oral and maxillofacial surgery*, Philadelphia, 2015, Saunders.)



• **Figure 7-4** Computed tomography (CT) scan is ideal to assess condylar fracture position and displacement.

- Ramus: Area from the posterior border of the masseter to the height of the sigmoid notch. A "subcondylar fracture" is typically within the region of the ramus.
- Condyle:
  - *Intracapsular:* A fracture of the condylar head, which is bound by the capsule (Figure 7-4).
  - *Extracapsular/Condylar neck*: A fracture from the height of the sigmoid notch to the attachment of the capsule. These fractures can be further subdivided based on their distance from the sigmoid notch. A "high" fracture is at or just below the capsule and can denote difficulty in achieving fixation. A "low" fracture is near the notch and can be fixated by conventional means.
- Coronoid: The area of the coronoid process superior to the height of the sigmoid notch.
- Dentoalveolar: A fracture of the alveolar bone and supporting root structure; it does not involve the basal bone of the mandible.

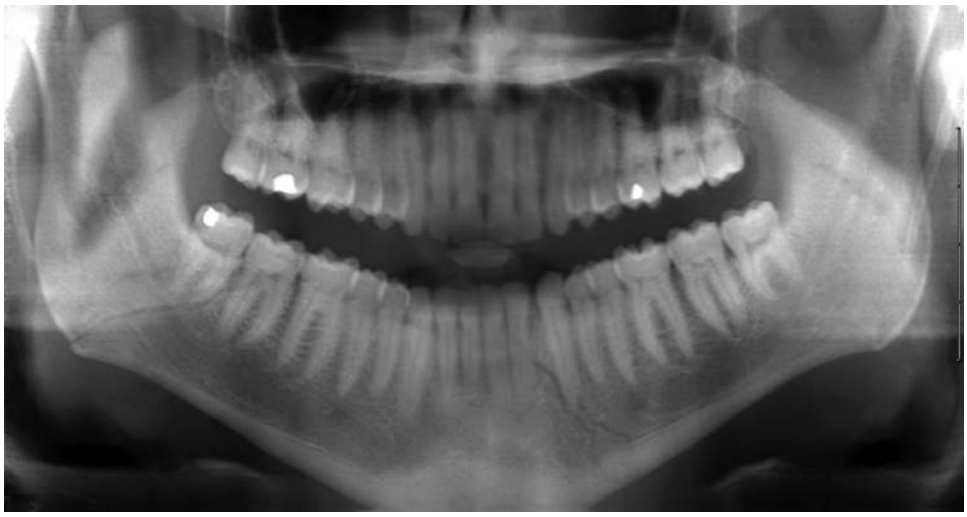
The mental foramen, the third molar/angle area, and the mandibular canine sites are particularly susceptible to fracture due to the bone density at these locations. As a result, parasymphyseal and angle fractures constitute the majority of fracture sites. The coronoid process, however, is the least common mandible fracture site because of the protective effect of the zygomatic arch and masseter muscle shielding. Condylar process fractures are the most common fracture seen in the pediatric population and are termed intracapsular or extracapsular based on the association with the temporomandibular joint capsule. Mandibular body fractures are seen most commonly with in atrophic mandibles that have lost significant bone height and width due to changes associated with premature tooth loss and aging. The body of the mandible also has limited muscle attachments as opposed to the symphysis or ramus. Muscle attachments usually have a positive impact on bone density with regard to physiologic strain and blood supply. Last, dentoalveolar fractures without complete fracture of the mandible are a unique entity requiring reduction with reapproximation to the premorbid occlusion using Erich arch bars or dental splints affixed to the adjacent teeth.

Biomechanics

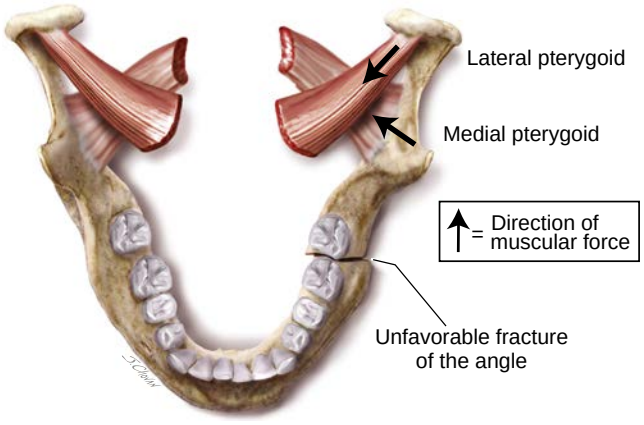
Understanding of the muscle attachments and the forces imposed on the mandible will aid the surgeon in management decisions. A mandible fracture has three forces acting on it: compression, tension, and torsion. These forces vary in magnitude depending on the location of the fracture. The muscles responsible for vertical displacement are the masseter, temporalis, and to a degree the medial pterygoid. Horizontal displacement can be caused by the lateral and medial pterygoid, and torsion by the mylohyoid, digastrics, and geniohyoid.

Displaced fractured segments are more or less well buttressed based on the vectors of muscle pull. A favorable fracture is one where the innate muscle forces have a tendency to reduce the fracture and thus contribute to buttressing. An unfavorable fracture is one in which the opposite is true, and the segments are displaced by muscle pull. This concept is most important when using closed reduction methods on fractures where the proximal segment of the fracture is wholly removed from the tooth-bearing mandible (condyle and angle fractures most typically) and the occlusion cannot be used to reduce both segments.

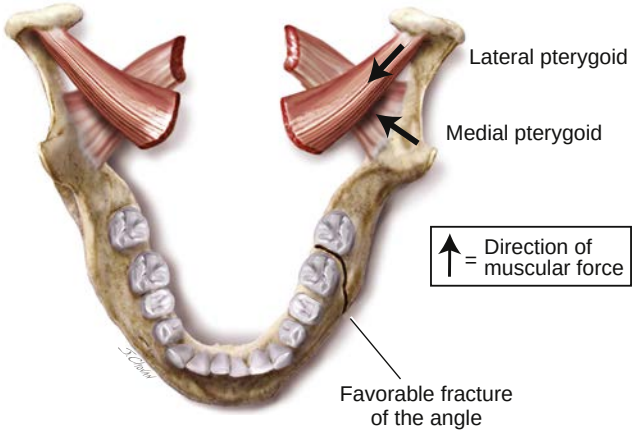
The favorability and unfavorability are described based on the plane of the films obtained; a "horizontally unfavorable" fracture is displacement noted on an orthopantomogram or Panorex (Figure 7-5). Conversely, a "vertically unfavorable" fracture is displacement noted on an anterior/posterior film. This can be confusing at times because the vectors of the muscle pull are opposite to the plane of the film. It is probably more important simply to denote whether or not a fracture is favorable or unfavorable. This feature of the fracture significantly affects the treatment plan. For example, the buttressing effect seen in some favorable fractures will make these more amenable to closed reduction and maxillomandibular fixation (MMF) (Figures 7-6 to 7-10). In contrast,



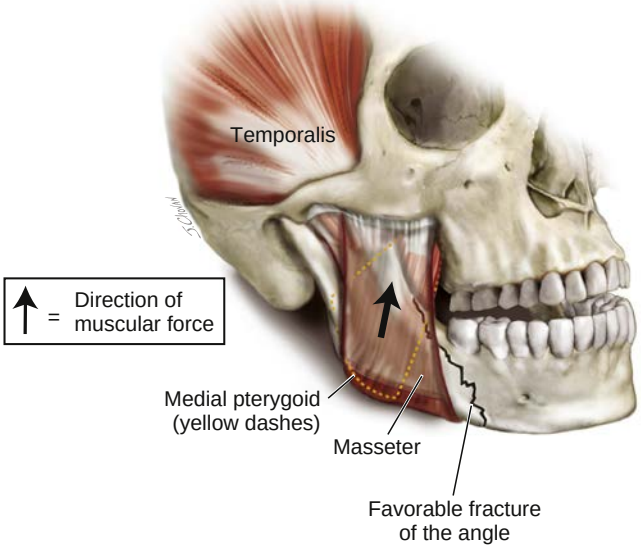
• **Figure 7-5** Panorex radiograph is an excellent modality for identifying mandible fractures. Radiograph shows a right body minimally displaced extending posteriorly to the angle of the mandible and left parasymphyseal fracture.



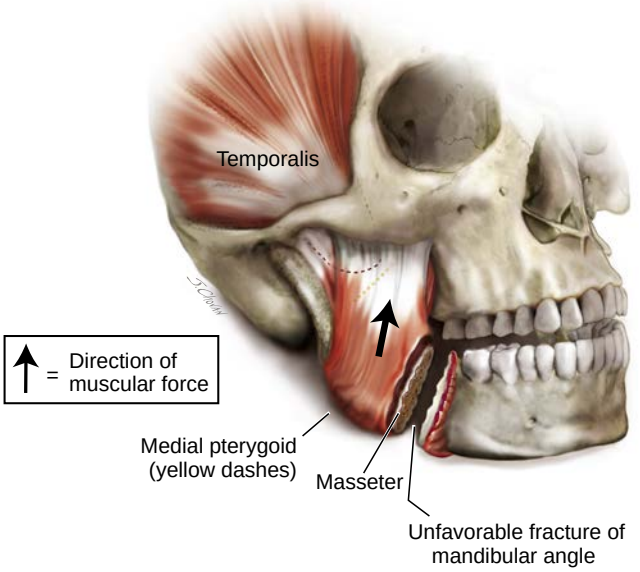
• **Figure 7-6** Horizontally unfavorable fracture.



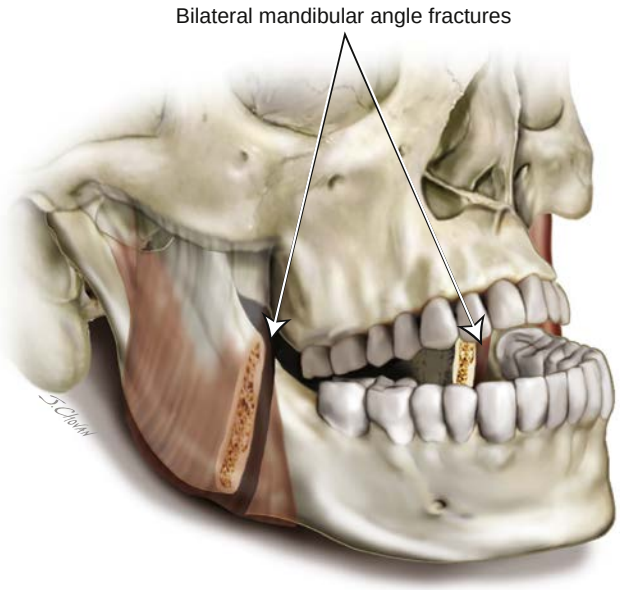
• **Figure 7-7** Horizontally favorable fracture.



• **Figure 7-8** Vertically favorable fracture.



• **Figure 7-9** Vertically unfavorable fracture.



• **Figure 7-10** Bilateral mandible fractures can create posterior displacement of the distal segment due to glottic forces. This is termed the flail mandible and may have implications for the patient's airway.

cial trauma provides better diagnostic information in terms of favorable versus unfavorable compared with traditional radiographs.

Mandibular fracture displacement is defined as:

- Favorable (stable): When the fracture line and the vector of the muscle pull keep the fracture buttressed and appropriately reduced.
- Unfavorable (unstable): When the fracture line and the vector of the muscle pull cause displacement.

Similarly, a condyle fracture can be favorable or unfavorable biomechanically. Unfavorable fractures will be either displaced or dislocated. The decision to treat a condylar neck fracture open or closed can be greatly influenced by the degree of displacement or dislocation.

- Dislocated: Where the head of the condyle is dislocated from the glenoid fossa.
- Displaced: Where the head of the condyle remains in the glenoid fossa, but the neck of the condyle has been pulled out of alignment with the ramus. This can be in any direction, but most commonly is anteromedial because of the pull of the lateral pterygoid muscle.

Fracture Patterns

- Open (compound): A fracture that has communication with the external environment via skin, mucosa, or the periodontal ligament. Any fracture involving a tooth-bearing segment is an open fracture by definition.
- Closed (simple): A fracture that has no communication to the external environment.
- Comminuted: Multiple segments of bone that are shattered, crushed, or splintered.
- Greenstick/nondisplaced: The fracture is incomplete and/or only involves one cortex.
- Pathologic: Fracture occurring from preexisting disease that has structurally weakened the bone.
- Complex (complicated): Can be either a simple or compound fracture that is associated with significant adjacent soft tissue injury.
- Multiple: Two or more fractures within the same bone, but the fractures do not communicate with each other. A mandible will fracture in at least two locations approximately 50% of the time.[18]
- Atrophic: A fracture that occurs predictably at the body (often bilateral) due to mechanical weakening because of atrophy. An atrophic mandible is defined as an edentulous mandible that has 20 mm or less in height.
- Indirect: A fracture that occurs at a site distant from the area of impact—for example, the classic "guardsman fracture," involving bilateral condylar necks and the symphysis. The point of impact at the chin creates multiple fractures, a direct symphysis fracture and indirect condylar neck fractures.
- Impacted: A fracture that has segments "telescoped" on each other.

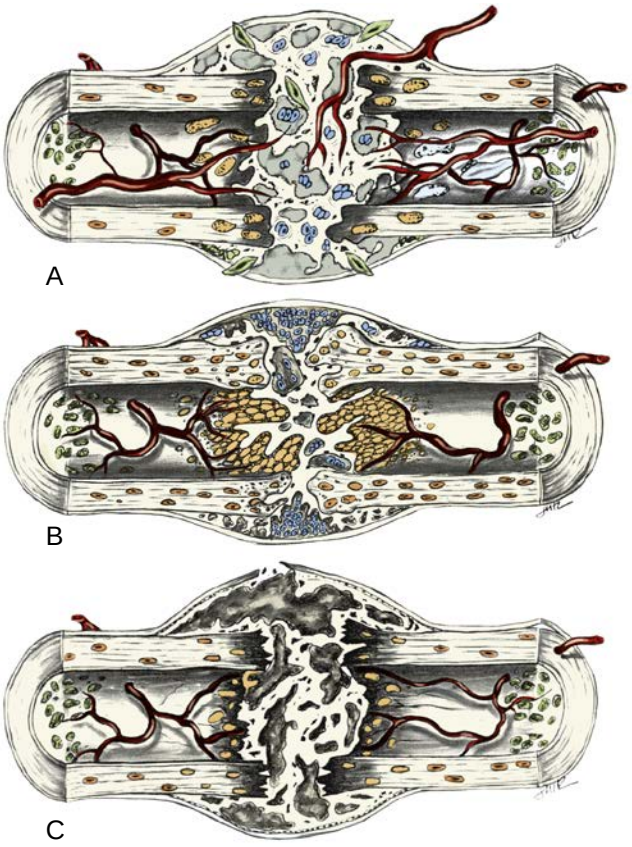
Open mandible fractures do not need to be treated with the same degree of urgency as our orthopedic colleagues would apply to open extremity fractures. Good outcomes can be expected with judicious and timely treatment, as well as with perioperative antibiotic use. In the case of open mandible fractures or mandible fractures involving tooth segments, perioperative antibiotics have been shown to be beneficial to reduce postoperative infections.[20,21] The same benefit has not been extended with the use of postoperative antibiotics.[22]

Fracture Biology

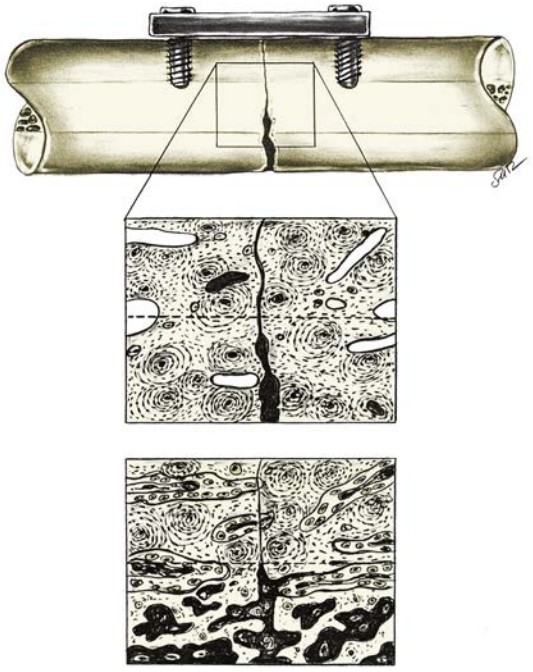
It is important for surgeons to understand the physiology of bone healing in addition to the biomechanics of facial bone function to best treat patients with any skeletal fracture. This is particularly helpful when determining the technique for fixation as well as the time allotted for the return of function. There are two processes by which a mandible fracture can heal; primary (direct) or secondary (indirect) bone healing. Either process will appropriately heal the mandible to a state that will withstand the biomechanical stress of function and form (Figures 7-11 and 7-12).

Primary healing occurs with direct contact of injured haversian systems that can remodel and form lamellar bone. The use of rigid fixation immobilizes and stabilizes well-buttressed segments to optimize contact healing without the formation of an intermediate callus. This type of healing more rapidly returns the fracture patient to the pre-injury state.

Secondary bone healing occurs with closed treatment of mandible fractures, such as when intermaxillary fixation is used for a favorable, minimally displaced angle fracture. During the healing process, a cascade of healing elements



• **Figure 7-11** Early fracture with **(A)** hematoma; **(B)** fibrocartilage callus; **(C)** hard callus. This process is common with delayed healing or secondary healing.



• **Figure 7-12** Primary (direct) bone healing on the superior portion closest to the plate due to close bone contact. Gap healing is the inferior portion as the bone is not in direct contact.

occupy the fracture site, beginning with hematoma formation and the subsequent inflammatory stage. This progresses into a soft callus and ends with remodeling. The periosteum and muscles place stresses on the fracture segments to create areas of apposition and resorption. This concept of mechanical stress dictating healing is Wolff's law.[23] If mechanical loading is placed on bone such as occurs with muscle pull, the bone will respond by remodeling and increasing in strength. This ultimately leads to equilibrium between stress and load. To achieve remodeling of the mandible to a full load-bearing state requires 4 to 6 months (less time than for long bones). The initial healing process, in order to return to normal function, typically takes an average of 4 to 6 weeks (depending on the type and severity of the fracture) and occurs in four stages.

- Inflammatory stage: The fracture causes a disruption of the vascular supply within the bone. Initially the fracture site hemorrhages, with the formation of a hematoma at the site. This is followed by an inflammatory process that involves the recruitment of macrophages, monocytes, neutrophils, and platelets. The vascular compromise initially causes necrosis of bone at the fractured edges, but a reparative process of angiogenesis ensues, as well as the formation of osteoprogenitor cells, mesenchymal cells, and fibroblasts.
- Cartilaginous stage: The initiation of a cartilaginous (soft) callus which is composed of fibrocartilaginous tissue. At the conclusion of this stage, the mobility across the fracture is eliminated.
- Bony callus stage: The conversion of the cartilaginous callus to a bony callus composed of immature woven bone, which typically occurs within 3 to 4 weeks of the injury. This is initiated by the conversion of chondrocytes to osteocytes, leading to the formation of endochondral bone.
- Remodeling stage: The return of the osseous tissue to its pre-injury state; continues for months following the injury. It is the final stage and results in the conversion of endochondral bone to mature lamellar bone.

Patient Assessment

Trauma centers evaluate and triage patients according to the principles of Advanced Trauma Life Support (ATLS). The primary survey is performed and the patient is stabilized. Soon thereafter, the secondary survey is conducted, including the craniomaxillofacial and neck examinations. Images can then be obtained based on suspicions brought about by clinical findings.

A history and physical exam are critical to managing head and neck injuries, and notes should be made concerning the mechanism of injury and loss of consciousness during the event. The physical exam should include an assessment from the skull to the clavicles for soft tissue injuries, ecchymosis, and asymmetries, as well as midline structures including the larynx and trachea. Neck zones I to III should be examined for penetrating trauma, crepitus, and hematoma.

The mandible and lower facial third should be examined and palpated for mobility, mucosal lacerations, fractured or avulsed teeth, malocclusion, bony steps or discontinuity, and any hematomas/ecchymosis of the floor of the mouth (Figures 7-13 and 7-14). The patient should be asked about paresthesia, anesthesia, or pain during the exam, and facial nerve integrity should be confirmed.

If a cervical collar is present, in-line stabilization should be used while the collar is removed for a thorough exam, so long as the patient is compliant. If a cervical spine injury is diagnosed, steps will have to be taken to immobilize the cervical spine during the definitive treatment of the facial fractures.



• **Figure 7-13** Step deformity seen with left mandibular body fracture.



• **Figure 7-14** Hematoma accompanying bilateral mandibular body fractures. The patient complained of progressive difficulty breathing and swallowing.

Imaging

The standard contemporary imaging modality is computed tomography (CT) to investigate maxillofacial trauma at the same time as other associated injuries. CT imaging highlights the bony structures better than other modalities, and three-dimensional reconstruction of the images can give the surgeon a comprehensive view of facial injuries. Level I trauma centers require access to CT capabilities, and the head/face/neck study can be included with a multisystem assessment when suspicion for injury exists. A mandible series of radiographs or a panoramic radiograph can also be ordered for centers without readily available CT. Right and left lateral oblique, panoramic, and reverse Townes views give the most thorough assessment of lower facial injury (Figure 7-15).

CT angiography can be used in the setting of blunt or the neck is contraindicated.

Treatment of Mandible Fractures

With all factors and possible implications considered, the treatment technique of mandible fractures is either open or closed. Technique decisions are based on the characteristics of the fracture as well as patient preference when appropriate. A Cochrane meta-analysis performed in 2013 by Nasser and colleagues was unable to recommend a single approach in the management of mandibular fractures without condylar involvement.[24]

Closed techniques use either tooth-borne or bone-borne stabilization to immobilize fracture segments to allow secondary healing. The keys to this technique are immobilization and approximation. This technique is reserved for patients who are capable of being placed into proper, premorbid occlusion, can be compliant, and possess no relative or absolute contraindication to a closed technique (seizure disorder, etc.). Whereas simple favorable fractures lend themselves to closed reduction and fixation, severe comminution of fractured segments may also be more appropriately treated using closed techniques to minimize devascularization of smaller bone fragments. There is evidence of cost effectiveness with closed reduction techniques, mostly due to materials and operative time.[25] The minimum time for adequate bony union is 4 to 6 weeks, but closed treatment can be extended to as long as 8 weeks with more severe facial injuries, comminution, or compromised patient healing capacity. The following appliances are commonly used for methods of maxillomandibular fixation:

Tooth-borne

- Erich arch bars
- Interdental wires (Ivy loops, eyelet wires, etc.)
- Lingual splint

Bone-borne

- Skeletal suspension wires



• **Figure 7-15** Radiographs such as these are less commonly used in major trauma centers but are useful in diagnosing mandible fractures. A mandible series showing a left angle fracture using **(A)** anteroposterior, **(B)** reverse Townes, and **(C)** lateral oblique views. **D,** A right mandibular body fracture is stabilized temporarily with a dental bridle wire. Typically this will be placed two teeth on either side of the fracture, if teeth are stable and present.

- External fixators
- Intermaxillary fixation (IMF) screws
- Hybrid systems (Stryker SMARTLock)

Erich arch bars have been the standard maxillomandibular fixation device for decades to render treatment in any number of settings: office, emergency room, or operating room. The stainless steel wire and arch bars are inexpensive compared to other methods of MMF. Arch bars are also excellent stabilizers for dentoalveolar fractures that may not be suitable for miniplates. The semirigid fixation adapts to neighboring teeth to reestablish intra-arch dimensions and

The arch bar does have several disadvantages: risk of operator or patient wire-related injury during placement, difficulty with patient hygiene, damage to the alveolar peridontium, and unintentional tooth movement or extrusion. Pediatric patients in the mixed dentition stage may be better served by other methods of closed treatment because of problems with arch bars engaging the height of contour and/or possible extrusion of deciduous teeth or underde-

wires may be better options.

One of the more recent additions to the closed treatment/reduction armamentarium within the past several years has been the SMARTlock Hybrid MMF system (Stryker CMF, Kalamazoo, MI). The bone-borne titanium arch bar significantly reduces reliance on teeth for fixation techniques, similar to IMF screws but incorporates a full-arch distribution of forces similar to Erich arch bars.

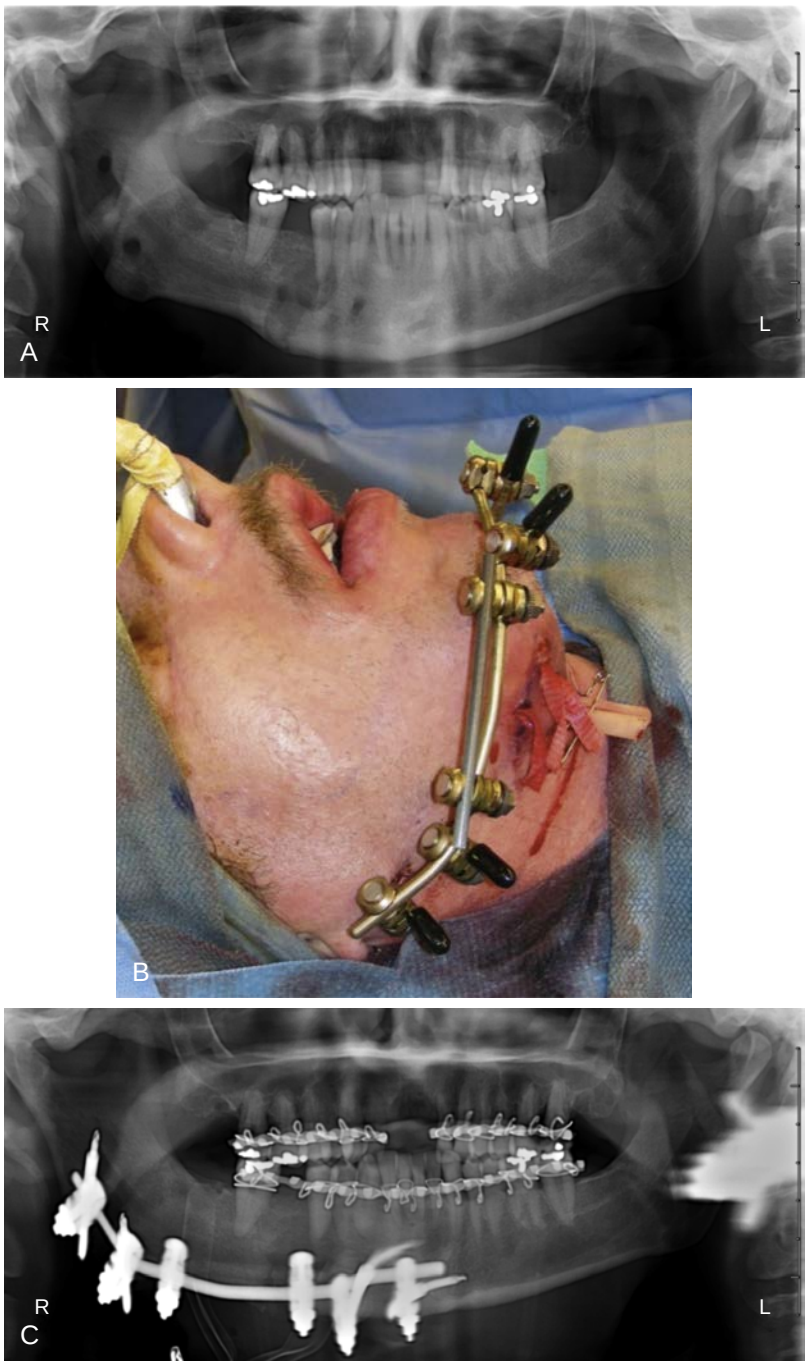
The lingual splint is a technique with which the maxillofacial trauma surgeon should be familiar. It can be useful in the pediatric patient because of the challenges posed by mixed dentition. This phase precludes the use of internal fixation for the potential damage to tooth buds and potential for changes in growth. The lingual splint can be used in adult patients with a dentition that does not provide a stable base (i.e., partially edentulous) to reliably apply MMF. Obviously this will require impressions and casts of the maxilla and mandible. This may be difficult to obtain because of pain and trismus, and it may require the patient to undergo anesthesia. Impressions can also be made complicated by the presence of significant oral soft tissue injury and edema, or by the presence of an endotracheal tube. Before the fabrication of the lingual splint, the mandibular casts may need to be sectioned in order to reestablish an appropriate arch length and alignment. The splints can have arch bars incorporated into the acrylic and can be secured to remaining teeth/mandible with circumdental and skeletal wires.

External fixation has played a significant role in the treatment of comminuted mandible fractures and the atrophic mandible fracture for a number of years (Figure 7-16). Currently, however, the use of rigid fixation and microvascular reconstructive surgery has diminished its relevance. There are occasional instances where external fixation can be used as a bridging technique. In these situations, when the surgeon is waiting for the stabilization of soft tissue or recalcitrant infection, external fixation can be used to maintain the continuity defect and form. Once soft tissue stabilization is achieved, the definitive repair can be undertaken and the external fixation removed.

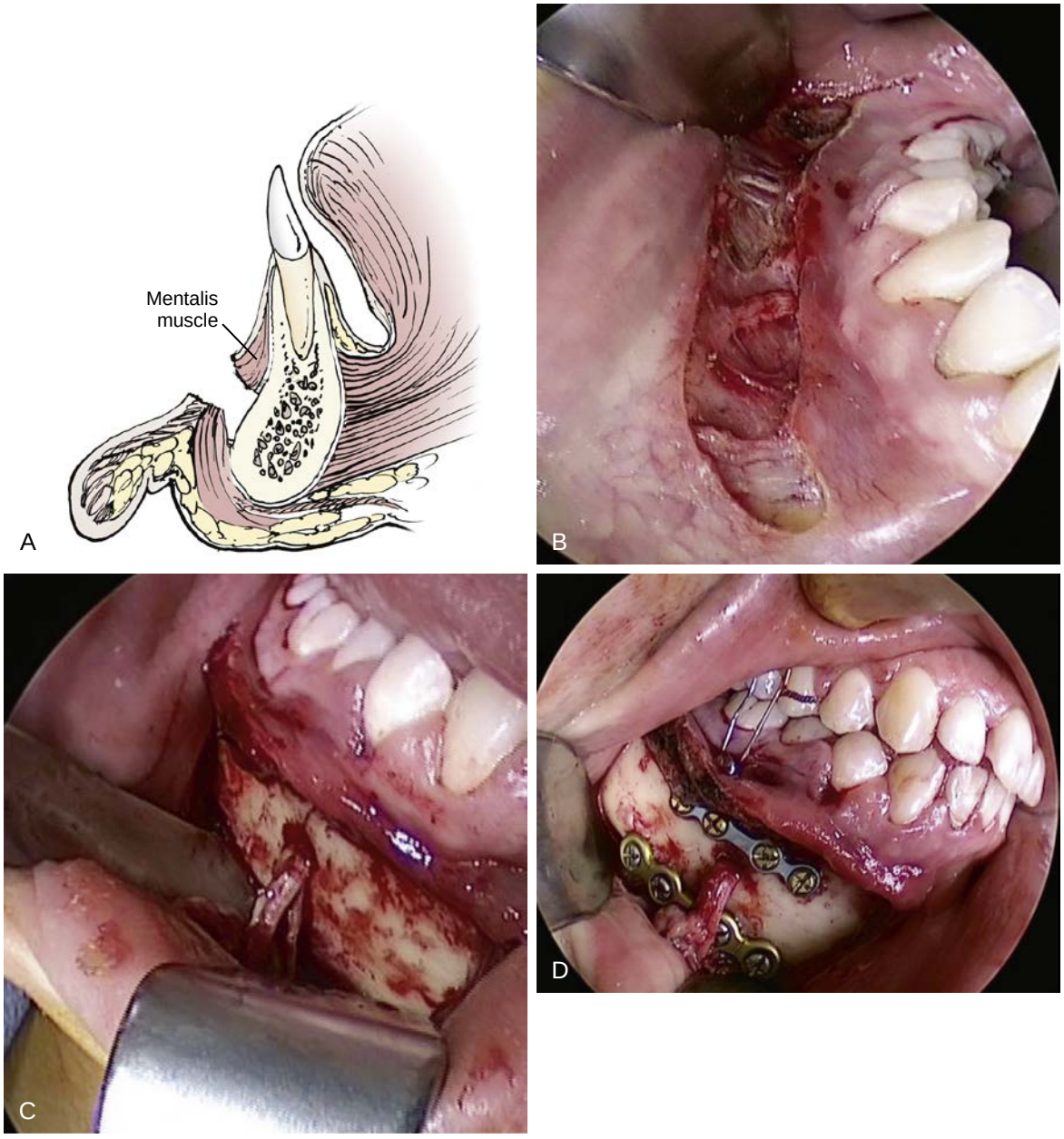
Open techniques have been revolutionized by advances in rigid fixation. Surgeons and patients appreciate an earlier return to function and avoidance of being "wired shut." Most mandible fracture segments can be accessed through oral and/or percutaneous (transbuccal) approaches. As a fracture's displacement or severity increases, the use of transcervical, retromandibular, or preauricular approaches may be warranted. Ramus and condyle fractures are typically accessed through neck and preauricular incisions; however, endoscopic approaches can be used as well.

Intraoral/Transbuccal approach (Figures 7-17 to 7-21)

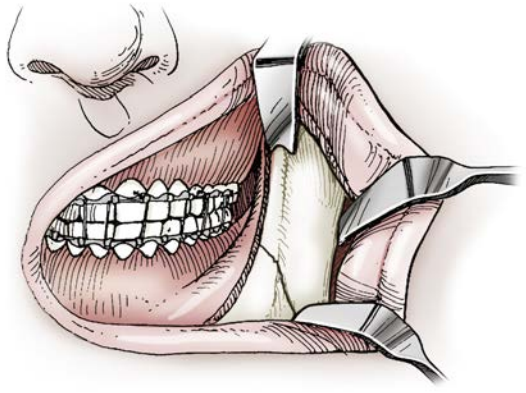
1. Local anesthetic with epinephrine can be infiltrated throughout the field to aid in hemostasis.
2. An incision is made approximately 5 to 7 mm apical to the mucogingival junction. The incision is only through mucosa to aid in identification and preservation of mental nerve branches around the canine/premolar region. The foramen itself is typically located close to the apex of the second premolar; however, preoperative assessment and localization is helpful with a panoramic radiograph or CT scan. An alternative approach can be accomplished via sulcular incisions with generous releases. This approach will avoid vestibular scarring and localization of the mental nerve along its extrabony course, but might limit access and visualization for some fractures.
3. Anteriorly, the mentalis muscle is divided, leaving a cuff of muscle for closure, and posteriorly the buccinator is elevated from the mandible. A subperiosteal dissection is performed anteriorly or posteriorly using the blunt end of a periosteal to identify the mental foramen, which will help in nerve preservation.
4. The mental nerve and its branches should be identified and preserved. Skeletonization at its bony exit may be helpful for retraction and performed by incising along the periosteum overlying the nerve using a blade and tenotomy or iris scissors. If the fracture does involve the foramen, care must be taken to avoid unnecessary nerve injury during mobilization and reduction of the fracture.
5. Any granulation, clot, or fibrous soft tissue preventing proper reduction should be removed.
6. The fracture sites should be copiously irrigated to dilute microbial contamination.
7. Before fixation, all fractures should be accessed and mobilized as described.



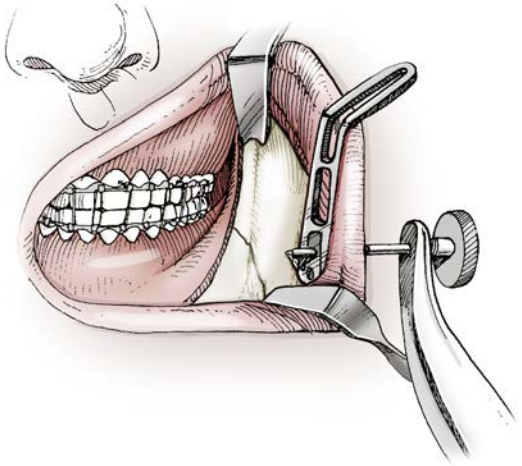
• **Figure 7-16** External fixation systems are an additional tool in the armamentarium for clinicians unable to immediately fixate segments in the setting of infection, nonunion, or noncompliance. **A,** This patient presented several weeks after sustaining a right parasymphyseal fracture with osteomyelitis and a submandibular space infection**. B,** Intraoperative photo of treatment as well as radiograph **(C)** showing fixation in place and Erich arch bars.



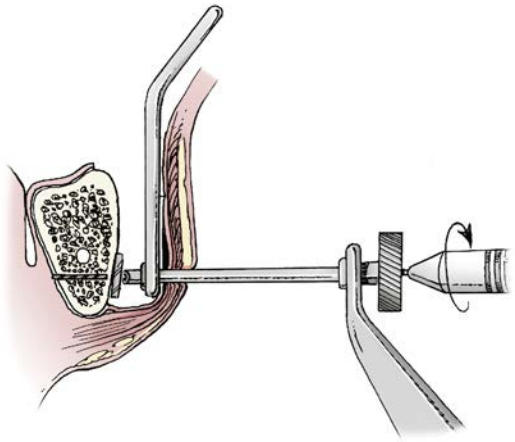
• **Figure 7-17** **A,** Path of dissection to the anterior mandible through mandibular vestibule. Mentalis muscle is incised and used later for layered closure. **B,** Access along the vestibule of the right mandible through mucosa, taking care to preserve the mental nerve. Similar vestibular access of the left angle fracture was completed. **C,** Identification, skeletonization, and protection of the mental nerve branches. IMF screw maxillomandibular fixation was used to reduce the fractures. **D,** Superior monocortical and inferior bicortical fixation is used to complete the fracture repair.



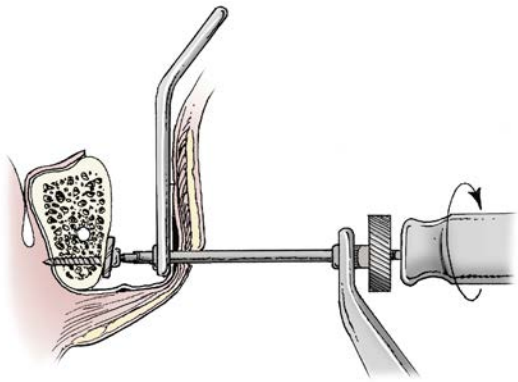
• **Figure 7-18** Transbuccal approach using subperiosteal dissection along ramus.



• **Figure 7-19** Transbuccal trocar in place with cheek retractor.

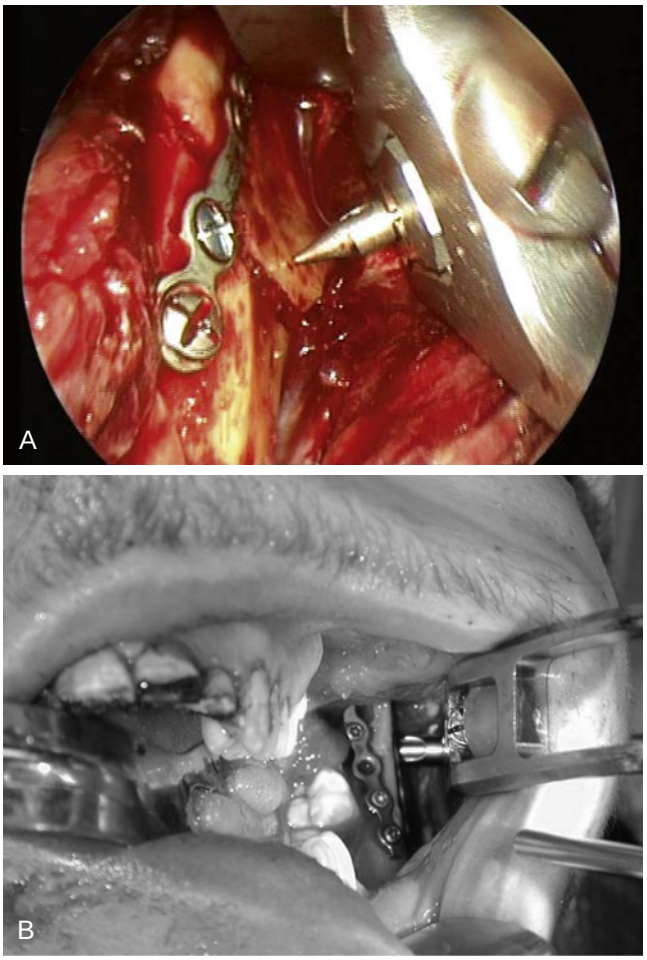


• **Figure 7-20** Preparation of inferior border bicortical plate fixation.



• **Figure 7-21** Bicortical screw placement based on accurate depth measurement to engage both cortices.

8. Fixation is then accomplished by any of several techniques. The authors prefer rigid fixation following AO/ASIF principles. Two-plate techniques place fixation along zones of tension and compression, typically a miniplate at the superior border and a fracture plate at the inferior border. Two-screw fixation is used on either side of the fracture with both plates for proper fixation. A single reconstruction plate (2.3 to 2.5 mm) at the inferior border can be used with three-screw fixation on either side of the fracture as an alternate technique. The authors prefer locking plates in the inferior border position.
9. A transbuccal puncture may be required to access more posterior body or angle plates (Figure 7-22). A cutaneous stab incision can be made through the cheek with a No. 15 blade overlying the portion of interest of the fracture. Blunt subcutaneous and trocar dissection is then carried out through the remainder of the cheek in order to manipulate the site for superior and inferior plate access both proximally and distally.
10. Resuspension of the mentalis muscle should be performed at closure to prevent a "witch's chin" deformity. Mucosa can then be closed using a continuous running 3-0 chromic gut suture.

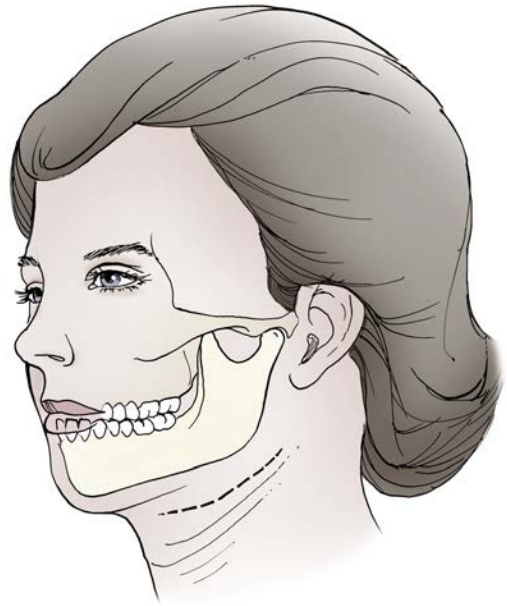


• **Figure 7-22** **A,** Transbuccal systems can be used for open reduction and provide good posterior access and visualization of the fracture and fixation. **B,** Transbuccal approach to left angle.

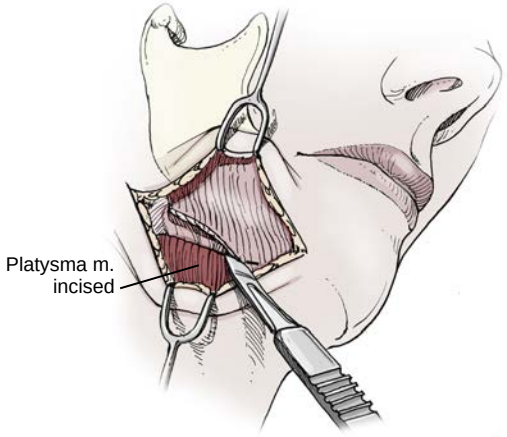
Transcervical-Submandibular Approach (Figures 7-23 to 7-28)

A skin crease is identified approximately 2 cm (or more) below the inferior border of the mandible at the approximate area of the fracture with enough extension on either side to allow for the appropriate sized plate placement and necessary retraction. If the surgeon wishes to assess the facial nerve during the procedure, muscle relaxant should be avoided after intubation. The authors prefer a high apron incision and an anatomic approach where nerve monitoring is not used.

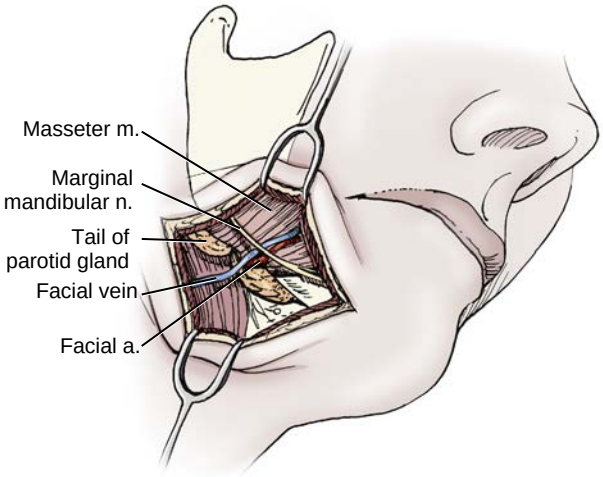
1. The skin, subcutaneous fat, and platsyma should be incised to identify the superficial layer of deep cervical fascia investing the submandibular gland. The marginal mandibular branch of the facial nerve will be deep to the platsyma and within the superficial layer of the deep cervical fascia.
2. The superficial fascia is divided at the inferior aspect of the submandibular gland, and a subcapsular dissection can be performed to protect the facial nerve. The facial vein can be divided at this point and retracted superiorly



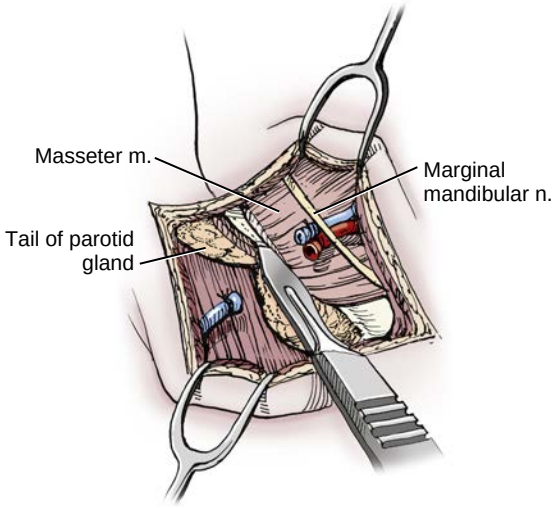
• **Figure 7-23** Extension of submandibular approach to the mandible using natural skin neck crease.



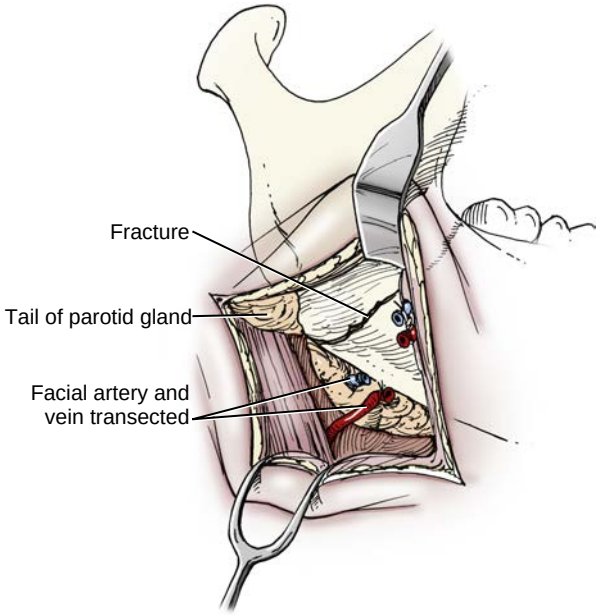
• **Figure 7-24** Incision through skin and platysma.



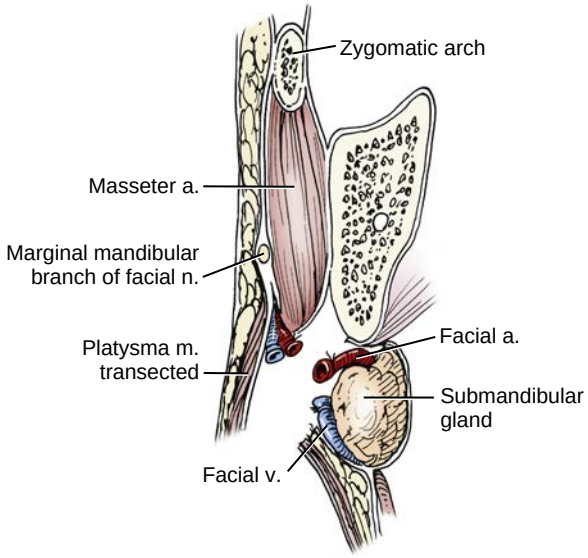
• **Figure 7-25** Dissection in subplatsymal plane to identify capsule of submandibular gland and facial vessels (artery and vein).



• **Figure 7-26** Division of the pterygomasseteric sling.



• **Figure 7-27** Identification of the fracture along a subperiosteal plane.



• **Figure 7-28** Coronal view of dissection planes.

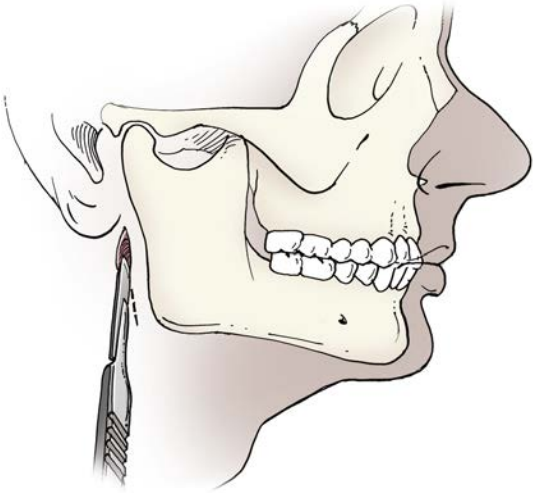
to guide dissection and protect the facial nerve (Hayes-Martin maneuver). The facial artery should be identified near the posterior aspect of the gland and isolated/divided as necessitated by access. A cadaveric study by Dingman and Grabb identified the marginal mandibular branch of the facial nerve at most 1 cm below the inferior border of the mandible 81% of the time when posterior to the facial vessels. Anterior to the vessels, the marginal mandibular branches course inferior to the mandibular border only 19% of the time.[26] Nerve simulators can be used if there is any doubt or question of the tissue dissection.

3. Anterior to the gland and facial vessels, a plane of dissection deep to the superficial layer of deep cervical fascia should direct the surgeon to the anterior digastric muscle. This can be safely dissected superiorly to its insertion at the anterior mandible.
4. Using the Hayes-Martin technique of ligating and elevating the facial vein/artery, the facial nerve is protected for direct access to the inferior border of the mandible,[27] though often the anterior course of the facial artery/veins must be encountered and managed. The pterygomasseteric sling will be encountered and is incised as needed depending on location of the fracture. The periosteum is incised at the most inferior aspect of the mandible, and a subperiosteal dissection can be developed to identify the fractures.
5. Care should be taken to avoid any damage to the mental foramen while approaching and degloving the mandible from below.
6. Once the fractures have been identified, debrided, and mobilized, the patient can be placed into MMF. The fractures may need additional reduction and immobilization with reduction forceps prior to plating. Occlusion should be verified prior to final rigid fixation. ORIF principles are followed as described earlier.
7. Closure of the platsyma over a bulb suction round drain is recommended to manage dead space and prevent hematoma formation. Resorbable suture is used for platysma and deep dermal sutures. Skin can be closed with running nonresorbable monofilament or staples.

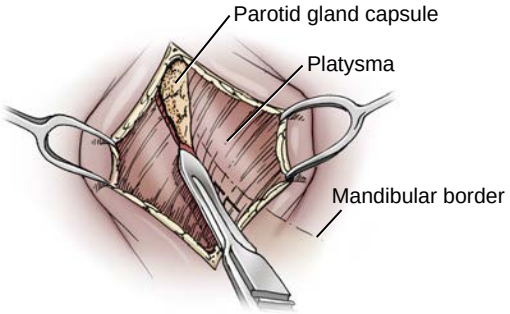
Transcervical-Retromandibular Approach (Figures 7-29 to 7-33)

A skin line several centimeters in length is marked paralleling the posterior border of the mandible 5 to 10 mm below the earlobe. The incision should be placed about 1 cm posterior to the ramus to allow elevation of the parotid gland.

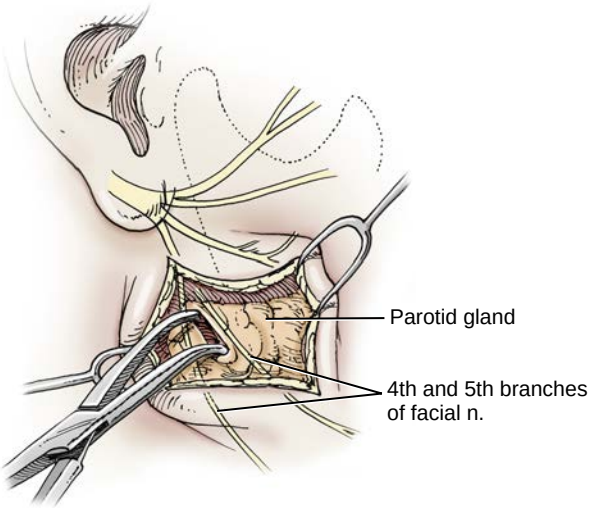
1. Skin and subcutaneous fat are incised. Platysma may be encountered and should be incised as well. Identification of the superficial musculoaponeurotic system (SMAS) that invests the parotid gland and masseter and the anterior border of the sternocleidomastoid posteriorly will guide the dissection.
2. At this point two approaches are used, depending on the surgeon and level of fracture: the transparotid for higher condyle fractures, or the sub-parotid approach for lower ramus fractures.



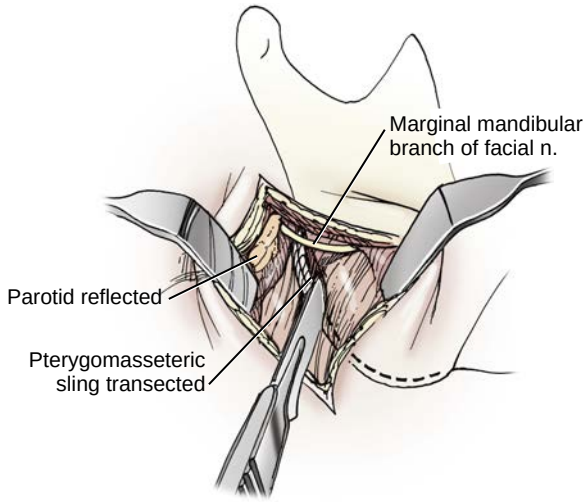
• **Figure 7-29** Retromandibular approach.



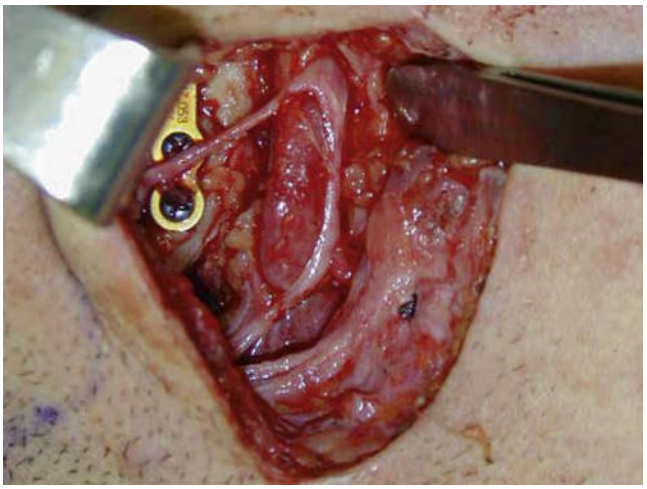
• **Figure 7-30** Incision through platysma muscle.



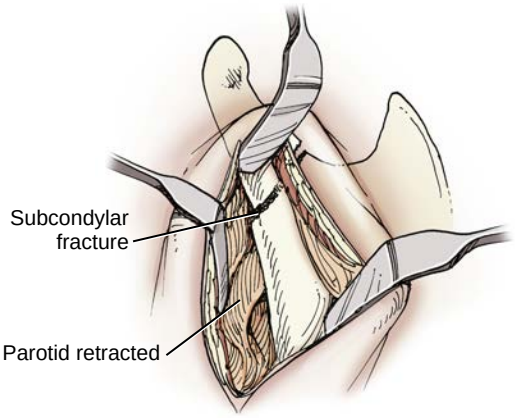
• **Figure 7-31** Dissection through the parotid bluntly to avoid facial nerve damage.



• **Figure 7-32** Incision through pterygomasseteric sling.



• **Figure 7-34** Identification of facial nerve branches (buccal and marginal mandibular).



• **Figure 7-33** Exposure of condylar or mandible fracture in subperiosteal plane.

a. The transparotid directly divides the parotid capsule, and blunt dissection is used to dissect through the gland to the mandible. The buccal and marginal mandibular branches are routinely identified and retracted to access the condyle fracture (Figure 7-34). A nerve stimulator is used to verify branches of the facial nerve, and bipolar electrocautery is used for hemostasis. Transient facial nerve injury in the transparotid approach has been documented, but function usually returns by 6 months.[28] Careful retraction of the soft tissues enveloping facial nerve branches will limit the transient paralysis postoperatively.
b. The sub-parotid approach elevates the parotid superiorly to protect the facial nerve and provide access inferiorly along the posterior aspect of the mandibular angle. This approach is better suited for lower ramus fractures but can be elevated to expose up to the neck of the condyle. In this approach, the facial nerve is still susceptible to traction injury.

3. The masseter and periosteum should be incised and elevated to identify the posterior aspect of the mandible and associated fractures. Care should be taken to stay within the subperiosteal plane to avoid damage to the retromandibular vein.
4. If the sigmoid notch is encountered, a subperiosteal dissection should be maintained to avoid damaging the masseteric branch of the maxillary artery.
5. Fractures are mobilized, debrided, and reduced. Condyle fracture reduction should be reconfirmed after establishing MMF and accomplishing reduction of all other fractures. Occasionally segments of the condyle/condylar neck will be difficult to reduce with the patient in MMF.
6. Fixation should be applied as deemed appropriate. Several condyle-specific plates are currently available that are suited to the unique contours and space limitations of the anatomic region. Watertight closure of the parotid capsule using resorbable sutures will help prevent salivary leak. A round bulb suction drain can once again aid in the elimination of dead space and avoid seroma or hematoma formation. A pressure dressing can also aid in hemostasis and prevention of a salivary leak. Platysma is reapproximated and skin closed with running nonresorbable, monofilament suture.

Endoscopic Approach

Endoscopic approaches to the subcondylar and condylar region are used to minimize facial nerve damage as well as facial/neck scars. The approach uses a sagittal split/lateral mandibular vestibule access to manipulate segments and place miniplates. A less than 1 cm submandibular incision can be used with minimal dissection deep to the pterygomasseteric sling to place the endoscope. A 3- to 4-mm Storz endoscope can be used for the procedure. As previously mentioned, mobilization and reduction techniques should be carried out, but this time using direct endoscopic view and instrumentation. Right-angle drills and screwdrivers can be used to avoid percutaneous access higher on the face.

The technique requires considerable patience and typically will increase the surgical time by 1 to 2 hours.[29] The benefit is largely a reduction in facial scars when endoscopic approaches are compared to open access, along with decreased rate of facial nerve complications.[30] More details of endoscopic approaches to mandible fractures are presented in additional chapters.

comes and hastened return to function. There are two broad categories of fixation methods:

- Semirigid fixation
- Rigid fixation

Semirigid fixation (with or without maxillomandibular fixation):

- Champy's technique (monocortical miniplate fixation)
- Resorbable plates
- Monocortical plate fixation (non-Champy)

Maxime Champy was a pioneer of semirigid fixation techniques.[12] Using the lines of osteosynthesis, based on his understanding of torsion, compression, and tension, miniplate semirigid fixation could be placed with proper buttressing to reduce the fractures and encourage primary healing within very specific parameters of wound management (Figure 7-35). This type of fracture fixation is best used with compliant patients who have well-buttressed fractures or along with a brief period of maxillomandibular fixation.

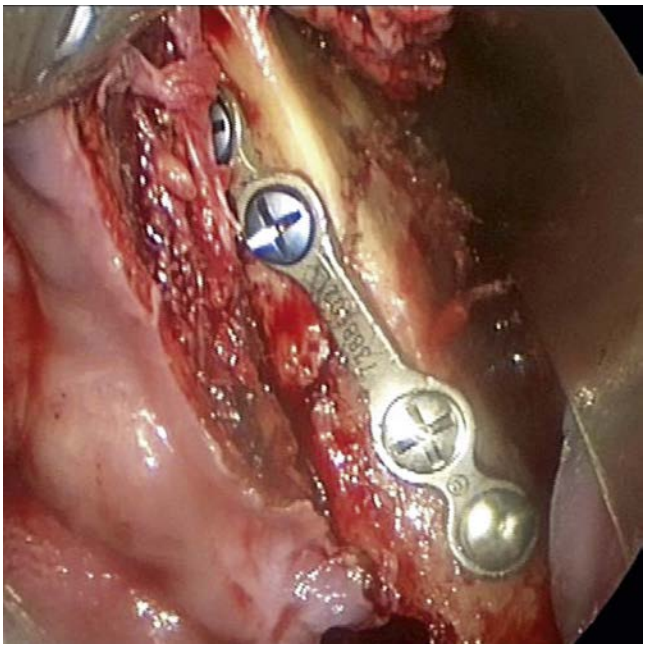
In pediatric patients, resorbable plates can add some rigidity to the reduction of a mandible fracture without the possibility of having to remove hardware due to translocation concerns. Poly-L-lactic or polyglycolic acid are major components of the current resorbable plating systems available. These constructs are reduced to water and carbon dioxide at about 8 to 18 months, depending on the polymer material composition. Most plating companies use a proprietary polymer with similar strength and resorption properties.[31] Resorbable plates should not be used as primary load-bearing plates, but several sources highlight their use with reduced or equivalent complication rates when compared with titanium plates and screws in well-buttressed fractures[32-34] (Figure 7-36). The cost and nature of the technique can be a deterrent for some surgeons.

Transosseous wire fixation has limited use in today's realm of miniplate and rigid fixation. Occasionally with comminuted fractures, smaller fragments can be transiently realigned with wire in preparation for placement of a reconstruction plate or more stable fixation.

Rigid fixation can use a number of techniques:

- Two-plate technique (superior monocortical tension-band and inferior border bicortical compression plate)
- Reconstruction plate
- Lag screw

The two-plate technique traditionally uses a superior tension band, low-profile/miniplate (or dental arch bar) to prevent fracture distraction at the alveolar process level, while a more rigid intermediate-profile plate is placed in the compression zone at the inferior border. The superior border plate is a monocortical plate respecting the local dental anatomy. The inferior border plate is fixated with bicortical screws to maintain rigidity, immobility, and fracture reduction.



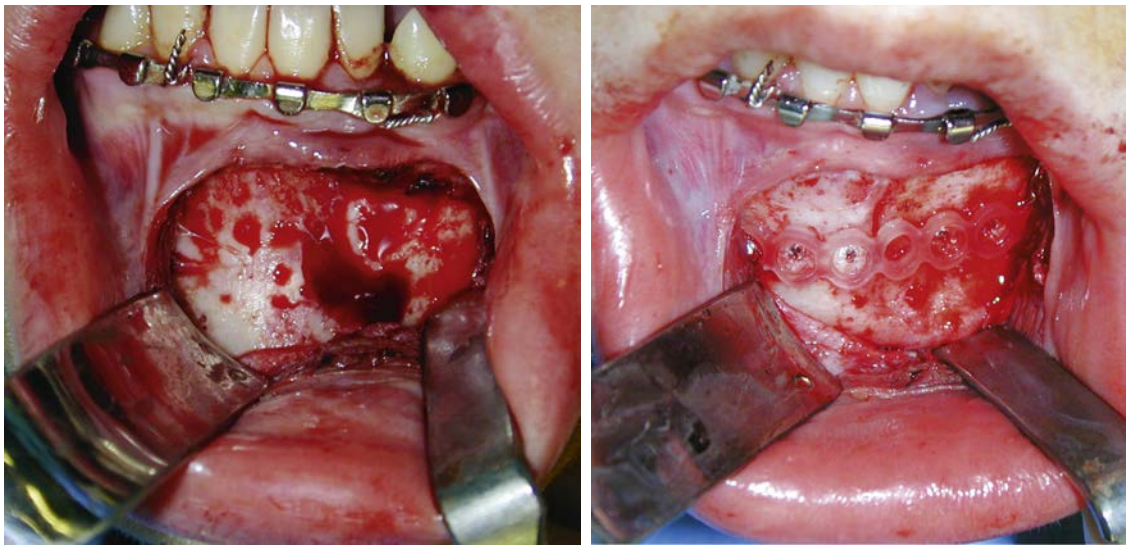
• **Figure 7-35** Favorable mandibular angle or ramus fractures may be amenable to Champy-style tension plates where compressive forces at the inferior border maintain fracture reduction. This obviates the need for transcervical or transbuccal approaches and the need for long-term maxillomandibular fixation.

A reconstruction plate is a rigid, higher-profile plate meant to temporarily restore form when a continuity defect is anticipated or when used to serve as the sole form of fixation. These plates are used for more load-bearing situations such as atrophic mandible fractures or continuity defects that require rigidity, flexion, and torsion strength (Figure 7-37).

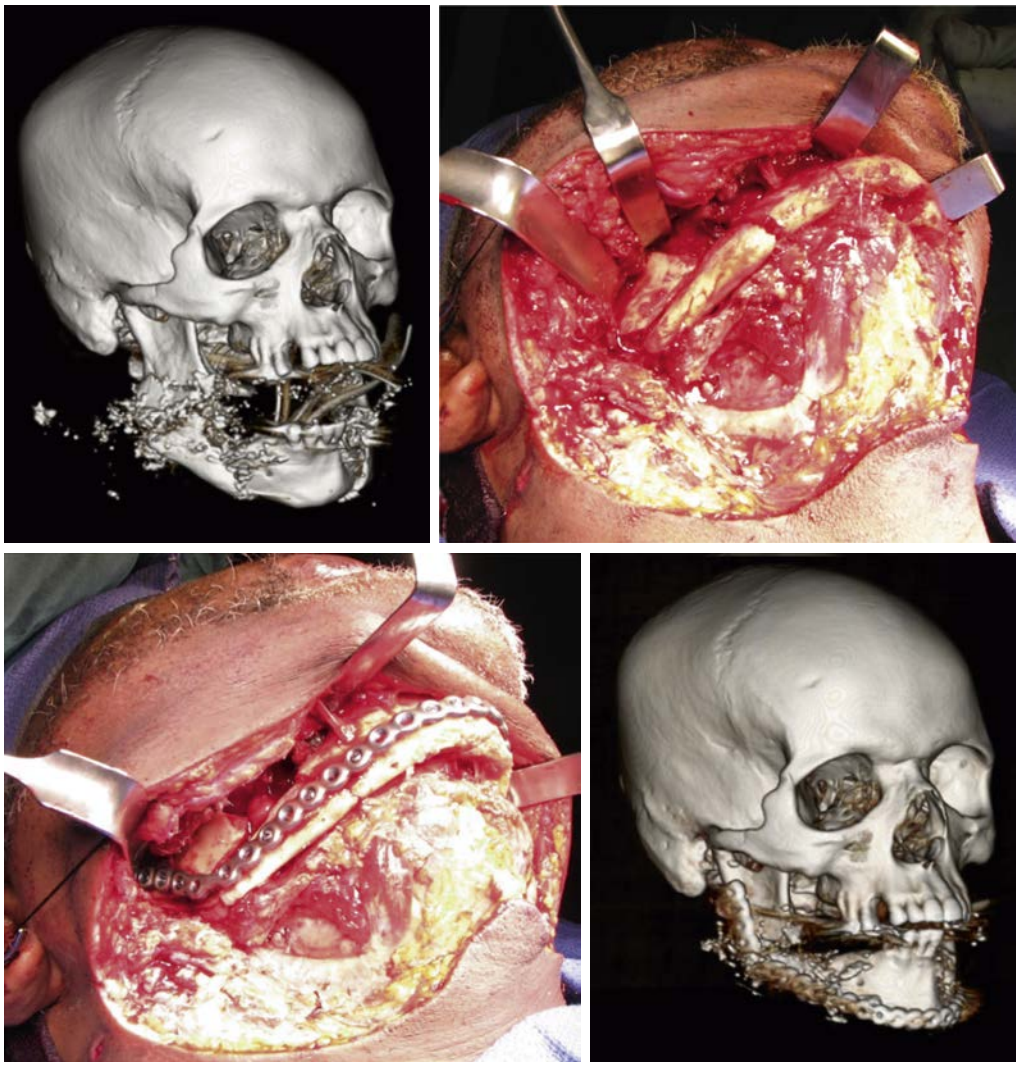
Hardware Materials

Principles of orthopedic surgery in reduction and fixation were the initial concepts adopted and applied to mandible fractures. AO/ASIF introduced compression techniques to orthopedics in 1969, but required the additional modification of tension banding in the mandible to prevent displacement.[35,36] Compression plates have now largely fallen by the wayside. Contemporary plate manufacturers instead typically produce two kinds of fixation plates and screws: locking and nonlocking (bone plates). Depending on the scenario, either can be used with good results, so long as there is an understanding of the biomechanics and limitations of each device.

Nonlocking plates and screws do not have the capability of creating the single functional unit that a locking

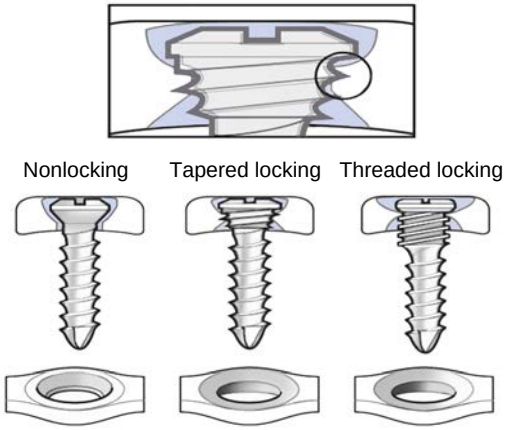


• **Figure 7-36** Resorbable systems can be used to treat pediatric fractures when there is concern that ongoing growth may result in translocation of hardware.

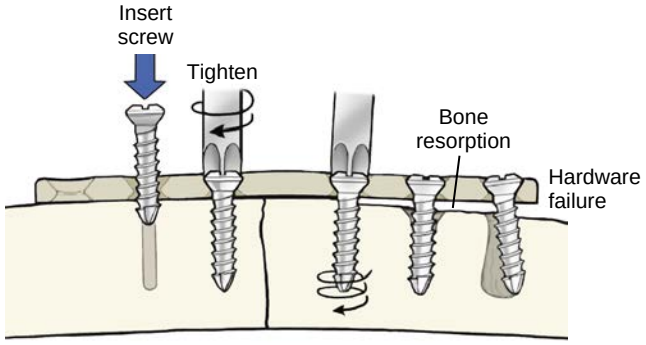


• **Figure 7-37** With severely comminuted mandible fractures, load-bearing fixation is used. This patient sustained a low-velocity gunshot wound to the mandible. Using virtual planning technology, a prefabricated titanium reconstruction plate was used to accurately reconstruct the lower jaw contour.

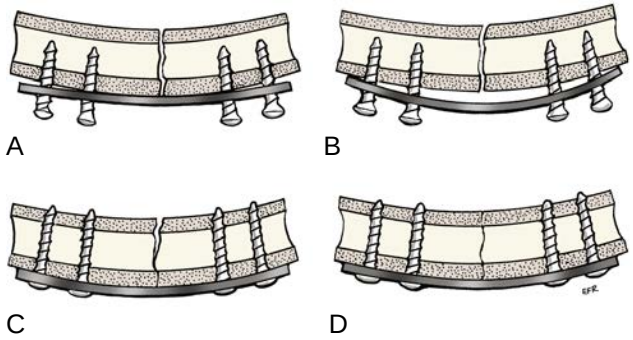
system does from the screw engaging the plate (Figures 7-38 to 7-40). Therefore, a compressive force is transmitted to the cortex once the screw is put to depth, which can compromise the vascularity of the bone adjacent to the plate, causing bone resorption. Additionally, the force transmitted from plate to bone can distract the fracture when plate position is not completely passive. The sum total of these two ill effects (hardware loosening and non-anatomic fracture reduction) can result in nonunion with low-load but persistent shear forces preventing bridging bone formation.



• **Figure 7-38** Plating and screw designs.



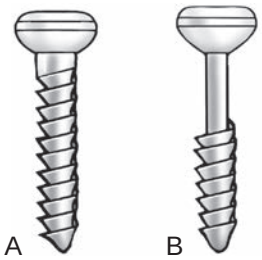
• **Figure 7-39** Bone resorption leading to hardware failure with nonlocking screws and plate.



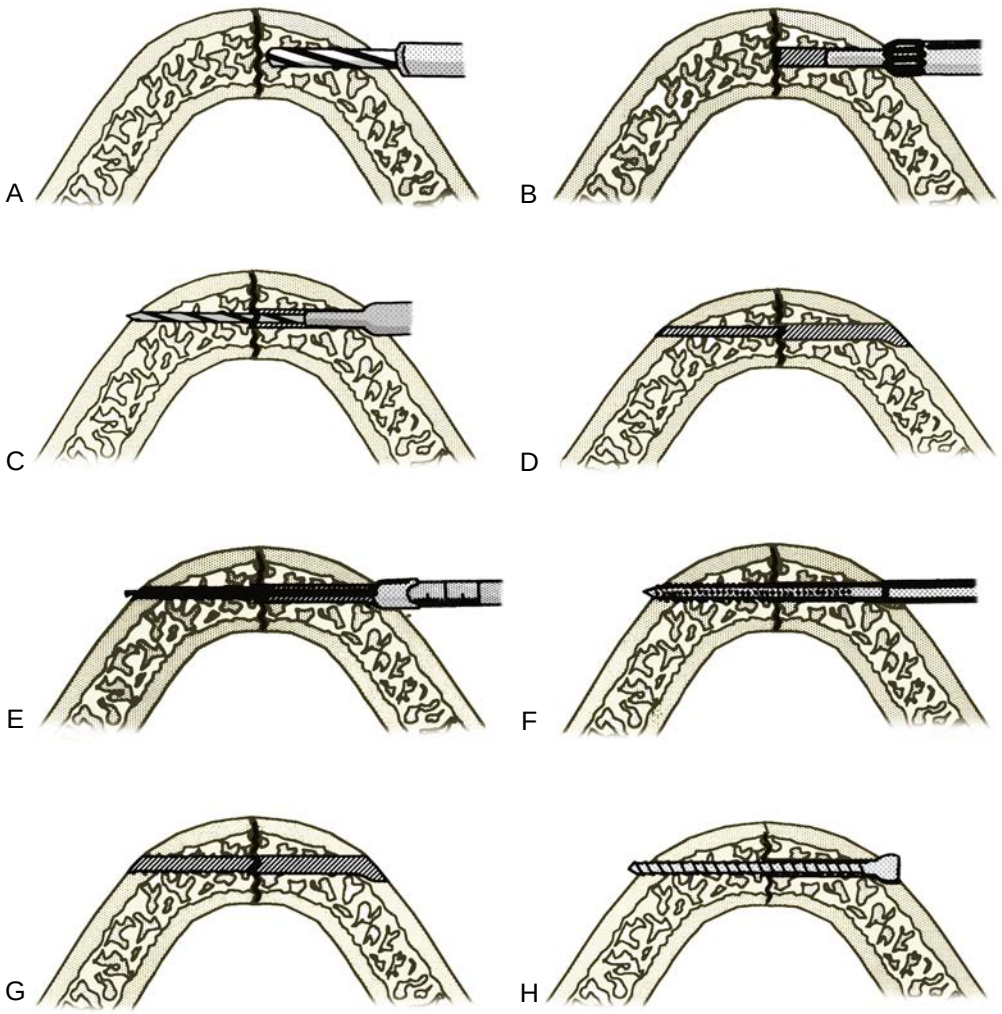
• **Figure 7-40** Plating situations: **A,** Underbent plate with gap healing. **B,** Lingual gap with tightened undercontoured plate. **C,** Overcontoured plate with gap. **D,** Tightened overcontoured plate with good bony reduction. (From Baker S, Dalrymple D, Betts NJ: Concepts and techniques of rigid fixation. In Fonseca RJ, Walker RV, editors: *Oral and maxillofacial trauma*, ed 2, vol 2, Philadelphia, 1997, WB Saunders.)

Locking plates and screws allow machine-placed threads in the screws to engage the plate and rigidly stabilize the entire unit without transmitting forces from the plate to the bone. This concept was initially introduced in 1987 as the titanium hollow-screw osteointegrated reconstruction plate (THORP).[37] A titanium plate was adapted to a fracture and positioned with hollow-bone screws. An expansion screw was then placed in the head of the bone screw to engage and lock the hollow screw into the titanium plate. The design was short-lived and replaced quickly by the contemporary locking screw that threads directly into the machined threads of the plate (thread-lock).[38] The locking plates allow for less precise adaptation of the plate to the bone without affecting the anatomic reduction of the segments. Other locking designs soon emerged (tapered-lock), each with advantages and disadvantages. There is limited evidence to show the locking design to be superior in terms of complications or surgical outcome when compared with nonlocking systems.[39]

The lag screw technique is a cost-effective rigid fixation method that applies a compressive force across reduced bony segments, maximizes bony buttressing, and eliminates the need for plate bending (Figures 7-41 and 7-42). The concept was first adapted from orthopedic surgery and applied to mandibular fixation in 1970 as a simple and effective mode of treatment.[40] This technique is ideally used in vertical well-buttressed fractures of the anterior mandible using two lag screws paralleling each other, and placed from opposite sides of the fracture. The lag technique prevents torsion and flexion of the mandible, maximizes fracture surface contact, and provides rigidity. The biomechanics of the technique compresses bony segments using a threaded hole in the opposite cortex and an unthreaded overdrilled portion of the cortex nearest the head of the screw. Countersinking of the screw head is optional for better contour. Screw stripping, shearing, fracture displacement, and instrument failure are inadvertent sequelae that can all occur using this technique.



• **Figure 7-41** **A,** Passive bone screw. **B,** Lag screw with unthreaded superior section. (From Baker S, Dalrymple D, Betts NJ: Concepts and techniques of rigid fixation. In Fonseca RJ, Walker RV, editors: *Oral and maxillofacial trauma*, ed 2, vol 2, Philadelphia, 1997, WB Saunders.)



• **Figure 7-42** Protocol for lag screw placement for symphyseal fractures of the anterior mandible. **A,** Outer cortex wider diameter hole (2.7 mm) with **(B)** countersinking. **C,** 2.0-mm drill through opposing cortex through mandible. **D,** Resulting difference in proximal and distal segments of mandible based on 2.7-mm and 2.0-mm holes drilled. **E,** Depth gauge applied to assess fixation screw length. **F,** 2.0-mm tap then applied to distal segment. **G,** Screw threads present in proximal and distal segments. **H,** Lag screws inserted. Ideally a second screw would be applied in the opposite direction in an inferior and superior orientation. The lag screws would only engage the far cortex. (From Ellis E, Ghali GE: Lag screw fixation of anterior mandibular fractures, *J Oral Maxillofacial Surg* 49:13-21, 1991.)

Controversial Topics in Mandible Fracture Repair

Teeth in Line of Fracture

Most teeth involved in mandibular fractures do not require extraction, nor has any reduction in morbidity been demonstrated.[41,42] Indications for tooth removal include:

- Periapical pathology
- Active infection (acute or chronic)
- Interference with fracture reduction
- Root fracture

Some teeth in fracture sites can aid in buttressing fractures when maxillomandibular fixation is applied; however, recent literature has noted higher percentage of hardware failure when positioned over teeth in the line of the fracture[43] (Figure 7-43). If teeth become symptomatic, extractions can performed approximately 4 to 6 weeks after fracture union has been confirmed clinically and radiographically. Incision design, especially in angle fractures with planned removal of a third molar, should be tailored to promote primary closure over fracture sites and hardware.

Condyle Fractures

Fractures of the mandibular condyle can be within the TMJ capsule or extracapsular—at the neck/subcondylar. There is significant controversy surrounding the proper management of mandibular condyle fractures in the extracapsular classification. Several authors highlight better patient function and occlusion using open techniques.[44] The ultimate determining factor should be the ability to restore the occlusion



• **Figure 7-43** Panorex radiograph of left angle fracture splitting the lower left third molar. The tooth will require extraction to reduce postoperative complications.

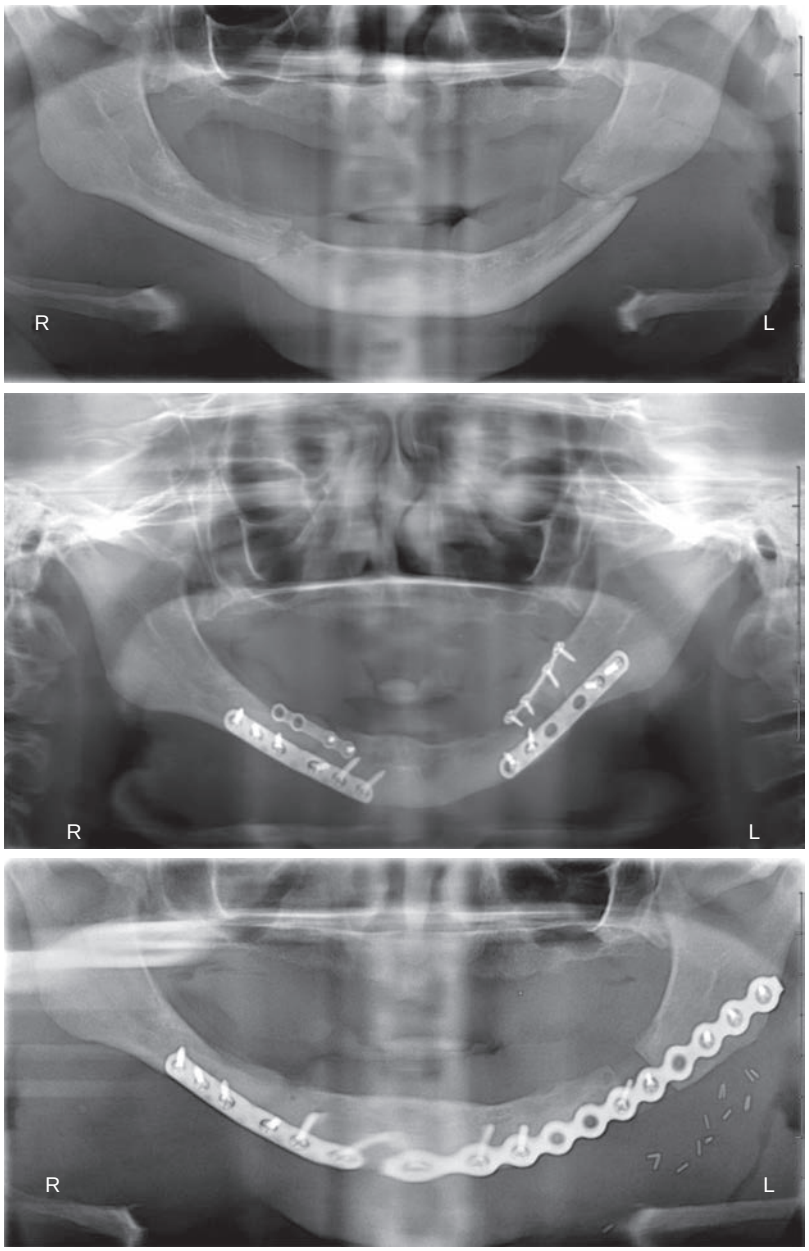
and the patient's ability to function without pain. Details of condylar fractures including open and closed indications are discussed in a separate chapter.

Angle Fractures

Angle fractures are one of the most common fracture sites treated and are more likely to occur with an impacted third molar.[45] Managing the area is complicated by the distracting forces imposed by a network of muscle attachments (masseter, pterygoids, temporalis, and ligament attachments) and the inability to use tooth-borne stabilization of the superior border, such as an arch bar. Unfavorable angle fractures treated solely with maxillomandibular fixation may allow rotation of the proximal segment and subsequent malunion. The use of rigid fixation is currently advocated by many for the treatment of unfavorable displaced angle fractures, though Champy questioned the need for such treatment in nondisplaced or minimally displaced and favorable fractures. Using a single monocortical tension plate positioned on the external oblique ridge, semirigid fixation can be achieved to avoid neurovascular damage and damage to adjacent teeth, and to return function without maxillomandibular fixation.[12,46] In 1999, Ellis's prospective study reviewed eight methods for treating mandibular angle fractures. Transoral open reduction and semi-rigid fixation using the Champy tion plate resulted in the next lowest rate of complication at 7.5%. Suffice it to say that there are many valid techniques used to treat angle fractures, and aside from the treatment of condylar injuries, angle fractures may generate the most differing opinions. There are several issues to consider when choosing a modality of treatment, including fracture buttressing, the need for tooth extraction, the presence of soft tissue injury, medical comorbidities, concomitant upper facial injuries, and patient compliance. Once the appropriate fixation method has been chosen, most fractures can be treated with a transbuccal/transoral technique. Transcervical approaches are warranted for unstable fractures and those where anatomic reduction is necessary.

Atrophic Mandible Fractures

Decreased osteogenesis, mandibular basal bone atrophy, and reduction in bone perfusion are common occurrences in elderly individuals. The inferior alveolar artery provides little predictable blood supply to the mandible with age, and instead, the lower jaw relies on periosteal and muscle attachment for vascularity.[19] Mandibular atrophy is evaluated based on the presence or absence of alveolar bone and varying amounts of basal bone height that may help guide treatment. Less than 1 cm of height is graded as severely atrophic and is at the highest risk for fracture.[47] The most susceptible portion of the mandible is in the saddle area of the mandibular body, where the bone tends to resorb to its lowest point of muscle attachment, the mylohyoid. Conservative techniques exist, including Gunning splints, circum-mandibular wires, and soft diets. These were advocated by the first Chalmers J. Lyons study in 1976.[48] However, the second Chalmers J. Lyons study in 1993 by Bruce and Ellis[49] suggested that rigid fixation should have a role in the treatment of atrophic te open de the placement of fixation where there is adequate blood supply to maintain healthy bone stock, and the use of a load-bearing reconstruction plate. With open approaches, periosteal detachment is inevitable but should be limited to the buccal tissues. Primary or secondary titanium reconstruction plates appropriate for the given fracture are then chosen and configured to span the fracture(s) with fixation screws placed in the symphysis and ramus. This should allow sufficient bone healing at the relatively less vascular fracture sites without concern for screw loosening while maintaining its load-bearing capability to restore function. With proper rigid technique, a lower rate of complications can be expected with open versus closed treatment.[50] Grafting can be undertaken



• **Figure 7-44** Inadequate fixation of a bilateral atrophic mandible fracture required reoperative fixation with a reconstruction plate and anterior iliac crest bone graft.

simultaneously with this form of rigid fixation in anticipation of dental rehabilitation.

Pediatric Mandible Fractures

dental anatomy, and tooth loss experienced in the mixed dentition time frame. Nutrition and compliance are also distinctive considerations to this patient population. Greenstick fractures or monocortical fractures are more commonly observed because of the inherent flexibility of the mandible. Controversies exist and revolve around the use of titanium versus restorable fixation as well as the necessity of plate removal when titanium is used.

Minor malocclusions are more forgiving in the primary and mixed dentition as differential tooth eruption can help to compensate for this in subsequent growing years. Condyle fractures are the most common mandibular fracture in the pediatric population.[51] The treatment of condyle fractures in children (<12 years old) is less controversial than in adults where the mainstay of treatment is closed or observational only. Damage to the growth center of the condyle can result in altered growth and facial asymmetry if not monitored. A more thorough review of pediatric mandible fractures is undertaken in another chapter.

Complications

Infection is the most common complication reported with mandibular fractures. With the advent of perioperative antibiotic therapy and plate-based fracture fixation, infection rates have been reduced compared to the wire osteosynthesis era, but still remain a challenge for even experienced surgeons. Sources quote infectious complications anywhere from 0.4% to 32% of all cases.[52] A study in 1975 examining pre-procedure antibiotic therapy for mandible fractures comparing closed and open techniques found a reduction in infection rate from 50% to 6%.[53] However, more contemporary evidence using randomized controlled studies has demonstrated less of an impact.[54,55] There is also a correlative relationship between postoperative infections and patients who are either immunocompromised or substance abusers.[56] Infections have also been associated with delayed fracture management, with evidence showing that increased time from injury to definitive treatment (greater than 72 hours) is correlated with a higher infection rate.[57] Surgical intervention is required for abscess drainage, debridement of infected tissue, and removal of any fibrous union. Koury and Ellis were able to treat infected mandibular fractures with placement of rigid reconstruction plates at the time of debridement.[58] Rigid fracture fixation is critical to allow normal bone healing and prevent any further complications at the site. Colonized hardware and biofilms are a concern; however, the majority of these fractures go on to heal with a stable union whether or not hardware eventually has to be removed (Figure 7-45). Clinical mobility, however, may indicate loose or infected hardware and nonunion that requires immediate surgical attention and consideration for closed treatment such as maxillomandibular fixation or external fixation. Long-term antibiotics via a peripherally inserted central venous catheter (PICC line) may be warranted for certain cases.

Malunion and malocclusion are the result of improper fracture alignment that occurs less frequently than infections. The literature sites a 0% to 4% occurrence in treated mandible fractures.[52] Improper reduction, insufficient mobilization, poor patient compliance, or improper fixation techniques can all lead to malunions (Figure 7-46). Transient malocclusion may present in 17% to 19% of cases after an open procedure, with only 0.5% to 3% requiring a secondary revision surgery.[59,60] Temporomandibular joint swelling/hemarthrosis/effusion and pterygomasseteric sling detachment may cause a transient postoperative malocclusion. Occlusal adjustments, orthodontics, or corrective jaw surgery may be suggested to patients with significant dysfunction or malunion following resolution of surgical edema. To prevent a malocclusion from occurring, proper reduction and fixation should be executed with careful attention to the occlusion intraoperatively. Panfacial trauma repair also requires attention to facial width and skull base articulation to accurately restore form and function (Figure 7-47). Family members and oral health care providers can assist with pictures or records of anterior open bites, asymmetries, or other dental abnormalities.

Nonunion/fibrous union is a usually result of fracture site mobility and the unstable formation of fibrovascular bridges. A hypoxic and inflammatory state may persist that prevents osteoprogenitor cells from functioning properly and repairing the defect. Fibrous ingrowth results in impaired bone filling capability. Nonunion has a reported overall incidence of approximately 3%.[61,62] Reoperation with debridement of the fibrous union is necessary along with removal of colonized or mobile hardware. In some cases, the retreatment stabilize the segments if recalcitrant infection is the cause.

Nerve damage is a rare permanent occurrence in mandible fractures. The inferior alveolar nerve (IAN) is the most commonly injured nerve and is housed in a cortical canal that runs through the ramus, angle, and body of the mandible, and exits its bony conduit at the mental foramen. The foramen is a consistent weak point in the mandible architecture that is frequently involved in the fracture line. Transient paresthesia is reported in about 11% to 59% of displaced fractures.[63,64] These injuries are predominately categorized as neuropraxias, where the nerve has been stretched or crushed. Traction injury can be a consequence of treatment for symphysis, parasymphysis, and body fractures. The degree of displacement can affect the severity of injury to the IAN, but it is rarely severed. Some sources report sensory deficits of the IAN distribution in as many as two thirds of fractures with displacement.[65] The degree of paresthesia should be carefully assessed before repair to evaluate the role of iatrogenic injury caused by manipulation, reduction, and placement of fixation. In situations of axonotmesis or neurotmesis (Sunderland IV or V) and preoperative anesthesia, surgical neurorrhaphy can improve sensory outcomes when performed at the time of mandibular fracture repair.[66] This is more often the case in severely displaced mandible fractures. Preoperative Sunderland I, II, or III nerve injuries do not require surgical repair and in fact may worsen with open fracture surgery.[67]

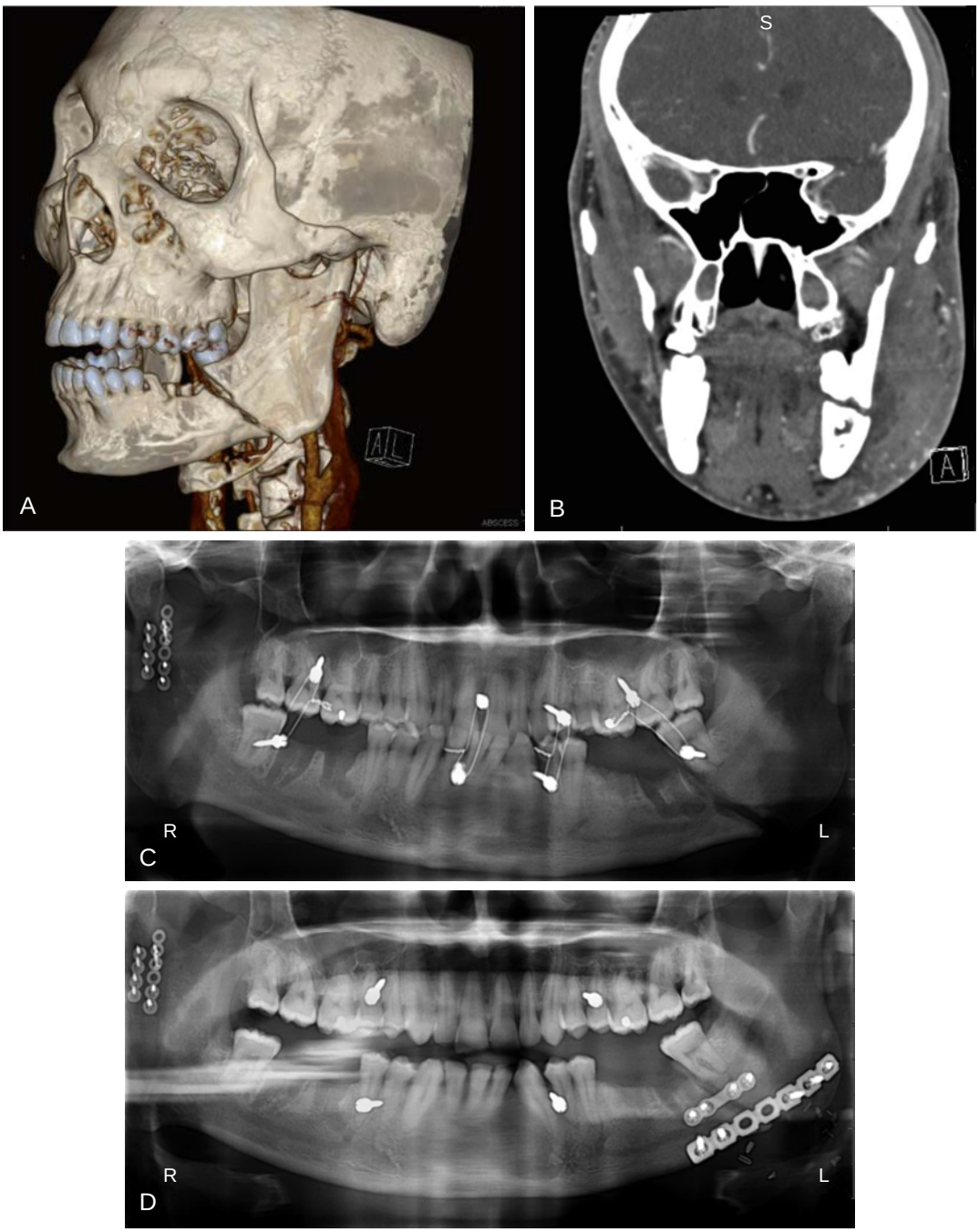
Facial nerve damage can be a result of access where a transcervical, retromandibular, or preauricular approach has been used. Significant dislocations of the condyle have been reported to cause facial nerve injury as well.[64]

Conclusion

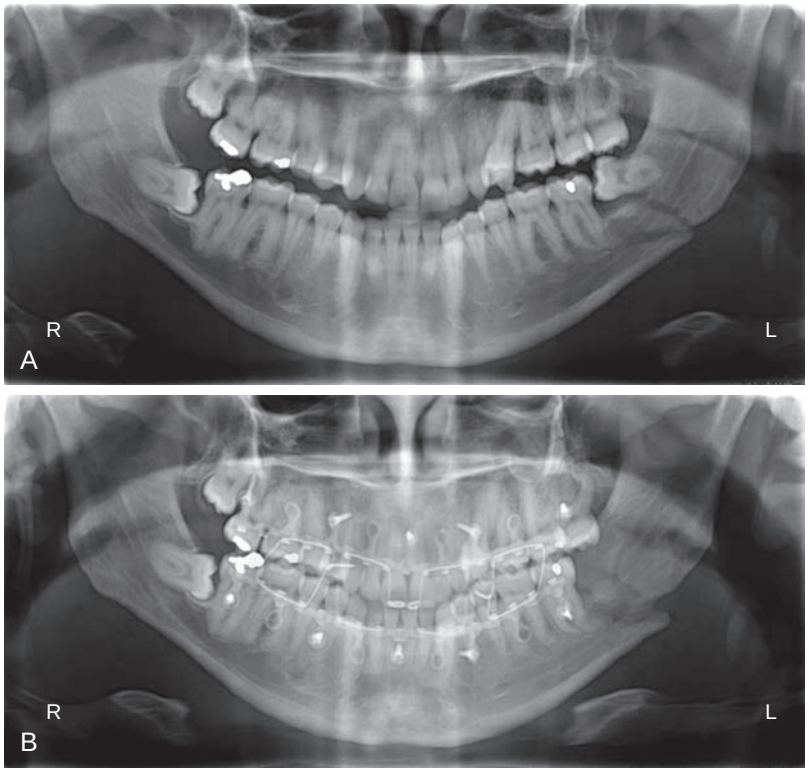
Mandible fracture management is a complicated and evolving process aiming to restore form and function with early mobilization and minimal morbidity. The treatment choices depend on a wide array of variables, patient factors, and resources; however, the predictability of fixation with modern hardware and stabilization principles allows for consistently excellent outcomes.

Acknowledgment

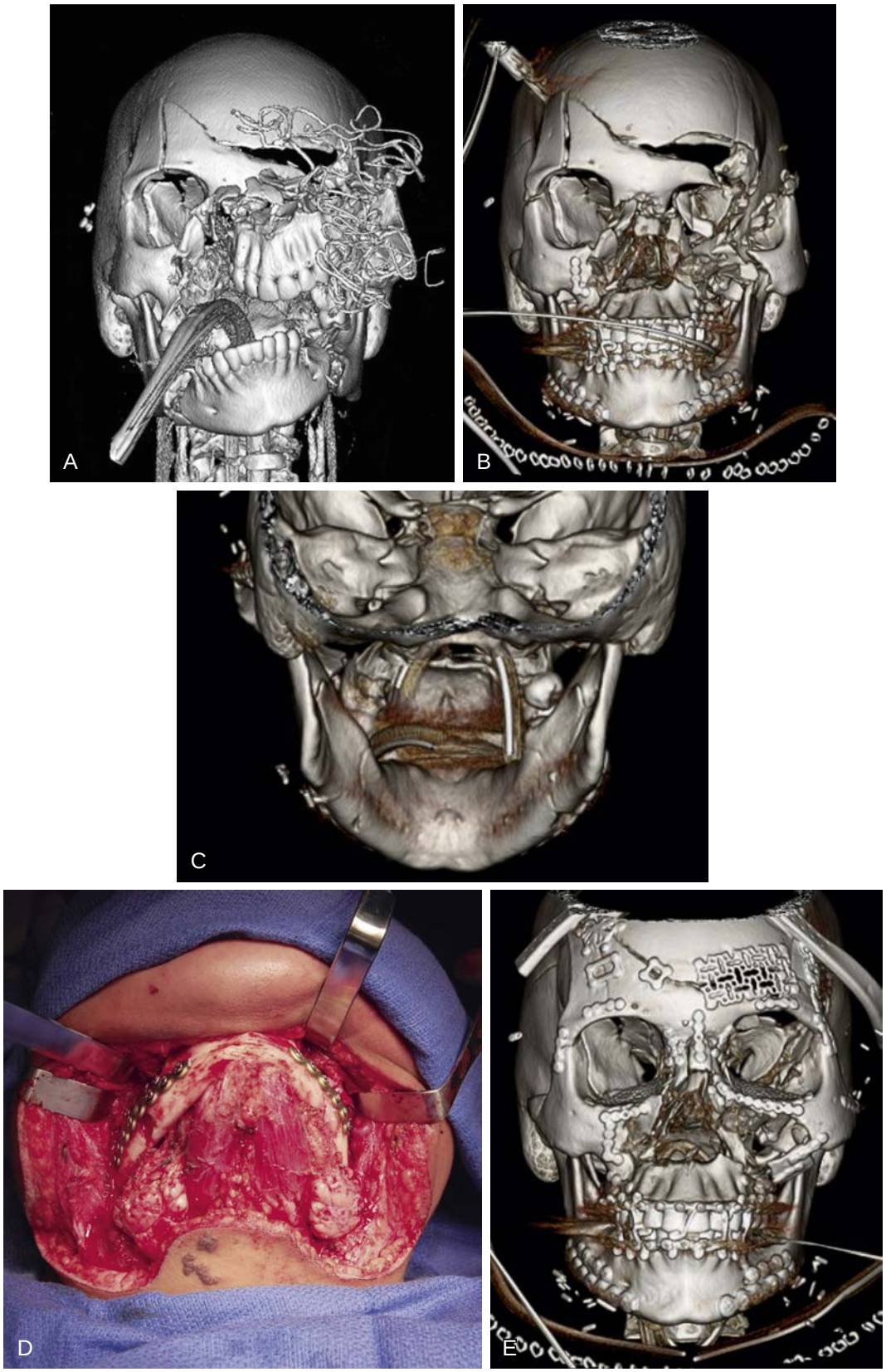
The editors wish to thank Drs. John Caccamese and Dominic Coletti for their previous contributions to this chapter as well as Dr. Daniel Meara for patient cases.



• **Figure 7-45** **A,** Delayed treatment of a left angle fracture resulted in multiple operative visits to clear a left submandibular and masseteric space infection as well as fixate the fracture. **B,** Computed tomography imaging of the left angle with associated infection. **C,** A concomitant left subcondylar fracture was plated using a retromandibular approach due to degree of displacement. **D,** Definitive treatment was delayed to clear left angle infection.



• **Figure 7-46** **A,** Closed reduction should be used with appropriate diagnosis and understanding of mandibular anatomy and muscle pull vectors. These images are the result of failure to diagnose and manage an unfavorable left angle fracture with attempted closed reduction and removal of horizontally impacted mandibular left third molar. **B,** Closed reduction attempted with rotation of the proximal segment due to muscle pull and lack of buttressing.



• **Figure 7-47** Patient was an unhelmeted passenger on an all-terrain vehicle that collided with a tree. **A,** There is severe comminution and displacement of facial fractures at the mid and upper face levels. Establishing an anatomically normal mandibular base is critical to the treatment of the remaining fractures. **B-C,** Staged repair was undertaken with tracheostomy, mandible fracture repair, and maxillary arch stabilization. Joint neurosurgical and upper facial repair ensued the following day. This allowed for the evaluation of the lower facial results. Note the excellent reduction of the mandible for purposes of establishing upper facial width. **D,** A transcervical approach allows the best visualization of the lingual and buccal cortices for anatomic reduction given the inability to use the maxillary dentition as a reference. **E,** Final result, largely built from the stable anatomic mandible and right midface.

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8

Nasal Fractures

LIKITH V. REDDY, SARAH C. HARDING

Introduction

Fractures of the nose are the most common facial fractures because of its prominence in the face. Compared to any other facial bone, less energy is required to fracture the nasal complex.[1-3] These fractures frequently occur in conjunction with other facial fractures. The prevalence of nasal fractures is high and often unnoticed by both physicians and patients. Patients with nasal fractures typically present with some combination of deformity, tenderness, hemorrhage, edema, ecchymosis, instability, and crepitation (Figure 8-1). However, these features may not be present or may be transient.[4] Edema can mask underlying nasal deformity, crepitation, and instability; thus, many physicians and patients fail to pursue further diagnosis and appropriate treatment. If left untreated, a nasal fracture can result in unfavorable appearance and function, espe-

esult of increased interpersonal violence in

res are caused by a variety of insults such as interpersonal violence, sports, motor vehicle accidents, and industrial injuries. Significant controversy exists about the treatment of nasal fractures. This is mainly in the timing of repair and the method employed—closed versus open approach. Untreated nasal fractures account for the high percentage of rhinoplasty and septoplasty procedures performed months to years after the initial trauma occurs. Nasal trauma can cause a dorsal hump deformity (Figure 8-2). Thus appropriate treatment should be rendered in a timely manner, before scarring and soft tissue changes occur. The incidence of post-traumatic nasal deformity requiring revision rhinoplasty ranges from 14% to 50%.[2] This shows that the initial approach to management of nasal fractures is suboptimal. Acute treatment of nasal fractures minimizes the amount of deformity, but the likelihood of additional treatment procedures should be considered.

Applied Anatomy and Pathogenesis

The nasal apparatus has a complex anatomy. Knowledge of this anatomy is of utmost importance in evaluation and management of nasal fractures. The nose occupies the middle third of the face and is attached at the top to the forehead; the free lower end of the nose is called the apex or tip. The upper part of the nose that is supported by the nasal bones is the bridge. The nasal bones and underlying cartilage are susceptible to fractures because the nose maintains a prominent position and central location on the face and because it has a low breaking strength. Patterns of fracture are known to vary with the momentum of the striking object and the density of the underlying bone.[5] As with other facial bones, younger patients tend to have larger nasoseptal fracture segments, whereas older patients are more likely to present with more comminuted fracture patterns[6] (Figure 8-3).

Skin and Soft Tissues

The skin of the nose can be divided into vertical thirds. It is generally thicker in males than in females, and major racial differences also exist. The upper third is fairly thick but tapers into a thinner mid-dorsal region. The inferior third regains the thickness of the upper third as a result of the more sebaceous nature of the skin in the nasal tip. The dorsal skin is usually the thinnest of the three sections of the nose. The difference in the skin thickness must be appreciated during dorsal reduction because minor imperfections or fractures in this area would be visible and perceptible. This would also make the dorsal area more susceptible to ecchymosis and lacerations with laterally directed forces on the nose. The skin thickness also varies between patients and must be considered during evaluation and treatment.

the procerus and levator labii superioris alaeque nasi. The depressors are the alar nasalis and depressor septi nasi. The



• **Figure 8-1** Acute nasal fracture with deformity, swelling, ecchymosis, hemorrhage, and nasal laceration. **A,** Immediately; **(B)** 3 days post-injury.

compressor of the nose is the transverse nasalis, whereas the dilators are the dilator nares anterior and posterior. The muscles are interconnected by an aponeurosis termed the columnar respiratory epithelium with abundant seromucous glands.

Hard Tissue Anatomy

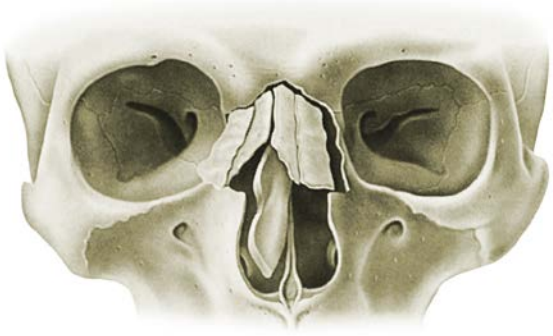
Superiorly, the bony framework consists of the paired nasal bones attached to the frontal bone. Superolaterally, the nasal bones are connected to the lacrimal bones, and inferolaterally, they are attached to the ascending processes of the maxilla. Posterosuperiorly, the bony nasal septum is composed of the perpendicular plate of the ethmoid. Posteroinferiorly lies the vomer, which in part forms the choanal opening into the nasopharynx. The floor consists of the premaxilla and the palatine bones. The lateral nasal walls contain three pairs each of small, thin, shell-like bones: the superior, middle, and inferior conchae, which form the bony framework of the turbinates. Lateral to these curved structures lies the medial wall of the maxillary sinus. Inferior to the turbinates lies a space called a meatus, with names corresponding to this structure, sloping down at an angle, is the bony face of the sphenoid sinus.

The nasal cartilages are paired upper lateral cartilages and lower lateral cartilages. These cartilages form the lower nasal valve. This valve regulates nasal respiration.[7] The upper lateral cartilages are triangular in shape. The internal nasal valve comprises the narrowest portion of the nasal airway. This valve regulates nasal respiration, and an angle wider than 15 degrees is needed in this area for adequate nasal breathing. They are connected to the maxilla laterally and to the septum medially. Caudal to the upper lateral cartilages lie the lower lateral cartilages. The paired lower lateral cartilages swing out from medial attachments to the caudal septum in the midline, called the medial crura, and then to an intermediate crus area. They finally flare out superolaterally as the lateral crura. These cartilages are frequently mobile, unlike the upper lateral cartilages. The two medial crura of the lower lateral cartilage curve inferiorly down the midline to support the columella. The lateral crus of the lower lateral cartilage supports the ala during respiration. Adjacent sesamoid cartilages are variably found lateral to the lower lateral cartilages in the fibroareolar connective tissue.

The nasal septum forms the main vertical support of the nasal complex. It acts like a strut to support the nasal bones and upper and lower lateral cartilages in the midline. The nasal septum is made up of a bony component and a cartilaginous component. The vomer and perpendicular plate of the ethmoid form the bony component. The cartilaginous component is quadrangular in shape. The inferior aspect of the septum articulates with the crest or maxillary groove of the maxilla. This allows mobility of the septum but is also a



• **Figure 8-2** Dorsal deformity with nasal hump attributable to nasal fracture.



• **Figure 8-3** Artist's conception of nasal fracture with dislocation of nasal bones and septal cartilage.

common location for dislocation of the nasal septum during trauma. The septum articulates posteriorly with the sphenoid bone through the vomer.

Weak areas are noted in the cartilage framework and in the junctions of the upper lateral cartilages with the nasal bones and the septal cartilage at the maxillary crest. The weak areas account for an increase in the rate of fracture/dislocation after nasal trauma. A lateral force of only 16 to 66 kilopascals (kPa) and a greater frontal force of 114 to 312 kPa can displace the bony dorsum.[5] A large force in any direction can cause comminution of the nasal bones with an associated C-shaped deformity of the nasal septum. Murray and colleagues reported that almost any deviation of the fractured nasal bones involves a concomitant fracture of the septal cartilage. Cartilage fracture lines are often oriented vertically in the caudal septum and horizontally in the posterior portions.[5]

Lateral impact injuries are the most common type of nasal injury leading to fracture.[8] Lateral injury produces a depression of the ipsilateral nasal bone that usually involves the lower half of the bone, the nasal process of the maxilla, and a variable portion of the pyriform margin. Nasal fracture and displacement without septal fracture usually occur with weaker applied forces; however, with increased force, displacement of the bilateral nasal bones can be noted, and the septum is usually dislocated and fractured as well.[6]

Other injuries that are commonly associated with nasal fractures include midface injuries involving the frontal, ethmoid, and lacrimal bones; nasoorbitoethmoid (NOE) fractures; orbital wall fractures; cribriform plate fractures; frontal sinus fractures; and maxillary Le Fort I, II, and III fractures.

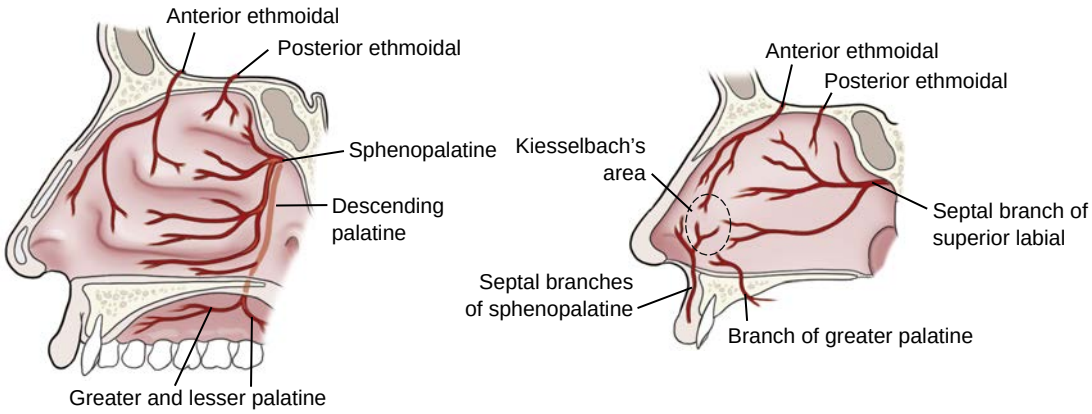
Blood Supply

(2) branches from the external carotid, namely, the sphenopalatine, greater palatine, superior labial, and angular arteries.

The external nose is supplied by the facial artery, which becomes the angular artery coursing over the superomedial aspect of the nose. The sellar and dorsal regions of the nose are supplied by the infraorbital artery, branches of the intermic arteries, and branches

no

posterior ethmoid arteries superiorly. The nasal septum also derives its blood supply from the sphenopalatine and anterior and posterior ethmoid arteries with the added contribution of the superior labial artery (anteriorly) and the greater palatine artery (posteriorly). The Kiesselbach plexus, or the Little area, represents a region in the anteroinferior third of



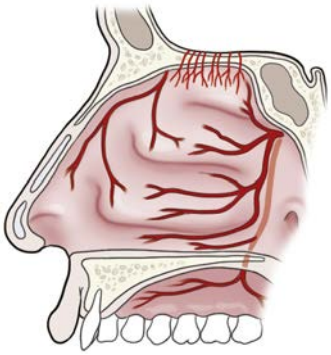
• **Figure 8-4** Blood supply to lateral and medial walls of nasal cavity.

Veins in the nose essentially follow the arterial pattern. They are significant for their direct communication with the cavernous sinus and for their lack of valves; these features potentiate the intracranial spread of infection. Even with the abundant blood supply of the nose, smoking does compromise postoperative healing.

Lymphatics arise from the superficial mucosa and drain posteriorly to the retropharyngeal nodes and anteriorly to the upper deep cervical nodes and/or submandibular glands.

Nerves

The sensory innervation to the nose is from the trigeminal nerve, whereas the motor supply to the nasal muscles is from the facial nerve. Sensory branches are from both the first and second divisions of the trigeminal nerve. Branches of the first division of cranial nerve V are the infratrochlear and external nasal branches of the anterior ethmoidal nerve. The supratrochlear nerve contributes slightly to the bridge of the nose. The infraorbital nerve supplies the inferolateral regions and the tip. The nasal septum is innervated by the anterior ethmoidal, nasopalatine, and maxillary nerves[1,7] (Figure 8-5).



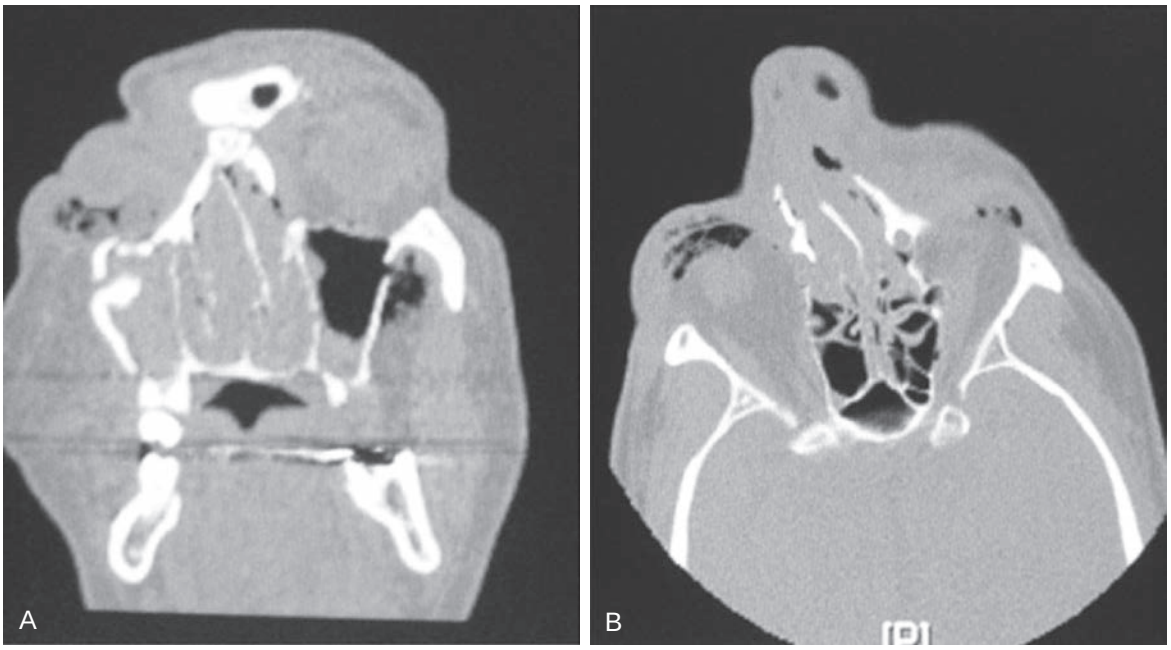
• **Figure 8-5** Innervation of lateral nasal wall.



• **Figure 8-6** Right-sided septal hematoma caused by septal fracture.

Diagnosis and Evaluation of Nasal Fractures

A thorough evaluation of nasal fractures is mandatory before embarking on any kind of treatment. Many of the post-traumatic nasal deformities are attributed to incomplete examination. History includes inquiring about the mechanism of injury, time elapsed, and previous nasal fractures or nasal surgery. Head injury must be ruled out first. Proper lighting, a nasal speculum, and a vasoconstrictor are required. History of epistaxis is important because it indicates mucosal injury. A complete examination of the nasoorbitoethmoid (NOE) complex and visual acuity is mandatory. Increased intercanthal distance (>30 mm) is a good indicator of a concomitant NOE complex fracture. Examination of other facial bones is undertaken to rule out other facial fractures. The nose is examined for gross deformity and external lacerations. Gentle palpation of the nasal bones provides an idea of the underlying mobility. Marked edema may mask an underlying nasal deformity. Review of old photographs or a driver's license can be very helpful. Intranasal examinations require a minimum of a nasal speculum. Rhinorockets or Afrin-soaked pledgets may be used for vasoconstriction. The examiner should look for mucosal lacerations and septal hematoma (Figure 8-6). A complete assessment of the nasal septum is the most important determinant of the outcome of nasal reduction. About 1% to 4% of the general population has some degree of septal deviation.[2,7] The entire septum is evaluated including dislocation of septal cartilage from the maxillary groove, and deviation



• **Figure 8-7** **A,** Coronal and **(B)** axial computed tomography scans showing nasal and septal fractures with other associated fractures.

or mobility is noted. Rohrich describes the pattern of fracture-dislocation of the septum in low-velocity injuries to be along the vomerine groove.[2]

High-velocity injuries tend to result in more extensive fractures of the quadrangular septal cartilage and perpendicular plate of the ethmoid. Following fracture, nasal bones unite in the direction of the deviated septum; therefore, proper alignment of the septum is the key to adequate nasal reduction.[2,9] Rohrich and colleagues developed a nasal fracture data sheet that is comprehensive of all the pertinent points to consider for minimizing further nasal fracture deformities.[2] They have also adopted a simple nasal fracture classification based on physical examination. They classify nasal fractures into simple, comminuted, complex (associated septal hematoma or open laceration), and associated NOE fractures.[2] Haug and Prather designed a different classification of nasal fracture based on the specific bones fractured.[10]

The use of computed tomography (CT) scans or plain films for the diagnosis and management of nasal fractures has been controversial; however, several small studies have shown that use of these modalities is neither cost-effective nor beneficial to the patient or physician. Nasal fractures are usually evident and can be verified by means of careful history-taking and physical examination. Rarely is the radiologic confirmation of these injuries needed.[1,7] This is because old fractures with bony deformities are very common and can be confused with new fractures.[1] Yabe and colleagues recommended routine preoperative and postoperative x-rays and CT scans, claiming that some slightly depressed nasal fractures are more easily diagnosed on lateral x-rays than on CT scans.[11] Nonetheless, patients determined by x-rays to have displaced nasal fractures are at a higher risk for long-term nasal deformity.[1,2,12] Although routine radiographs may be important from a medical/legal point of view, treatment is predicated on the basis of the physical examination alone. CT scans are indicated when a concomitant NOE or other facial fractures are suspected (Figure 8-7).

Although the use of plain images is not suggested, the preferred examination includes the acquisition of Waters' and lateral nasal views.

Classification of Nasal Fractures

Many different and often complex methods of classifying nasal-septal fractures have been proposed. However, the clinically pertinent understanding of a given nasal fracture lies in each individual patient's history. When predicting the amount of damage a patient may have sustained, attention should be given to the patient's age, the object that caused the fracture, and the force and direction of the object. The fracture patterns seen vary distinctly with the application of frontal and lateral forces. Lateral forces account for most nasal fractures. Most clinicians base their diagnosis and interventions on anatomic findings. Rohrich and Adams proposed a simple classification that might guide treatment[2] (Table 8-1).

Treatment of Nasal Fractures

Fractures of the nasal bones are the most site-specific bone injury of the facial skeleton. If left uncorrected, the loss of structural integrity and the soft tissue changes that follow may lead to both unfavorable appearance and poor function. Thus appropriate and timely treatment is warranted to

TABLE 8-1 Nasal Fracture Classification

Type	Description
I	Simple unilateral
II	Simple bilateral
III	Comminuted
a	Unilateral
b	Bilateral
c	Frontal process of maxilla
IV	Complex (nasal bone fractures with septal disruption)
a	Associated with septal hematoma
b	Associated with open nasal laceration
V	Associated NOE fracture/midface fracture

NOE, Nasoorbitoethmoid.

decrease morbidity in patients with these fractures. Because of the intimate associations of the bony and cartilaginous portions of the nose with the nasal septum, it is unusual to observe fractures to either structure without damage to the other. A common mistake in reduction of nasal fractures is to reduce the bony fracture without attention to the septum, which leads to progressive nasal obstruction as the septum heals with fibrous scar tissue. Septal fractures tend to activate interlocked stresses, and during the process of healing by fibrosis they may produce septal twisting of various configurations (C-shaped, S-shaped, or spurs) (Figure 8-8). Fracture lines are commonly vertical when located anteriorly and horizontal when located posteriorly.[13] Septal fractures also are frequently associated with a "telescoping" of the fractured edges, causing a retruded appearance of the cartilaginous portions of the nose.

Medical Management

Elevation of the head and use of cold compresses in the periorbital and nasal regions can be helpful while waiting for edema to subside. Even in the presence of significant edema, a nasal deformity often may be obvious. In a patient with no apparent abnormality at the initial visit, reassessment of the nose after the edema subsides may reveal findings necessitating repair. Surgical intervention may then be undertaken. Many patients who sustain nasal trauma present with profuse bleeding, which can usually be controlled with clot removal and the application of a topical vasoconstrictor. If this approach is unsuccessful, gauze packing, balloon catheterization, or other procedures may be required, but the ligation of vessels is rarely necessary. Nasal packing is the most common procedure performed to control bleeding after topical vasoconstrictors fail. Packing material is placed directly at the area of hemorrhage to supply pressure; however, bilateral packing is occasionally necessary to control bleeding from several areas. The packing is commonly removed in 2 to 5 days, and nasal reduction can be performed at the same time.



• **Figure 8-8** Septal deformity resulting from untreated nasal fracture.

Surgical Management

Injuries limited to the nasal soft tissues without concomitant nasal fracture are treated by debridement and closure. Landmarks of the nose are approximated first to prevent distortion, which may lead to a cosmetic deformity. Extra care is taken with through-and-through lacerations. In these situations the intranasal laceration is closed first using a resorbable suture, then cartilage is approximated, and finally skin is closed. Indications for repair of nasal fractures include abnormal nasal function, abnormal appearance, and presence of early post-injury complications. The preoperative evaluation should rule out nasofrontal and ethmoid fractures because these may require other types of surgical intervention. Injury to the nasofrontal duct, cribriform plate, or medial canthal ligaments must be recognized. Dorsal nasal reconstruction with rib graft or calvarial bone grafts is necessary in patients with severe nasal injuries, significant saddle-nose deformity, loss of dorsal projection, and shortened nasal length; the reconstruction must be discussed with the patient (Figure 8-9). These fractures are discussed in detail in Chapter 14.

There are three major considerations in the plan for reduction of a nasal fracture. The first consideration is whether to perform open reduction or closed reduction; the second is the use of local or general anesthesia; and the third is the timing of reduction. Considerable debate exists in the literature regarding reduction of nasal fractures. Although many studies advocate simple manipulation for reduction of nasal fractures, there is enough evidence to indicate that simple manipulation can and does result in significant post-traumatic nasal deformity. Crowther and O'Donoghue reported that only 9% of patients required septorhinoplasty as a result of inadequate simple manipulation.[12] Other authors cite a



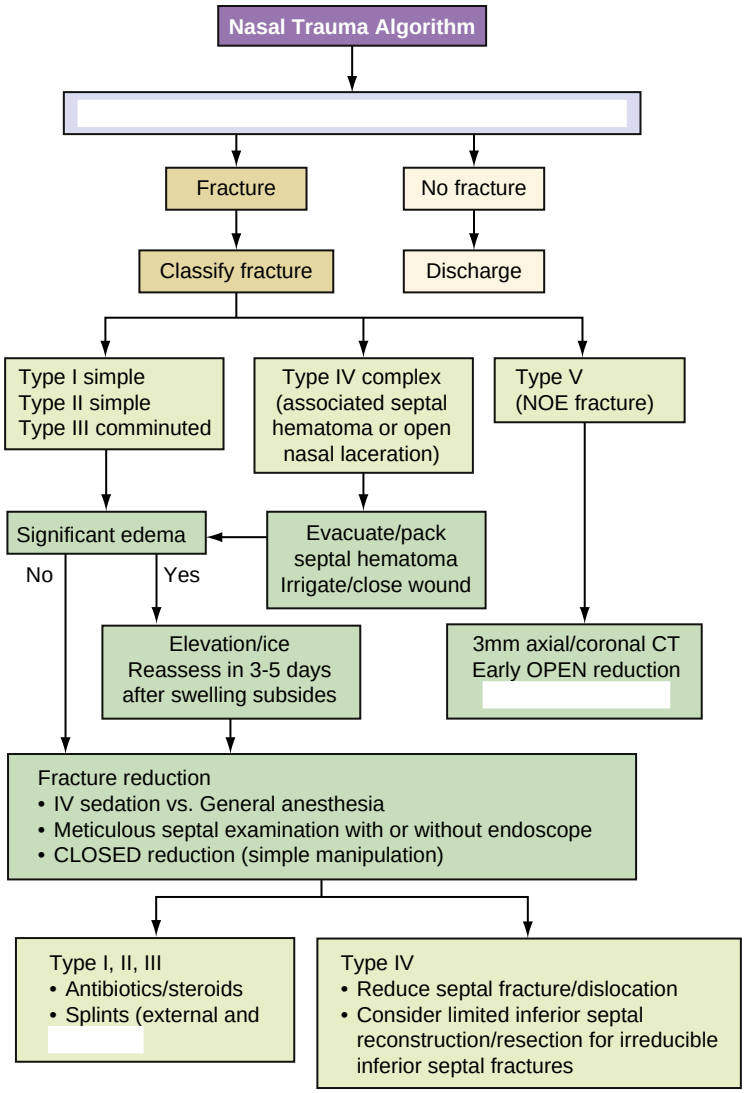
• **Figure 8-9** **A,** Nasoorbitoethmoid (NOE) fracture with saddle-nose deformity, loss of dorsal projection, and shortened nasal length. **B,** NOE fracture reconstructed with calvarial bone graft.

higher percentage. Many studies suggest that all fractures be managed by simple manipulation while reserving open reduction for those cases that have failed simple manipulation. This would appear to be a more economical solution, but given the high incidence of post-traumatic nasal deformities requiring open septorhinoplasty, this might not be so. Nasal fractures cannot be approached in a cookbook fashion, but at the same time some form of an algorithmic approach is necessary. Another debate exists about the use of local versus general anesthesia. Historically, most studies found local anesthesia to be as effective as general anesthesia in the simple manipulation of nasal fractures. Cook and colleagues supported the use of local anesthesia, considering the many advantages of local anesthesia over general anesthesia.[14] However, Al-Moraissi and Ellis conducted a meta-analysis that demonstrated a statistically significant difference in patient satisfaction concerning nasal esthetics with treatment under general anesthesia when compared to treatment with local anesthesia alone. This resulted in decreased need for subsequent revision surgery.[15] Although it may be uncomfortable to undergo manipulation under local anesthesia, the advantages are obvious. Certainly the risks of general anesthesia cannot be ignored. However, it is certainly beneficial to consider initial treatment under general anesthesia for an accurate and controlled reduction when a septal fracture is present. Nasal fractures are best treated either immediately or after 7 to 10 days when all the edema has resolved. Most patients do not heal significantly before 3 weeks, and therefore closed reduction may be attempted any time in the first 2 to 3 weeks. After 3 weeks the fracture has healed such that it cannot be reduced easily and open reduction must be performed. Because of the maturing scar tissue and fibrosing cartilage, rhinoplasty must be delayed 3 to 6 months to obtain optimal results.

There are three options for treatment of nasal fractures: simple closed reduction, closed reduction with minimal septal work, or open septorhinoplasty. An algorithm developed by Rohrich and Adams serves as a good framework for decision making.[2] It should be used to supplement clinical impression, to minimize the incidence of post-traumatic deformity requiring revision septorhinoplasty (Figure 8-10). Mildly deviated fractures can be managed with closed reduction in the absence of moderate or severe septal deviation. Fractures with significant septal and nasal deviations with new dorsal hump deformity most likely require open reduction techniques that range from septoplasty or osteotomies to full septorhinoplasty.

Closed Reduction

The nose is anesthetized using 4% cocaine as an intranasal solution (maximum adult dose 8 mL) with 1:100,000 epinephrine-soaked pledgets. Afrin-soaked nasal pledgets can also be used if 4% cocaine is not available. This shrinks the nasal mucosa sufficiently to allow adequate intranasal examination. This is supplemented with external nasal field blocks using 2% lidocaine with 1:100,000 epinephrine along the nasal dorsum, lateral to the nasal pyramid, and at the base of the anterior septum. Transorally, infraorbital nerve blocks are performed. Injection in the greater palatine foramen achieves sphenopalatine blocks. This markedly reduces posterior nasal cavity bleeding and improves anesthesia. Transcutaneous infiltration bilaterally along the dorsum is helpful to anesthetize the infratrochlear nerve and the external nasal branch of the anterior ethmoidal nerve.



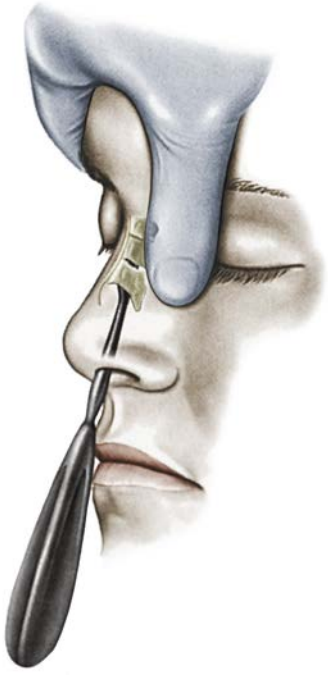
The pertinent points of emphasis in this algorithm are:
1. Swelling is allowed to resolve for proper reduction.
2. The septum is the key to management of nasal fractures.
3. All septal pathology must be identified.
4. Patients should be informed initially regarding the possibility of further nasal procedures.

• **Figure 8-10** Nasal trauma algorithm.

nasal septum. If a transcolumellar incision is planned, injection at the base of the columella can be performed. Cook and colleagues have found external infiltrative anesthesia to the nasal dorsum to be as effective as and better tolerated than specific blocks to the infraorbital, external nasal, and infratrochlear nerves.[14] The minimum amount of local anesthesia should be injected to avoid additional distortion. Accuracy of placement is more important than the volume deposited. The surgeon should allow adequate time for the anesthesia to work before manipulation; otherwise, excessive bleeding will persist throughout the procedure.

The patient may be given oral or intravenous sedation to enhance the anesthesia. Even if general anesthesia is used, good local anesthesia is required to reduce bleeding. About 15 minutes should be allowed to maximize the vasoconstrictive property of the medication. After adequate anesthesia has been achieved, reexamination of the nose is performed.

Reduction of the bones is done first followed by reduction of the cartilages. This is accomplished by re-creating the fracture while molding with fingers. Few instruments are needed for fracture reduction. These include Asch and Walsham forceps, a large Kelly clamp with protective rubber tubing over the blades, Boies or Ballenger elevators, intranasal specula, and a head light. The majority of nasal fractures can be reduced by upward and outward forces with an instrument placed in the nose under the nasal bone. The instrument is inserted intranasally to a point 1 cm caudal to the nasofrontal angle. The depressed fragment is elevated



• **Figure 8-11** Lateral nasal wall fracture reduction with elevator.

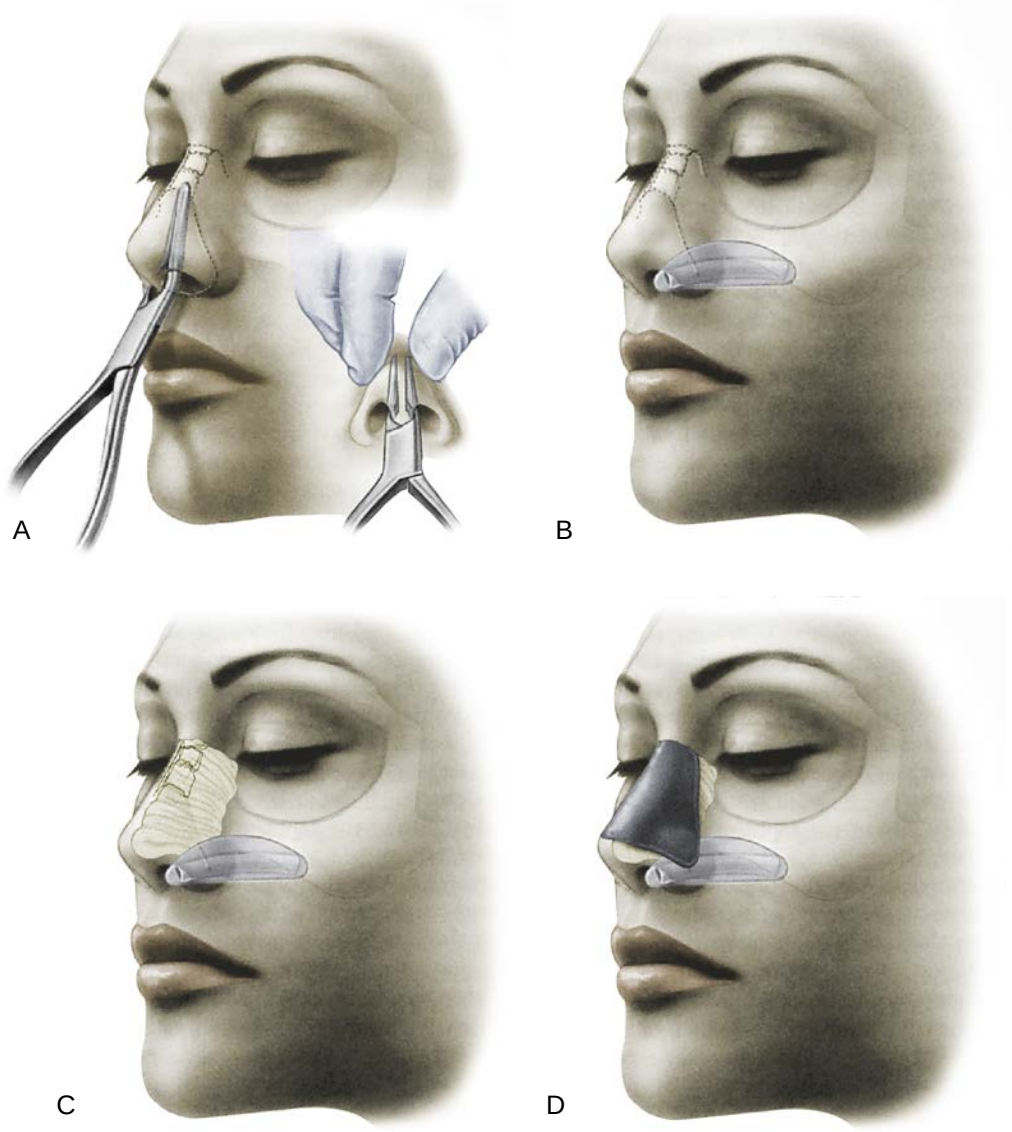
by exerting force in the direction opposite to the fracturing force, usually anterolaterally. The reduction instrument is held with the dominant hand and the nasal bones are reduced in an anterior and superior direction perpendicular to the edge of the nasal bones. The less dominant hand is used to exert counterpressure to mold the bones and soft tissues against the forceps in an anteroinferior direction (Figure 8-11). If the opposite nasal bone is displaced laterally, that bone is moved medially to its normal position. The Asch or Walsham forceps may be used by inserting one blade in each nostril or by placing one blade in the nose under the nasal bone and the other blade on the overlying skin. Pressure should not be exerted too high in the nose (under the thick nasal bone near the nasofrontal suture) because this area is rarely fractured and manipulation can result in mucosal tears and subsequent bleeding. Reduction can usually be accomplished with the fragments remaining in position, but digital molding may be necessary in some patients. Septal alignment is the most important determining factor in preventing post-reduction deformity with loss of dorsal support and/or nasal obstruction. Reducing the nasal bone fragments first often reduces the septum simultaneously; if not, the Asch or Walsham forceps usually permit gentle elevation of the nasal pyramid while pressure is applied over the displaced septal region (Figure 8-12).

Once the septum is reduced into a satisfactory position, Doyle splints with an airway lumen are placed on either side of the septum. These are sutured to the septum using 3-0 silk or nylon trans-septal sutures. Care must be taken not to make the trans-septal sutures too tight; otherwise, pressure necrosis of the septum may result. Packing with antibiotic gauze or Merocel can be used to control hemorrhage, but most of the time this is unnecessary.[10] Packing is also used by some surgeons to prevent inward collapse of nasal bones.[16] The two main types of packing are the nonabsorbable polyvinyl acetate sponge (Merocel, Medtronic Inc., Minneapolis, MN) and the absorbable synthetic polyurethane foam (Nasopore Forte, Polyganics, Groningen, The Netherlands). Recent meta-analyses have suggested that Nasopore is better tolerated by patients due to ease of removal without the epistaxis encountered with removal of Merocel.[17-19] Last, external nasal splints are applied. The nasal skin is cleaned and degreased, and ½-inch Steri-Strips are applied. Either thermoplastic or metallic Denver splints can be used. Care must be taken not to disrupt the nasal bones when applying the splint. The splint should be used to cushion the nose; remind the patient to be careful with physical contact to the nose. Splints should not be used to maintain an unstable nasal reduction.[7] If there are concomitant maxillofacial fractures that require maxillomandibular fixation and the nose is packed, a tracheotomy might be needed.[7] Postoperative instructions, analgesics, and antibiotics are given to the patient. If Vaseline gauze nasal packs are used, they can be removed in 2 to 3 postoperative days. Nasal splints and Merocel sponges are typically removed in 7 to 10 days. If a Nasopore Forte sponge is used, it can easily be suctioned from the nose at this point with minimal pain. Fracture stability is checked at the 10-day postoperative visit, and if there is instability, the external splint should be replaced for another week; otherwise, it may be discarded. The patient is instructed to avoid physical contact to the nose, keep the head elevated, and apply ice packs for 24 hours. The patient is also cautioned not to wear glasses for 6 weeks. If glasses are needed, the patient can be instructed on how to tape the bridge of the glasses to the forehead to prevent undue pressure on the nose; otherwise, unattractive depression on the nasal bridge can occur. Patients are followed up at regular intervals for 6 weeks.

Because incomplete greenstick fractures of the septum and nasal bones can account for later deviations, Manson recommends that fracture lines be completed before reduction.[20] Some authors perform submucosal resection on C-shaped septal fractures (Figure 8-13). An aggressive submucous resection may cause a loss of nasal height and resultant dorsal nasal irregularities. A safer method is to attempt closed reduction and warn the patient of possible need for future rhinoplasty.[20] If the fracture cannot be reduced by closed reduction, the operation should be immediately converted to an open reduction. For this reason many authors advocate the use of the operating room for all closed reductions.

Open Reduction

The nose is anesthetized and prepared in a similar manner as in closed reduction. The operative procedure chosen is dictated by the patient's type of fracture-dislocation. Most cases needing open reduction are due to an interlocked segment of cartilage and/or bone. The goals of treatment of severely comminuted nasal fractures include narrowing of the nasal dorsum, maintenance of adequate nasal airway,

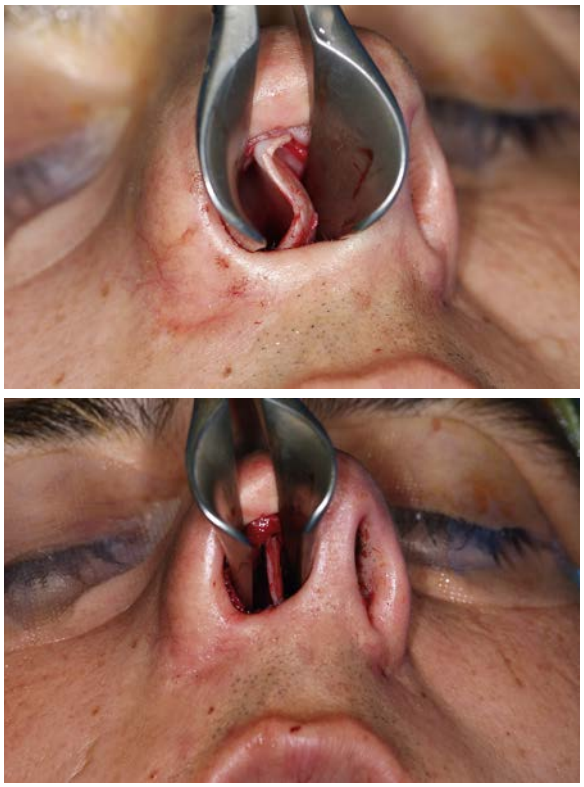


• **Figure 8-12** Methods of treatment of isolated nasal fractures. **A,** Asch forceps reducing fractures. **B,** Doyle splints in position. **C,** Gauze packing layered in nose. **D,** Denver splint in place. (Redrawn from Haug RH, Prather JL: The closed reduction of nasal fractures: an evaluation of two techniques, *J Oral Maxillofac Surg* 49:1291, 1991.)

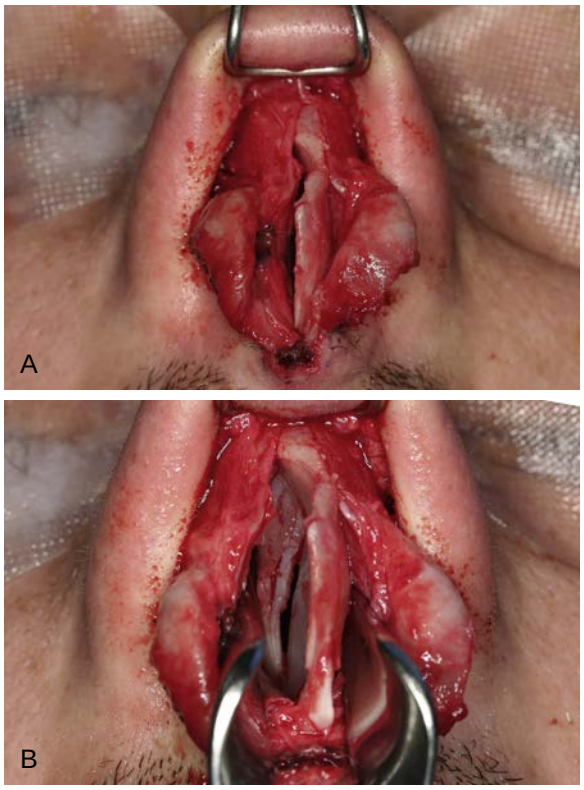
and maintenance of projection of the nose.[21] Stability of reduction of nasal fractures is dictated by the nasal septum. Recurring nasal deformity usually arises from failure to center the septum. The septum is the central support of the nose and can be easily placed in the midline over the nasal spine at the time of manipulation while the posterior portion remains uncorrected (Figure 8-14). Subsequently, the stronger posterior portion will re-displace the anterior portion. It is not uncommon to find that a perfectly reduced nasal fracture has re-displaced by the time the nasal splints are removed.

The septum is approached through a hemi-transfixion incision on the side of dislocation (complete transfixion incisions predispose to lower tip height and introduce additional structural instability). Further access to the fracture line is gained through lateral intercartilaginous incisions (Figure 8-15). The dorsal skin is elevated off the upper lateral cartilages and the periosteum is elevated from the nasal bones. Pyriform aperture incisions provide access to the lateral fracture lines. Common findings are dislocation of the quadrangular cartilage off the maxillary crest, or a C-shaped fracture of septal cartilage and bone, as described by Murray and associates (Figure 8-16).[5]

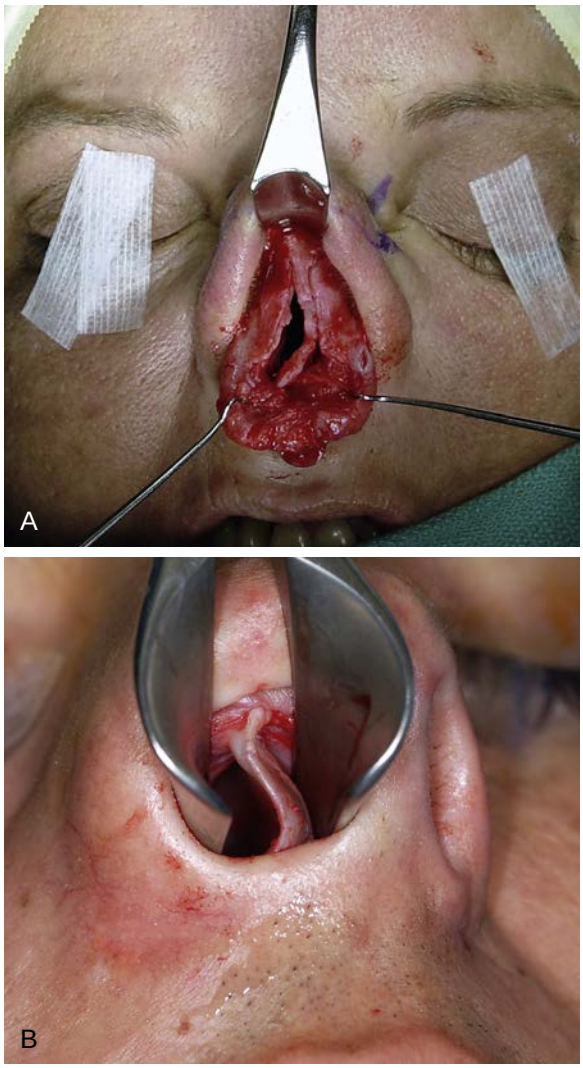
The cartilaginous segments are exposed and reduced. Sometimes a segment of cartilage must be resected adjacent to the fracture. A Cottle elevator is used to excise small strips of cartilage, allowing the septum to swing like a "trapdoor" back into its normal position. A small chromic stay suture may be placed through the periosteum near the anterior nasal spine and the inferior portion of the cartilaginous septum to maintain its reduction. Often a displaced maxillary



• **Figure 8-13** Submucosal septal resection for correction of septum.



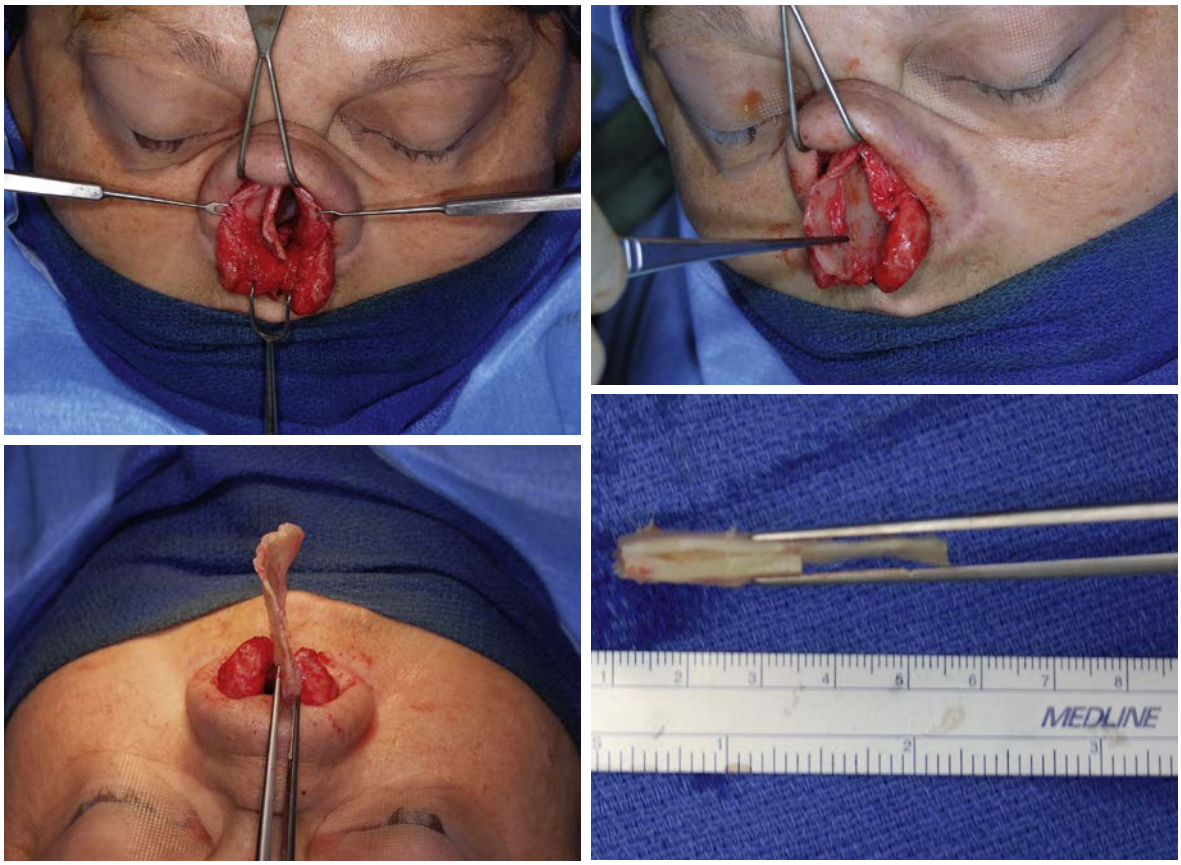
• **Figure 8-14** **A,** Demonstration of nasal septum with significant posterior deformity compared to the anterior deformity. **B,** Demonstration of fracture of posterior septum.



• **Figure 8-15** Exposure of septum. **A,** Dorsal approach by open rhinoplasty; **B,** transfixion incision.

crest must be removed entirely. Radical resection of cartilage or bone is avoided to preserve support and limit fibrosis and contracture. After septal surgery of this type, satisfactory reduction can almost always be accomplished.[20]

Open reduction is reserved for severe nasal fractures with or without an associated NOE complex fracture. Open reduction allows direct visualization of the fractures with more precise reduction. It also allows placement of grafts in areas of deficiency. Many surgeons defer open reduction to secondary corrective procedures or to cases that have failed closed reduction. In some cases early aggressive treatment may avert the need for secondary nasal revision. Open reduction can be done through a variety of approaches. An existing laceration gives an advantage to the surgeon. If necessary it may be minimally extended for better exposure. Standard closed rhinoplasty incisions allow improved access to reduction of the fragments. If more extensive exposure is required, then an open rhinoplasty approach provides the most exact and stable repair. This allows great exposure to the dorsum, septum, and tip region (Figure 8-17). Another



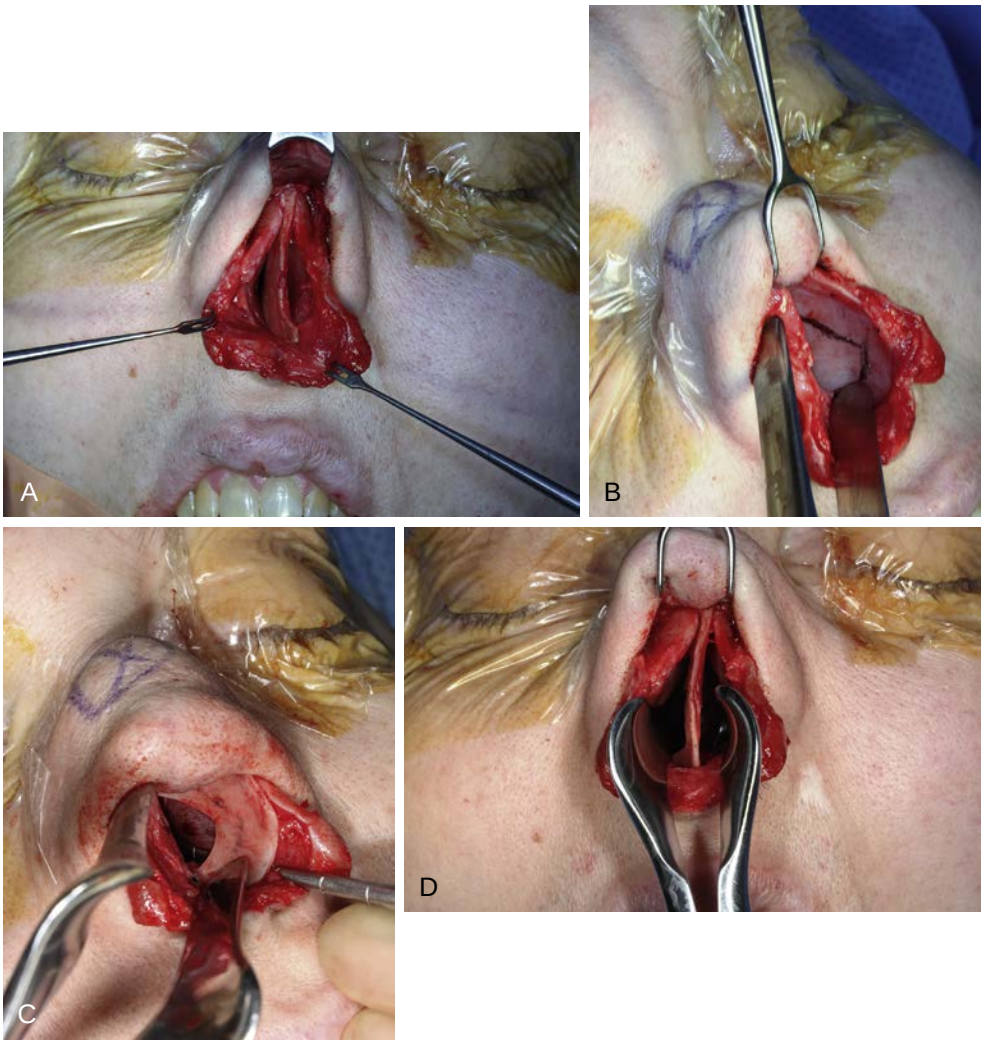
• **Figure 8-16** Correction of severe septal deformity; complete removal of cartilage and straightening on the table.

technique is the Lynch incision. This involves bilateral medial canthal incisions extended upward on either side along the medial orbital wall into the brow. This approach may be indicated when there is severe comminution associated with the NOE complex; this approach provides access to the nasal bridge and ethmoid sinuses, and laterally to the maxilla. When the two Lynch incisions are connected by an incision across the radix, this is called the open-sky approach or H incision. This approach provides great access for repair of multiple fractures under direct vision, but has fallen out of favor because facial aesthetics may be compromised. If there are preexisting lacerations, they may be used for part of the open-sky approach. The fourth approach is the coronal incision. It is mainly indicated when there are other associated fractures such as NOE, frontal sinus, or superior orbital rim. This approach allows great access to the entire forehead, NOE complex, and midface. If both maxilla and mandible need to be treated, a tracheotomy may be required.[2,7,12] If there are other maxillofacial fractures, the nose should be treated last to ensure adequate protection.[7]

Nasal repair, especially if the NOE complex is also involved, can be done through different techniques. Intranasal wiring can be used to correct traumatic telecanthus. Fine 26-gauge wires are used to connect through small holes drilled in the bone fragments.[23] The wire loop should include the medial canthal tendons on either side to ensure proper reduction of the telecanthus. Wire fixation can produce an accurate reduction, but it can also produce palpable sharp edges when the wires are twisted. The presence of wires can pose difficulty if subsequent revision rhinoplasty is considered. Some surgeons prefer slowly resorbing sutures in place of wires.[16] These are used in a figure-of-eight pattern to lock bone edges into close apposition. Miniplates can be used when there is severe comminution. Erosion of skin over the plate is possible, especially if eyeglasses are worn, but is generally uncommon. The advantage of plates over wires is that plates allow a better three-dimensional repair. Split-thickness free bone grafts can be used if a significant amount of bone is missing or unsalvageable.

If a coronal approach was used, then calvarial grafts can be easily obtained. Bone is harvested from the right parietal eminence. Soft tissue augmentation techniques can also be used to fill in soft tissue defects. Septal work is carried out in the fashion described previously. Septal hematoma is evacuated to prevent necrosis of the septum. Fractures of the septum usually occur in the quadrangular cartilage. If the fracture is too comminuted, the fragments are removed. Sound clinical judgment must be used in order to not compromise the support provided by the septum, leading to a saddle-nose deformity. Figure-of-eight sutures can be used to avoid overriding of the edges.

When the patient presenting with nasal fracture also has chronic nasal deformities from prior injury, the question arises as to whether to address those issues at the time of



• **Figure 8-17** **A,** Open rhinoplasty with dorsal septal approach for exposure to the dorsum, septum, and tip region with precise correction of nasal septum. **B,** Marking for resection of deviated septum. **C,** Resection of deviated septum. **D,** Corrected septum.

nasal fracture reduction or delay them until later. Traditionally, nasal fracture reduction has been performed separately, with more refined septorhinoplasty being reserved until later. In carefully selected cases, extended septorhinoplasty may be performed during the nasal fracture reduction, especially in repair of the nasal septum. More refined procedures such as tip work are more effective when delayed until all the effects of edema and distortion are gone and the affected tissue has matured.

Nasal Fractures in Children

Many septal deformities in adults are due to minor trauma that occurred during childhood or as a newborn that went unrecognized. As the slight deviation matures, progressive nasal obstruction and deformity occur. A child's nose differs from that of an adult in several ways. Specifically, the underdeveloped nose has less frontal projection, is largely composed of cartilage, and possesses several growth centers. As a result, pediatric nasal trauma often presents a unique diagnostic and therapeutic dilemma. The immature nose is more likely to be associated with other fractures of the face because the nasal projection is much less prominent. Since the child's nose is more cartilaginous than its adult counterpart, it is easily compressible and absorbs little of the energy from the striking force as it passes across the face. The resul-

e

an exacting examination may not be possible. Extensive edema with facial trauma and the lack of rigidity of the nasal skeleton tend to produce a less than optimal situation for evaluation, even in the cooperative patient. The cartilaginous structures of the nose tend to buckle and twist with the trauma rather than to fracture.

Management of nasal fractures in children differs from that in adults in that general anesthesia is usually required. The prevailing method of managing pediatric nasal fractures is closed reduction. The nose with splayed nasal bones and no impactions can be reduced with bilateral digital

compression on the dorsum for 10 to 15 minutes. Often, nasal deviation to one side can also be reduced by digital compression on the side of the deviation. The cartilaginous elements do not move into place as readily, and when they are mobilized, they do not "snap" into place as do adult dislocations. The bony elements frequently are involved in a greenstick fracture and may be resistant to maintenance of the desired position. Although many nasal surgeons have advocated immediate repair of all septal deviations secondary to birth trauma, correction is necessary only in the case of nasal airway obstruction, as newborns are obligate nasal breathers.[24,25]

Nasal fractures can be associated with nasofacial disproportion, especially a long nose, in 21% of patients who were followed long-term. A long nose deformity was observed to develop during puberty, normally a time of rapid growth for the nose. These findings correlate with the three periods of nasal development: age 1 to 6 years (rapid growth), age 6 to 11 years (slow growth), and age 12 to 16 years (rapid growth).[26] Nasal surgery can be performed between the ages of 6 and 11 years when practical to potentially prevent nasofacial disproportion.

Complications of Nasal Fractures

Complications from nasal fractures include cosmetic deformity and airway obstruction. Problems arising from nasal fracture complications may be mitigated by adequately recognizing and treating the injury at the time it occurs. The complications can be broadly categorized into early and late.

Early Complications

Septal hematoma may develop either as a result of the injury or because of the repair, and is often bilateral. The fracture allows blood to pass into both mucoperichondrial planes, undrained. This may lead to fibrosis or to organization as a thick obstructive section of septal cartilage. If the hematoma is under excessive pressure, necrosis and perforation are likely results. Loss of septal support will cause collapse of the cartilaginous dorsum with a resultant saddle-nose deformity. If a hematoma is suspected, palpation for fluctuance may be done with cotton-tipped swabs followed by needle aspiration. Treatment is by horizontal incision at the base of the septum so as to produce dependent drainage. Bilateral hematomas are treated with a unilateral offset incision with preservation of the septum. Silastic splints, light packing, or mattress sutures for 2 to 3 days will prevent reaccumulation.

Edema, ecchymosis, and epistaxis usually resolve spontaneously. Packing is rarely necessary, but if used, it should be adequate to tamponade the vessel for hemostasis. Infection is a rare complication, but antibiotic prophylactics should be used in immunocompromised patients and those who have hematomas. Cerebrospinal fluid rhinorrhea is associated with more severe trauma and indicates fracture of the posterior frontal sinus table or the cribriform plate. Laboratory diagnosis is easily made by glucose level measurements of the rhinorrhea and serum and the presence of beta-2 transferrin or beta-trace protein in the fluid. Though not as sensitive as laboratory testing, a quick evaluation of the fluid can be done with the halo test on a napkin at the bedside. Neurosurgery should be consulted and the patient observed closely for 6 weeks. Occasionally a lumbar drain or bone grafting may be necessary. Emphysema of the face and neck may also occur and usually resolves spontaneously with avoidance of increases in upper airway pressure.

Late Complications

Untreated hematomas of the nasal septum may become organized, resulting in subperichondrial fibrosis and thickening with partial nasal airway obstruction. The septum may be as thick as 1 cm, and in cases of repeated trauma the cartilaginous septum may be largely replaced with calcified or chondrified material. Submucosal resection of the thickened portion of the nasal septum may be required, and in some patients a partial turbinectomy may be advisable.

Synechiae may form between the septum and the turbinate in areas where soft tissue lacerations occur and the tissues are in contact. If bothersome, these may be treated by division followed by the placement of nonadherent, petrolatum-impregnated material between the cut surfaces for a period of 5 days. During this time, epithelialization occurs. Obstruction of the nasal vestibule may occur because of malunion of fractures of the pyriform margin or scar tissue contracture from loss of vestibular lining. Osteotomy of the bone fragments corrects the former; however, the contracture resulting from loss of soft tissue or scar contraction may require excision of scar, and replacement with skin or composite grafts within the nasal vestibule.

Residual osteitis is seen occasionally in compound fractures of the nose or in fractures associated with infected hematomas. Rarely, a portion of the bony nasal framework may be lost as a result of infection and may require late replacement with bone grafts. In these cases, appropriate debridement and antibiotics constitute the preferred regimen of treatment. Obstruction of the opening of the nasolacrimal duct leads to epiphora. Dacryocystorhinostomy may be needed for its correction.

Slight malunion of nasal fractures is common after closed reduction because the exact anatomic position of the fragments can be difficult to detect by palpation alone, especially in the presence of edema. Residual deviation also occurs because of release of "interlocked stresses" following fracture of the cartilage. If troublesome, the resulting external deformities may require reconstructive rhinoplasty.[2] Intraoperative imaging using a C-arm or O-arm for immediate evaluation of the reduction has been reported to result in fewer complications and decreased need for reoperation when used appropriately.[27]

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9

Management of Zygomatic Fractures

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Introduction

Zygomatic fractures are common in facial trauma and, as is the case with other facial fractures, occur primarily among men in their third decade of life. Unpublished data from a recent 4-year retrospective chart review at the University of Kentucky resulted in finding 416 zygomaticomaxillary complex (ZMC) fractures and produced the following statistical data. The demographic data are similar to other review articles.[1-3] Fractures occur most commonly as the result of assaults (35.6%) or motor vehicle collisions (20.7%) with a mean age of 37.8 years (older than in other reviews). Anatomic incidence was found to be right orbital floor 37.3% and left orbital floor 34.9%, left ZMC left

formities of the midface related to the projection of the malar eminence, lateral projection of the arch, and position of the globe, which can affect vision. For these reasons, the appropriate diagnosis and treatment of these fractures are important for the functional and cosmetic outcome of facial trauma patients.

Anatomy

Because of its prominent position on the facial skeleton, the zygomatic bone is responsible for the anterior and lateral projection of the midface and thus is an important part of facial esthetics. Its outer (lateral) surface is convex; its inner (temporal) surface, concave. It is quadrilateral in shape and articulates with four other bones: maxilla, sphenoid, temporal, and frontal bones. Because it forms part of the lateral wall and floor of the orbit, fractures of the body of the zygoma usually involve fractures of the floor or the lateral wall of the orbit, or both (Figure 9-1).

The four processes of the zygoma are the frontal, maxillary, temporal, and sphenoid. The frontal process is sturdy; however, it narrows superiorly as it articulates with the zygomatic process of the frontal bone. It forms a large portion of the orbit and, together with the sphenoid bone, forms part of the orbital floor. The temporal process is narrow and thin. It articulates with the zygomatic process of the temporal bone, and together they make up the zygomatic arch. The body of the zygoma is sturdy, but its articulations are frequently the site of fracture.

Five muscles attach to the zygoma. The masseter muscle originates from its temporal surface; the zygomaticus major, the zygomaticus minor, and the levator labii superioris originate from its malar surface. The temporalis muscle and the temporalis fascia attach at the temporal process, specifically its posterolateral edge.

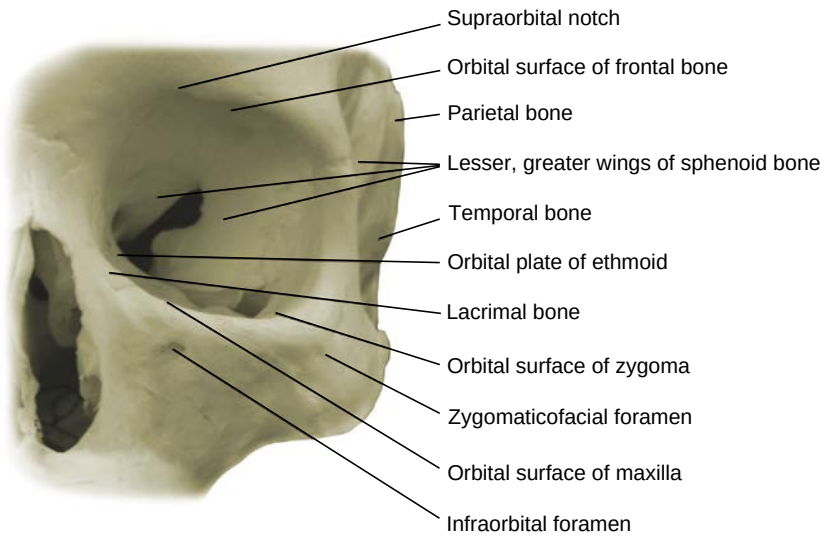
Two foramina arise from this bone. On the malar surface is the zygomaticofacial foramen, which provides exit to the nerve and vessels of the same name. The zygomaticotemporal foramen on its medial side transmits the zygomaticotemporal nerve and vessels.

From a frontal view, the ideal position of the zygomatic prominence is 10 mm lateral and 20 mm inferior to the lateral canthus. From a lateral perspective, the globe should be 1 mm anterior to the most prominent portion of the zygoma. Because these ideal measurements are not always found, an examination of the contralateral zygoma will determine the correct position of the injured zygoma in every patient who has no craniofacial anomalies.

For complex zygomatic fractures, multiple approaches

The upper eyelid consists of five distinct layers from skin to conjunctiva: the skin, the orbicularis oculi muscle, the orbital septum above or the levator palpebrae superioris aponeurosis below, the Müller muscle/tarsus complex, and the conjunctiva. The lower eyelid consists of at least four distinct layers: the skin and subcutaneous tissue, the orbicularis oculi muscle, the tarsus (upper 4 to 5 mm of the eyelid) or orbital septum, and the conjunctiva.

The layers of the scalp can be remembered with the simple mnemonic SCALP: s, skin; c, subcutaneous tissue;



• **Figure 9-1** Bony anatomy of the orbit and zygoma.

a, muscularis aponeurotic; l, loose areolar connective tissue (subgaleal fascia or subaponeurotic plane); and p, pericranium (periosteum). The skin and subcutaneous tissue of the scalp are surgically inseparable, unlike these same structures elsewhere in the body. The musculoaponeurotic layer consists of the paired frontalis (epicranius) and occipitalis muscles, the auricular muscles, and a broad aponeurosis. The aponeurosis is the true galea and has two portions, an extensive intermediate aponeurosis between the frontalis and occipitalis muscles and a lateral extension into the temporoparietal region known as the temporoparietal fascia. The superficial temporal artery lies on or in this layer.

The subgaleal fascia is usually referred to as the loose areolar layer or the subaponeurotic plane. This layer cleaves readily, allowing the skin, subcutaneous tissue, and musculoaponeurotic layers to be stripped from the pericranium. The loose tissue of the subgaleal fascia allows free movement of the skin over the periosteum when the frontalis muscle is contracted. This fascial layer is used only for its ease of cleavage. Anteriorly the subgaleal fascia is continuous with the loose areolar layer deep to the orbicularis oculi muscles. Laterally the subgaleal fascia is attached to the frontal process of the zygoma and continues along the superior surface of the zygomatic arch, above the external auditory meatus, and over the mastoid process. The subgaleal fascia terminates as it fuses with the periosteum along the superior nuchal line. The pericranium is the periosteum of the skull and can be elevated from the skull, although it is more firmly attached along cranial sutures.

History and Physical Examination

The patient's medical history is always important, because many of these injuries will require operative intervention. As is often the case, medical and surgical problems may need to be managed in concert. The patient's mechanism of injury most often provides the initial indications of a possible zygomatic fracture.

Indications for surgery are cosmetic deformities and functional deficits[4] (Box 9-1). Because of the prominent

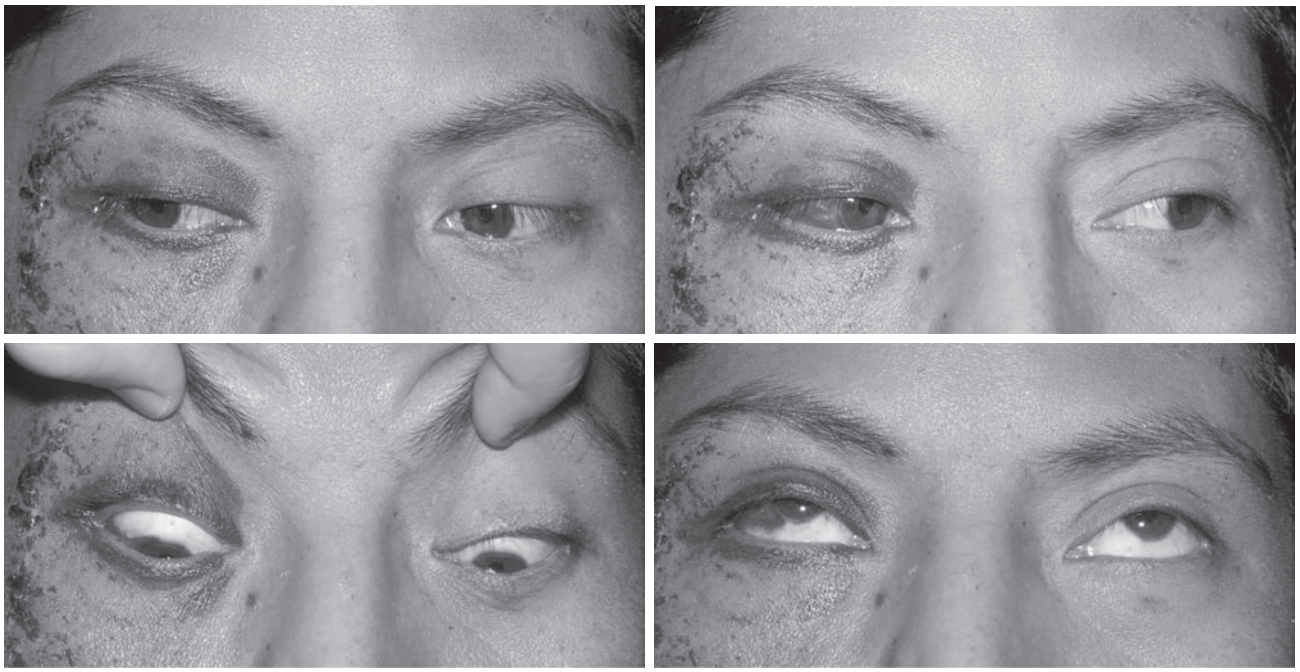
• BOX 9-1 Indications for Surgery

Depressed arch
Depressed malar eminence
Diplopia
Enophthalmos
Paresthesia in V2 distribution
Trismus

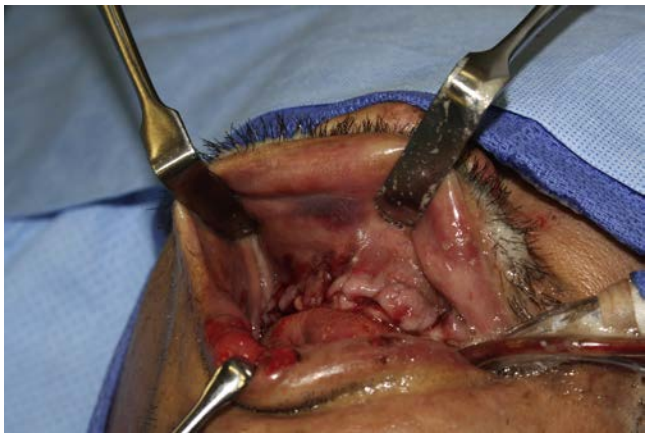
position of the zygoma on the face, zygomatic fractures can result in cosmetic deformities such as flattening of the malar eminence, widening or depression of the arch, orbital dystopia, or enophthalmos. These deformities can occur without severe impairment of function. However, fractures of the zygomatic arch can cause functional impairment by impinging on the temporalis muscle or obstructing the path of the coronoid and causing trismus. Zygomatic fractures impinging on the infraorbital nerve cause paresthesia or dysesthesia of the second division of the trigeminal nerve (V2). Disruption of the position of the globe can cause diplopia. Therefore, an examination of the orbit and the globe, including extraocular movements, an evaluation of the maxillary sinus, a determination of V2 sensation, and an examination of the range of motion of the mandible are essential in diagnosing zygomatic injuries (Figure 9-2).

Signs of zygomatic fracture are periorbital or maxillary vestibular ecchymosis, periorbital edema, flattened arch or malar prominence, deformity or displacement, trismus, displacement of palpebral fissure, enophthalmos, exophthalmos, chemosis, and conjunctival hemorrhage (see Figure 9-2; Figure 9-3), Symptoms that indicate zygomatic injury are pain, sensory deficit, crepitus from air emphysema, and diplopia.

Once the examination of the patient has been completed, the anatomic dislocation of the zygoma can best be evaluated by digital exploration. The patient should be in the cephalad position during the examination; the surgeon should compare the right and left sides simultaneously, beginning at the zygomaticofrontal suture and palpating



• **Figure 9-2** Extraocular movements. This patient shows no evidence of entrapment on exam. Note the subconjuctival hemorrhage of the patient's right eye.



• **Figure 9-3** Vestibular ecchymosis associated with a zygomatic fracture. Avulsed maxillary dentition as well due to injury.

inferiorly and medially along the infraorbital rim. Then the zygomatic arch should be evaluated for dislocation, comminution, or pain. The buccal vestibule and antral wall should be palpated intraorally for detection of crepitus or bony disruption. Palpation is important because acute swelling after an injury can mask the displaced fracture (Figure 9-4).

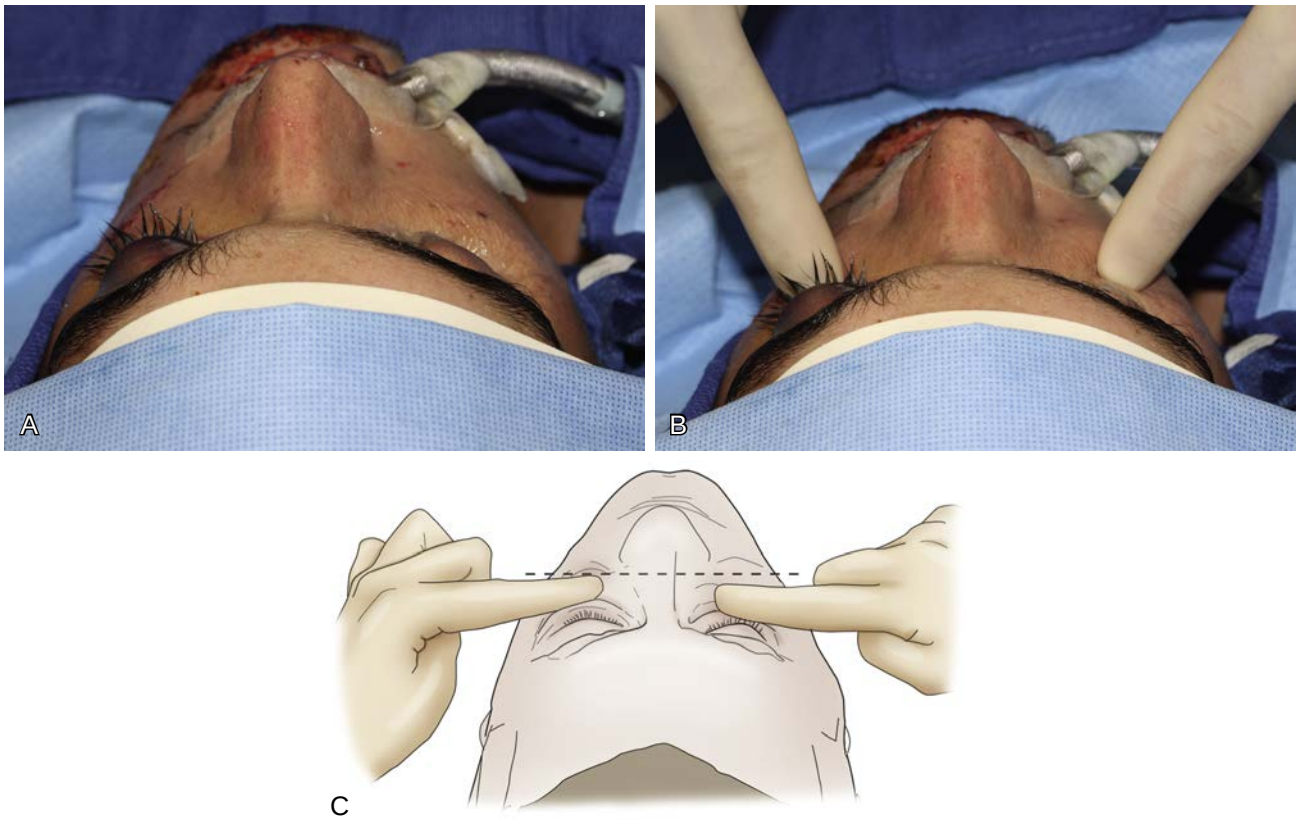
Many surgeons consider an ophthalmologic examination an essential part of the examination for zygomatic fracture. Depending on the mechanism of injury, as many as 28% of patients with zygomatic injuries may have moderate to severe ocular injuries.[5-7]

Indications for Radiographs and Surgery

After the primary and secondary trauma survey, when life-threatening injuries have been ruled out or managed, radiographic imaging should be considered. Currently, computed tomography (CT) is the gold standard for diagnosing bony injuries of the face. Images (either direct or reformatted) should be obtained in the axial and coronal dimensions (Figure 9-5). With improvements in CT scan images, three-dimensional (3D) reconstruction images can provide greater visualization of displaced and fractures segments (Figure 9-6).

In the unlikely event that obtaining CT scans is impossible, plain radiography can be used. The images that should be obtained are a lateral skull view, a Waters (posteroanterior oblique) view, or a reverse Waters (anteroposterior oblique) view, and a submental vertex view of the skull. The Waters or posteroanterior view provides visualization of the inferior or lateral rims or both and of the orbital floors, as well as the maxillary sinuses. Often the zygomatic arch can also be visualized. If the patient cannot be placed in a supine or upright position, the modified or reverse Waters view (anteroposterior oblique) may be used. With this technique the structures are farther from the film; thus, the structures are not as well defined as in the classic Waters view. The lateral skull view provides detail about the paranasal sinuses and the presence of air intracranially.

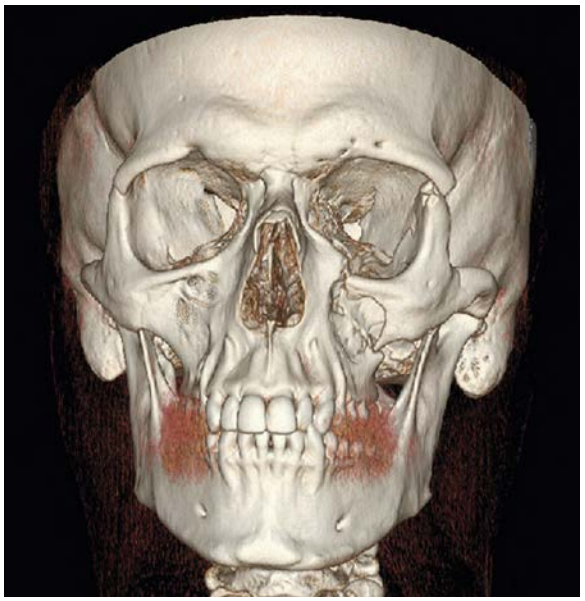
CT scanning provides finely detailed views of the bony architecture and pinpoints even the smallest fractures. Because CT scanning uses less radiation and provides views more rapidly than plain radiography, it is now the procedure of choice. The best evaluation of suspected zygomatic and orbital fractures is provided by 1.5-mm slices in the axial plane (for information about the medial and lateral walls) and the coronal plane (for specific information about the orbital floor). Many scanners provide reconstructed coronal images, which are



• **Figure 9-4** Facial swelling after trauma may mask a deformity that is easily palpated. **A,** Birdseye view demonstrating symmetric appearance due to edema. **B,** Palpating malar regions reveals depressed right zygomaticomaxillary complex (ZMC). **C,** Artist depiction of palpating depressed right ZMC.



• **Figure 9-5** **A,** Axial computed tomography (CT) scan image demonstrating fractured and displaced zygomaticomaxillary complex (ZMC). **B,** Coronal CT scan image demonstrating fractured and displaced ZMC.



• **Figure 9-6** Three-dimensional reconstruction computed tomography scan image showing depressed zygomaticomaxillary complex fracture and increased orbital volume on the affected side.

usually adequate with axial slices of 1.5 mm or less. Sagittal images provide useful information about the posterior extent of a floor defect and the amount of posterior bone that remains. Sagittal scans are not routinely performed and must be specifically requested. Three-dimensional reconstructions can be created and are often useful for diagnosing and planning the treatment of complex fractures.

CT scanning also provides information about soft tissues. It can visualize orbital injuries such as a ruptured globe, dislocated lens, or vitreous hemorrhage and can demonstrate retrobulbar hemorrhage or disruption of the optic nerve. The extraocular muscles are clearly visible, and the clinical assessment of entrapped muscles can be confirmed. Preseptal and postseptal hematomas can also be differentiated.

Treatment

During the consideration of treatment for zygomatic injuries, the patient's interests should be paramount. The patient's age and medical history should be factored into the decision-making process. If, after being informed about the risks and benefits of surgery or observation, the patient elects surgery, the decision about how and when to treat can be

an

seen on CT scans.[8-10] Fractures can be described as high-energy or low-energy injuries. A low-energy fracture typically results in mild to moderate displacement and is not comminuted. High-energy fractures often result in more severe displacement and comminution of the body of the zygoma. These injuries commonly require orbital reconstruction.[11]

The main reason not to treat zygomatic fractures surgically is the clinical absence of functional and esthetic compromise.[4,11] Another consideration is the degree of vision in the unaffected eye. Visceral and neurologic damage always takes precedence over a fractured facial bone. Although the risk to vision associated with the repair of a zygomatic fracture is low (<1%), it may be unwise to risk affecting the sight in the remaining functional eye.

Once the decision has been made to proceed with surgical treatment, the surgeon must decide when to operate. Waiting for residual edema to resolve, approximately 2 weeks, is usually acceptable. This delay allows time for adequately assessing and planning the case; in addition, findings associated with the injury manifest themselves during this time. Waiting longer than 2 weeks may complicate the surgical reduction of the fracture because early bone healing may begin during this time and may make osteotomy of the fracture site necessary. If soft tissue lacerations are present over the fracture sites, soft tissue fibrosis and contracture can make the soft tissue envelope more difficult to expand. Evidence of muscle entrapment on CT scan or on physical exam is an indication for immediate surgery. Pressure on the muscle from bone margins can lead to muscle necrosis and fibrosis, causing a permanent restriction of movement.

Surgical Approaches for Fractures of the Zygomatic Complex

The technique used to approach the facial skeleton depends on the individual fracture pattern and on the displacement of the fracture. For high-energy, comminuted fractures, or for multiple facial fractures, multiple approaches are necessary. For isolated zygomatic fractures, stable reduction can sometimes be achieved with less exposure. The order of the following approaches is based on the order in which they might be used for reducing an isolated, noncomminuted fracture of the zygoma (Figure 9-7).

Carroll-Girard Screw

The most direct approach in reducing a zygomatic fracture is to insert a Carroll-Girard screw. This T-shaped device has a handle at one end with a sharp screw portion perpendicular to it. This device must be placed into the body of the zygoma, thus requiring an incision directly over the malar prominence. This requirement is the main drawback of this approach; however, if the incision is performed properly, the scar is virtually invisible within 6 months. Alternatively, if



• **Figure 9-7** Exposure of zygomaticomaxillary buttress and infraorbital rim with placement fixation via preexisting laceration.

an infraorbital incision is used as an approach to the orbital rim, the screw can be placed through it. This screw is a useful device and provides traction in any direction. Some surgeons recommend placing this screw regardless of any other methods of reduction used (Figure 9-8).

Vestibular Approach

This technique can be used for a wide variety of midfacial procedures. It allows safe access to the entire facial surface of the midfacial skeleton, from the zygomatic arch to the infraorbital rim and the frontal process of the maxilla. With regard to zygomatic injuries specifically, this approach is required for visualization of the zygomaticomaxillary buttress. The greatest advantage of this approach is that the scar can be hidden. This rapid and simple approach is associated with few complications.

The path to the underlying facial skeleton is through mucosa, submucosa, facial muscles, and periosteum. The only important neurovascular structure encountered during this dissection is the infraorbital nerve, which is located approximately 7 to 10 mm inferior to the infraorbital rim and just medial to the zygomaticomaxillary suture.

After submucosal injection of a vasoconstrictor, the incision is placed approximately 3 to 5 mm superior to the mucogingival junction. This placement leaves a cuff of unattached mucosa at the inferior extent that must be closed at the end of the procedure. The incision extends as far posteriorly as is necessary for exposure, usually up to the first molar tooth. Whether the incision extends past the midline depends on whether the fractures are bilateral. The initial incision is perpendicular to the mucosa and then is angled perpendicular to the bone. The incision is carried through the periosteum, and a subperiosteal dissection is performed first anteriorly, then along the piriform aperture, and then posteriorly behind the zygomaticomaxillary buttress. Careful dissection at the buttress is advised so that the buccal fat pad is not exposed; such exposure is more of a nuisance than a complication of surgery.



• **Figure 9-8** Carroll-Gerard screw placement for manipulation of the body of the zygoma.

The unilateral maxillary vestibular incision is closed simply in one layer with a 3-0 resorbable suture. If a circumferential maxillary vestibular incision is made, the closure is more complex. An alar cinch with V-Y closure is performed, and the midline is then tacked; this technique creates a linear incision. The vestibule is then closed in a continuous fashion to the midline from both sides.

Approaches to the Zygomaticofrontal Region

When the fracture remains unreduced or unstable after a closed reduction and a vestibular approach have been attempted, the surgeon might then address the zygomaticofrontal region. It is not uncommon to find significant overlap of bone, with the inferior lateral orbital rim having been displaced medially and superiorly.

Lateral Canthotomy

If a lateral canthotomy is indicated (i.e., because exposure of the zygomaticofrontal suture is necessary), this is the initial incision. The initial incision is made with a No. 15 blade through the skin and dermis and proceeds for only approximately 1 cm. An anesthetic with a vasoconstrictor should then be administered under the conjunctiva and in the lateral canthotomy site as an aid to hemostasis. Administering the anesthetic after this incision helps avoid distortion of the tissue as the procedure progresses. The incision is completed with pointed scissors to the depth of the lateral orbital rim (7 to 10 mm). The layers that are incised are skin, orbicularis oculi muscle, orbital septum, lateral canthal tendon, and conjunctiva. Mobilizing the lower eyelid may require releasing the anterior limb of the lateral canthal tendon. Subperiosteal dissection is then continued on the lateral surface of the superior lateral orbital rim and is followed by reduction and placement of fixation.

Upper Eyelid Approach

The upper eyelid approach can also be used to access the lateral orbital rim, the lateral orbital wall, and the superior orbital rim. This approach is also known as the upper blepharoplasty, upper eyelid crease, and supratarsal fold approach. A natural skin crease in the upper eyelid excellently camouflages the scar. If there is no eyelid skin crease, a curvilinear incision should be along the supratarsal fold and should tail off laterally over the lateral orbital rim. Protection of the cornea is critical during surgery and can be achieved with a tarsorrhaphy or a corneal shield placed at the beginning of the procedure. When the location of the incision has been determined, the incision is made through the skin only. After the initial incision, a local anesthetic

with vasoconstrictor should be administered. Making the initial skin incision before administering the anesthetic is beneficial because distortion of the tissues after infiltration can make correct placement of the incision difficult. The incision should be placed at least 10 mm superior to the upper eyelid margin and 6 mm above the lateral canthus as it extends laterally (Figure 9-9).

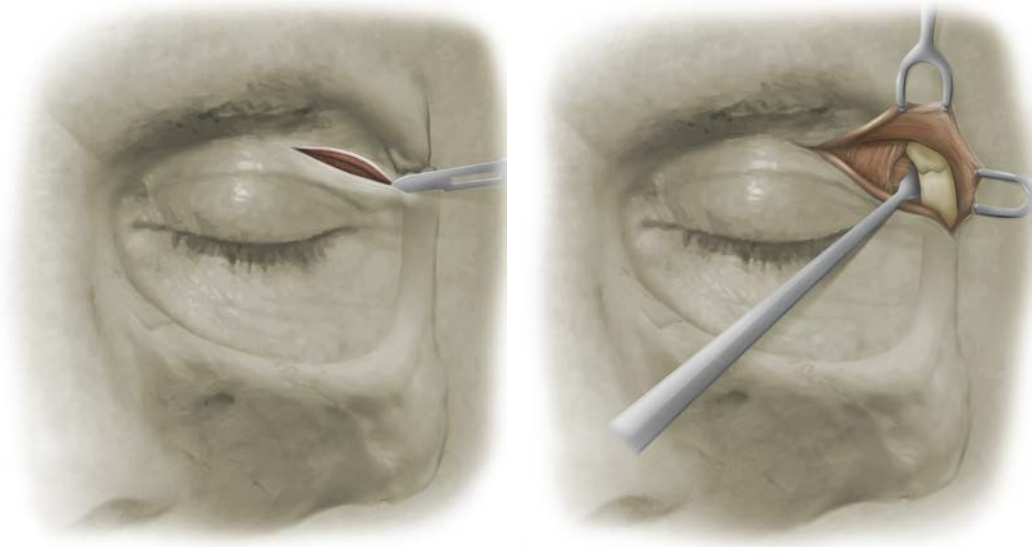
The incision is made through the skin and the orbicularis oculi muscle. The vasculature of the muscle maintains the viability of the skin; elevating this vasculature with the skin creates a skin-muscle flap. This flap can be developed laterally, superiorly, and, if necessary, medially. Dissection continues superiorly just below the muscle and superficial to the orbital septum. Once the periosteum has been identified over the superior orbital rim, it is incised, and the periosteum is dissected up for exposure of the fracture. Care should be taken near the superior-lateral orbital rim, because the lacrimal fossa and gland are located just inside the rim.

After the fracture has been fixated, closure is performed in layers: periosteum, muscle, and skin.

Eyebrow Approach

This approach to the lateral orbital rim is straightforward and rapid and offers a relatively well-camouflaged scar. No important neurovascular structures are encountered during this approach. If the patient has undergone cosmetic eyebrow removal, or if exposure of the inferior lateral orbital rim is also necessary, the scars may be more apparent, and the extent of exposure may be limited.

This approach is rarely indicated; when it is, the eyebrow is not shaved. An incision of approximately 2 cm is made; the inferior extent of the incision should stop at the end of the eyebrow and parallel to the hair of the eyebrow so that no hair shafts are cut. The incision should not be extended inferiorly along the orbital rim, because such an extension may cross the lines of resting skin tension (Figure 9-10).



• **Figure 9-9** Placement of an upper eyelid incision for approaching the zygomaticofrontal suture.



• **Figure 9-10** Placement of a lateral brow incision for approaching the zygomaticofrontal suture.

Once undermining has been performed in a supraperiosteal plane, the skin is retracted over the area of interest and a periosteal incision is made. Dissection is performed in a subperiosteal plane, but again, access is limited. Closure is performed in a layered fashion.

Approaches to the Infraorbital Rim and the Orbital Floor

Lower Eyelid Approaches

Lower eyelid approaches provide excellent exposure of the inferior orbital rim, the floor of the orbit, the lateral orbit, and the inferior portion of the medial orbital rim and wall. Placing the incision in the thin skin of the eyelid and in the natural resting lines of the skin results in a scar that becomes inconspicuous with time; transconjunctival incisions are perhaps the best hidden. Several external incisions exist and are named according to the inferior or superior position at which they are placed on the skin and also according to the level at which the muscle is transected for exposure of the periosteum. The subciliary incision, also known as the infraciliary or blepharoplasty incision, is made just below the eyelashes. The subtarsal approach, also known as the mideyelid or skin crease approach, is made 4 to 7 mm below the eyelid margin (Figure 9-11).



• **Figure 9-11** Subciliary, subtarsal, and mid-lid approaches to the infraorbital rim and orbital floor.

Transconjunctival Approach

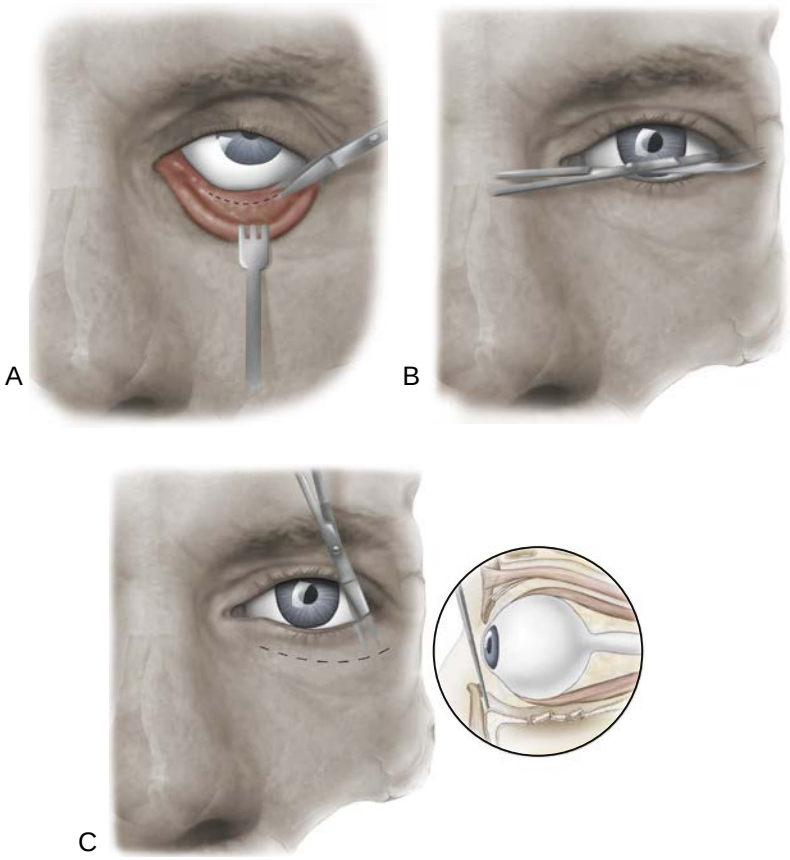
The transconjunctival approach can be used to expose the infraorbital rim and the floor of the orbit. However, when a lateral canthotomy is used in conjunction with this approach, exposure of the zygomaticofrontal suture and the lateral wall of the orbit can be obtained. Also with medial extension of the transconjunctival incision posterior to the caruncle (i.e., transcaruncular incision), the medial wall of the orbit can be exposed. Some authors separate the transconjunctival approach from the transconjunctival approach with medial extension (i.e., transcaruncular approach) and from the transconjunctival approach with lateral canthotomy extension. In this chapter, all of these are described under the transconjunctival approach.

The main advantage of this approach is that the scar is hidden; if a lateral canthotomy is used, an inconspicuous scar remains, usually in a skin crease. This approach is also rapid because it is not necessary to create a skin or a skin-muscle flap during dissection. With improper technique, the main disadvantage of this approach is entropion, which is more difficult to correct than the sequela of an improper skin incision (i.e., ectropion).

As is necessary with the previously described techniques, a forced duction test should be performed preoperatively and a corneal shield should be placed for protection. Two or three traction sutures, using 3-0 silk, can be placed into the lower eyelid approximately 5 mm inferior to the lid margin so that the tarsal plate is included in the suture.

The transconjunctival approach is begun by creating a small incision in the lateral conjunctiva with tenotomy scissors or with an electrocautery device. A subconjunctival plane is then bluntly dissected with the scissors, followed by completion of the conjunctival incision. This plane is easily found when this approach is combined with a lateral canthotomy. The incision is placed halfway between the inferior conjunctival fornix and the inferior margin of the tarsal plate. This incision can be placed as far medially as necessary as long as the lacrimal sac is not violated. This medial extension is called a transcaruncular incision because it was originally described as a 12- to 15-mm vertical incision through the conjunctiva and the lateral third of the caruncle. However, the incision can also be placed temporal to the caruncle. Either incision is carried superiorly through the conjunctiva to the level of the levator palpebrae aponeurosis, thereby exposing the underlying periorbita. Placing traction sutures in the vestibular conjunctiva can help hold the corneal shield in place and also help preserve the conjunctiva for closure at the end of the case (Figure 9-12).

After the incision has been made through the conjunctiva, the surgeon must decide whether to perform a preseptal or a retroseptal approach to the orbital rim. The advantages of the retroseptal approach are that it is more direct and may help avoid the scarring within the lower eyelid that is associated with the preseptal approach. However, with the retroseptal approach, periorbital fat will be encountered. Other than being bothersome throughout the case, no serious risk is associated with exposing this adipose tissue. With the retroseptal approach, the surgeon sharply incises the periorbita immediately posterior to the orbital rim, paying special attention to avoiding the lacrimal sac medially. This incision can be made with electrocautery or with a No. 15 blade. If a preseptal approach is used, blunt tenotomy scissors are used after the incision through the conjunctiva for dissection through the septum and the inferior lid retractor muscles. The dissection is continued anterior to the septum to the lower rim approximately 2 mm inferior to the superior border of the infraorbital rim. The periosteum is then incised sharply.



• **Figure 9-12** **A,** Location of the transconjunctival incision, inferior to the tarsal plate, and 3-4 mm superior to the conjunctival sulcus. **B,** Lateral canthal release. **C,** Blunt dissection to the orbital rim.

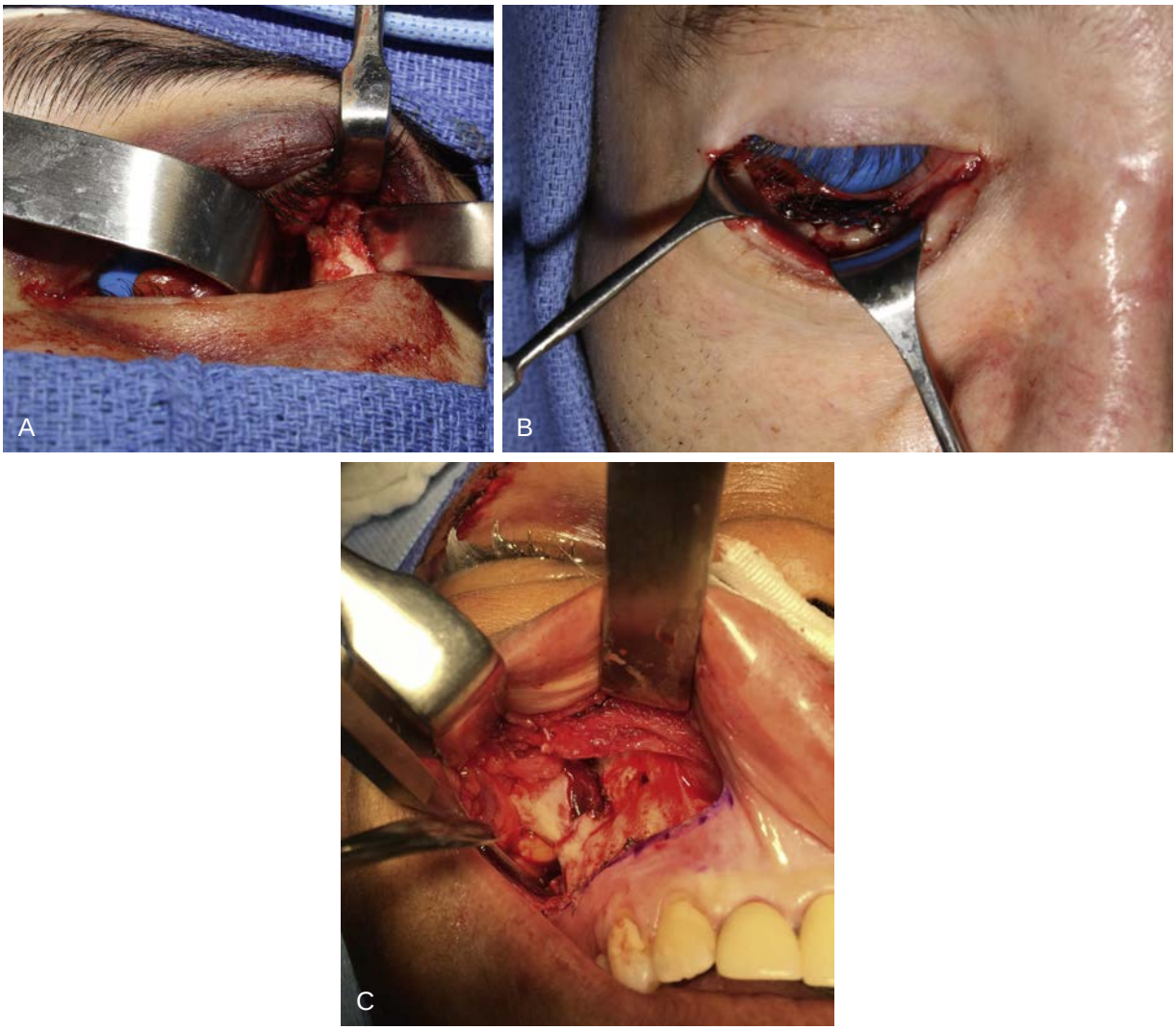
With both approaches, the periosteum can then be dissected off the anterior portion of the maxilla and zygoma, the orbital rim, and the orbital floor with periosteal elevators. Obviously, the extent of the dissection will be dictated by the initial exposure needed for identifying the fractures and determining the severity and location of the fractures (Figure 9-13).

These incisions should be closed in a layered fashion. If possible, the periosteum is closed with 4-0 resorbable suture. Closing the periosteum medially after a transcaruncular extension is quite difficult and is not essential. If a lateral canthotomy is performed, an inferior canthopexy suture should be inserted but not tied before the conjunctiva is closed. This technique allows open access for closure of the conjunctiva. A 4-0 long-lasting suture is used to reattach the lateral portion of the inferior tarsal plate to the residual superior portion of the lateral canthal tendon or to the fixed surrounding tissues. When the adequacy of this suture is assessed, the contralateral lateral canthus should be at a comparable level, and the lower lid should be adjacent to the globe. The surgeon should pull two ends of the suture to ensure that the suture is firmly attached to ligamentous tissue. The conjunctiva should be closed with 6-0 resorbable suture in a running fashion. If interrupted sutures are used to close the conjunctiva, the knots should be buried. After the conjunctiva has been closed, the canthopexy suture is tightened; this technique draws the lower eyelid into position. Subcutaneous and then 6-0 skin sutures are placed along the horizontal lateral canthotomy to complete the closure.

Subciliary Approach

This approach is begun by making a skin incision just below the eyelashes, 1 to 2 mm inferior to the lashes along the entire length of the eyelid. After the initial incision, local anesthetic with a vasoconstrictor should be administered in a manner similar to that described for the upper eyelid approach. Subcutaneous dissection is then performed 4 to 6 mm inferiorly along the entire extent of the incision.

Once the subcutaneous flap has been elevated, the incision is extended through the suborbicularis muscle, beginning at the lateral extent. The skin incision and the muscle incision are made at different levels so that hypertrophic scarring and exophthalmos can be avoided. This dissection is carried medially between the orbicularis oculi muscle and the orbital septum. An attachment of the orbicularis oculi muscle will remain; transecting this attachment inferior to the initial skin incision creates a "step" dissection. After the muscle has been transected, the orbital septum and periosteum will be exposed. The skin-muscle flap can be retracted inferiorly, and an incision can be made through the periosteum on the anterior surface of the maxilla and zygoma, 3 to 4 mm below or lateral to the orbital rim. Making the incision at this level avoids the insertion



• **Figure 9-13** **A,** Exposure of the zygomaticofrontal fracture via a lateral canthotomy incision. **B,** Exposure of the infraorbital rim via a transconjunctival incision. **C,** Exposure of the zygomatic buttress via a maxillary vestibular incision.

of the orbital septum along the orbital margin and the infraorbital nerve, which is located approximately 5 to 7 mm inferior to the orbital rim.

With the sharp end of a periosteal elevator, a subperiosteal dissection can be performed along the anterior maxilla, the orbital rim, and, if necessary, along the orbital floor. If exposure of the lateral orbital rim is required, the incision can be extended 2 cm past the lateral canthus. This extension will allow access to the zygomaticofrontal suture and will not pose any threat of injury to the temporal branch of the facial nerve, which crosses the zygomatic arch 3 cm lateral to the lateral canthus. Supraperiosteal dissection is performed superior to the zygomaticofrontal suture. The skin, muscle, and superficial limb of the lateral canthus are retracted superiorly, thereby exposing the underlying periosteum. The initial infraorbital rim incision connects to an incision made in the periosteum on the lateral side of the lateral orbital rim.

Closure is performed in two layers, the periosteum and the skin. The periosteum can be closed with resorbable suture (Monocryl preferred), and the skin can be closed with a running 6-0 nonresorbable or fast-resorbing suture. If the extended incision is made, an isolated lateral canthopexy can be avoided as long as the periosteum is meticulously repositioned and sutured along the lateral orbital rim. A suspensory suture (Frost suture) placed in the lower eyelid can counteract skin and septal scarring, thus reducing the risk of lower lid shortening and ectropion. This suture may be left in place for several days or until gross edema has resolved. A suture is placed in the gray line of the lower lid and suspended in the forehead via an 18-gauge Angiocath with a vertical slit superiorly (Figure 9-14). Vision can be checked by opening the upper eyelid.

Subtarsal Approach

The subtarsal approach is very similar to the subciliary approach; the differences are described next. The skin incision is placed at the level of the inferior margin of the lower



• **Figure 9-14** Frost suture secured to the forehead using a 20-gauge Angiocath.

tarsus, in the subtarsal fold. Practically, it is made in the mideyelid in a natural eyelid crease. The benefits of this more inferiorly based incision are that it is less frequently associated with scleral show and ectropion. This incision will provide adequate access to the orbital floor and the inferior orbital rim. If extension of this incision is required, the incision will be carried laterally and inferiorly, following the natural skin resting lines. An extended incision and dissection lateral to the orbital rim, as in the subciliary incision, should not be used because of the lateral inferior position in which the incision would have to be made.

Unlike the subciliary incision, which is carried simply through skin, this incision is carried through both skin and orbicularis oculi muscle; it stops at the orbital septum. The skin-muscle flap is then dissected from the orbital septum inferiorly for approximately 4 mm. Retracting the skin-muscle flap will leave the orbital septum and periosteum exposed. The incision through the periosteum, the dissection of the orbit, and the closure are the same as those described for the subciliary approach.

Approaches to the Arch and the Zygomaticotemporal Suture

Coronal Approach

A versatile approach, the coronal approach can be used to access the upper third of the facial skeleton and the zygomatic arch. With respect to the zygomatic complex, the coronal approach is used for severely displaced and comminuted complex fractures that require access to and fixation of the zygomatic arch.

Once the need for a coronal incision has been determined, the location of the incision must be considered. Factors that must be included in determining the location of the incision are the patient's hairline and the amount of inferior access that is required for the procedure. The incision is usually placed along a line extending from one preauricular area to the other, several centimeters behind the hairline, or even more posteriorly for balding men. For most women and nonbalding men, the incision may be curved anteriorly at the vertex, paralleling but remaining 4 to 5 cm within the hairline. The amount of skeletal exposure depends on the inferior extent of the incisions, not on the anteroposterior location of the incision. When exposure of the zygomatic arch is unnecessary, extension of the coronal incision inferiorly to the level of the helix may be all that is needed. However, when exposure of the zygomatic arch is necessary, the coronal incision must be extended inferiorly to the level of the earlobe as a preauricular incision. Extending this incision will also allow access to the temporomandibular joint and the infraorbital rims.

Before the incision is made, a vasoconstrictor should be injected into the subgaleal plane for promoting hemostasis, and hydrodissection should be performed. After the vasoconstrictor has taken effect, cross-hatches should be made across the proposed site of the incision; these marks will assist in properly aligning the scalp at the end of the procedure. The initial portion of the incision is made with a No. 10 blade extending from one superior temporal line to the other through skin, subcutaneous tissue, and galea; this incision reveals the subgaleal plane of loose areolar connective tissue overlying the pericranium. Limiting the initial incision to the area between the superior temporal lines (i.e., from lateral orbit to lateral orbit) prevents the surgeon from incising through the temporalis fascia and into the temporalis muscle. The skin incision below the superior temporal line should be to the depth of the glistening superficial layer of temporalis fascia. An easy method of ensuring that the incision is made to the proper depth is to bluntly dissect with curved scissors in the subgaleal plane from above, toward the zygomatic arch, and incise to that depth. Once the initial incision has been completed, Raney clips or electrocautery can be used for achieving hemostasis.

Dissection can then be carried out anteriorly and laterally with finger dissection, blunt periosteal elevators, or back-cutting with a scalpel. Dissection continues anteriorly in the subgaleal fascial plane to a point 3 to 4 cm superior to the superior orbital rims or to the most superior extent of a frontal sinus fracture. Once this point has been reached, an incision is made through the periosteum from one superior temporal line to the other. Subperiosteal dissection continues to the supraorbital rims, and the lateral portion of the flap is dissected inferiorly atop the temporalis fascia.

Once the lateral portion of the flap has been elevated to within 3 to 4 cm of the body of the zygoma and the zygomatic arch and to the root of the arch, the superficial layer of temporalis fascia is incised at the root of the zygomatic arch, just in front of the ear. This incision continues anteriorly and superiorly at a 45-degree angle, joining the cross-forehead incision previously made through the pericranium at the superior temporal line. Incision through the superficial layer of the temporalis fascia reveals the superficial temporal fat pad and areolar tissue. Further dissection inferiorly within this layer provides a safe route of access to the zygomatic arch, because the temporal branch of the facial nerve

is always lateral to the superficial layer of the temporalis fascia. Once the superior surface of the zygomatic arch and the posterior border of the body of the zygoma have become palpable or visible, an incision is made through the periosteum along their superior surface. The incision progresses superiorly along the posterior border of the body of the zygoma and the orbital rim, ultimately meeting the cross-forehead horizontal incision through the pericranium.

As with the other approaches, with the coronal approach closure is layered. Closed suction drainage may be necessary with a 7-mm flat drain exiting the hair-bearing region of the scalp posterior to the incision. Suture resuspension of the soft tissues is necessary and can be accomplished with 3-0 resorbable sutures passed through the deep surface of the periosteum of the malar region and then suspended to the temporalis fascia or another stable structure. The periosteum around the lateral orbital rim is closed with 4-0 resorbable suture. The inferior edge of the superficial layer of the temporalis fascia is sutured approximately 1 cm superior to the superior edge of the incised fascia with running 3-0 long-lasting resorbable suture. Closing the horizontal periosteal incision across the forehead is not necessary. The scalp incision can be closed in two layers with 2-0 resorbable suture through the galea/subcutaneous tissues and with staples for the skin. The skin staples are removed in 10 days; the drain can usually be removed after 24 hours.

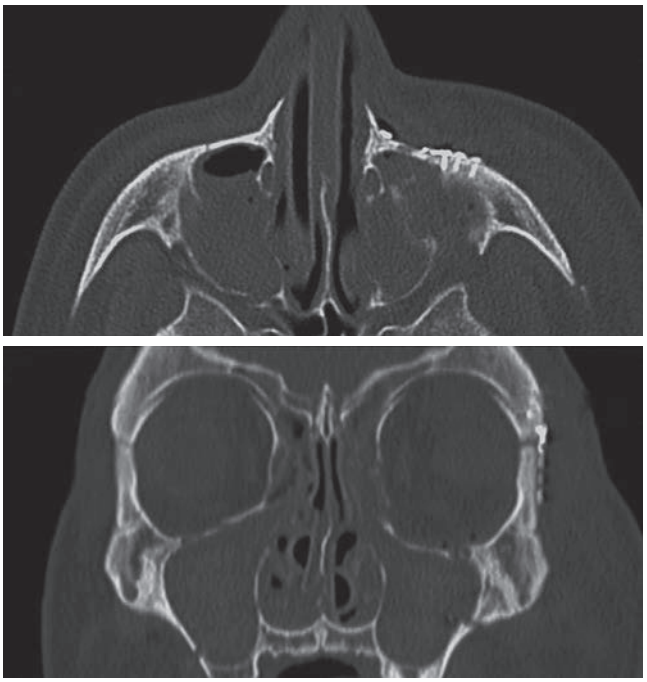
Fixation

Once the decision has been made to treat zygomatic injuries surgically, the need for fixation depends on the stability of the structures. Typically, low-energy injuries can be treated by Ellis and colleagues.[11] When the CT scan shows a displaced zygomatic fracture that is not comminuted and does not require orbital floor reconstruction, initial exposure should be obtained with a maxillary vestibular incision. If the fracture can be reduced and is stable, no fixation may be required; if the fracture is unstable after reduction, fixation should be placed. If the reduction remains unstable, exposure and fixation of the lateral orbital rim should be accomplished, followed by fixation of the infraorbital rim if necessary.

When evidence of a comminuted fracture exists, or when orbital floor reconstruction is anticipated, exposure of all fracture sites should be accomplished prior to placement of any fixation. This exposure would typically include an approach to the zygomaticofrontal region, infraorbital rim, and a maxillary vestibular incision. Fixation in each of these regions is usually necessary (Figures 9-15 and 9-16).

The Zygomatic Arch

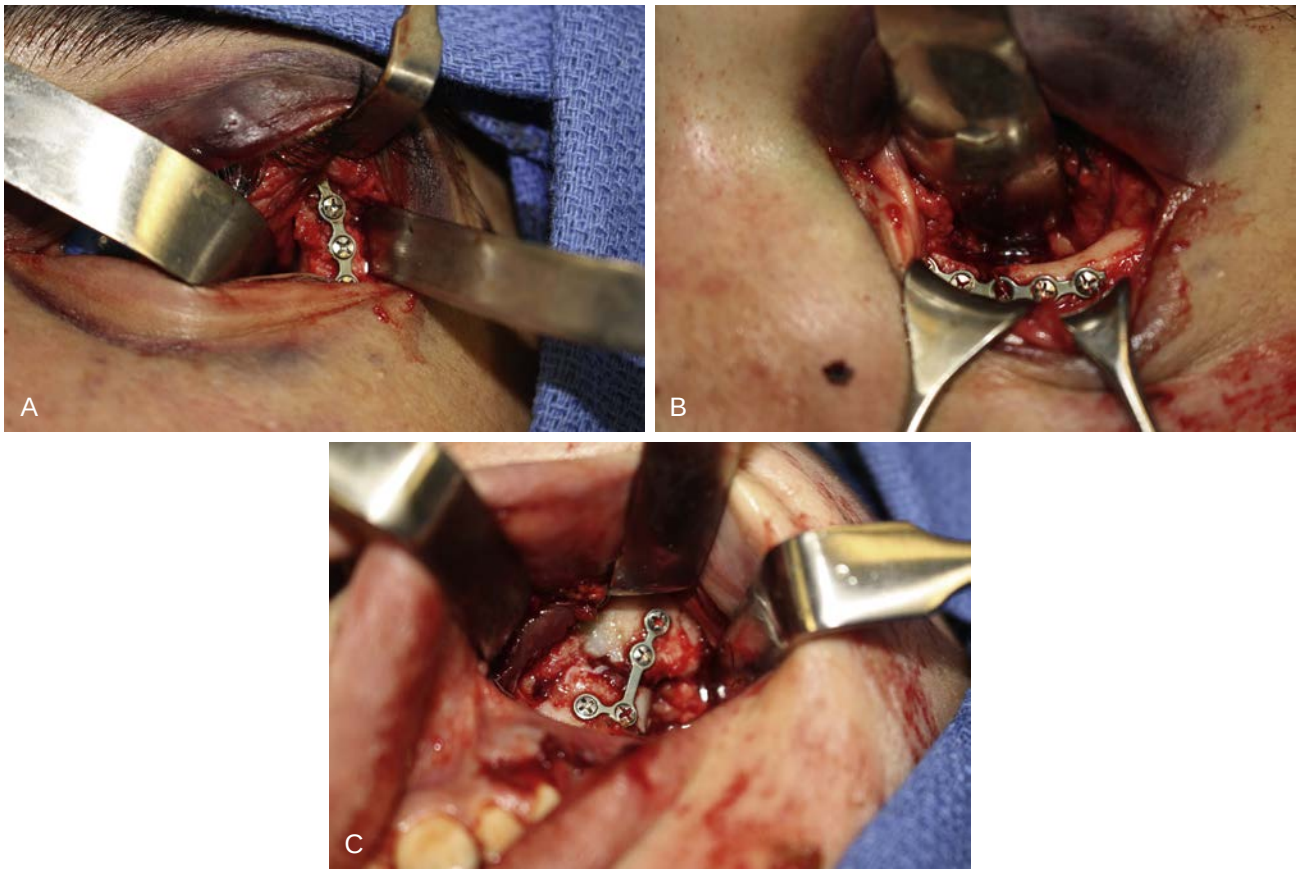
In contrast to the zygoma, the arch is a relatively weak bone. It is laterally positioned and is a combination of two bones: the zygoma and the temporal bone. These two features, lateral prominence and lack of strength, make fracture of the zygomatic arch a frequent occurrence. Such fractures may be of different types according to their cause. Isolated zygomatic arch fractures account for approximately 10% of all zygomatic fractures and are often the result of localized forces directed laterally with low impact (e.g., sports injuries and injuries caused by blows).[12,13] Fracture of the arch often occurs in combination with fractures of the zygomaticomaxillary complex and panfacial fractures.



• **Figure 9-15** Axial and coronal computed tomography scans following reduction of zygoma.

Systems for classifying fractures of the zygomatic arch have been described by Knight and North, Manson, and more recently by Yamamoto and Ozyazgan and col-[13-16] matic arch; and type II combined zygomatic arch fractures, in which the fracture in the arch was a component of a zygo-[13] I-B, more than two fractures; type II-A, one fracture; type II-B, multiple fractures. Yamamoto developed five types of isolated zygomatic arch fractures on the basis of the degree of displacement and the loss of bone contact at fracture lines as demonstrated by conventional axial radiographs, CT scans, or both.[16]

An isolated zygomatic arch fracture is not always discernible on examination because of overlying edema, but a fracture can usually be detected clinically by tenderness to palpation, depression in the region, and limited mouth opening. A severely depressed arch can limit mouth opening by preventing the coronoid process of the mandible



• **Figure 9-16** Fixation of fractures of the **(A)** zygomaticofrontal/lateral orbital rim, **(B)** infraorbital rim, and **(C)** maxillary buttress.

from moving forward during normal function or by trismus resulting from injury to the temporalis muscle.

The indications for treating zygomatic arch fractures are cosmetic and functional. If no cosmetic deformity and no functional deficit are apparent, the isolated fracture of the zygomatic arch can be observed without surgical treatment. However, if treatment is indicated, several techniques are available, including open reduction (coronal approach), intraoral elevation (Keen/vestibular approach), and extraoral elevation (Gillies method). The procedure should be carried out within 10 days; otherwise, early healing will make an anatomic reduction difficult.

Fixation of the isolated arch fracture is rarely required, but it may be necessary for type II fractures of the zygomatic arch. When the injury includes a severely displaced zygoma, the zygomatic arch will provide a point of reference for the reconstruction of the zygoma.[17] In such cases, fixation of the arch may be necessary.[18]

Existing lacerations, a hemicoronal incision, a coronal incision, or an extended preauricular surgical approach can be used for visualization of the zygomatic arch. The benefit of the coronal approach is that it enables visualization of the arch, superior orbital rim, and lateral orbital rim at the same time.

For arches that have not undergone fixation, numerous methods have been used to protect the arch from displacement during the healing period.[19-22] Ozyazgan and associates used an external splint made of a metal plate long enough to extend from the tragal region to the malar projection and shaped to fit the zygomatic arch.[13] This splint not only helped protect the unstable arch but also helped fixate the segment during healing.

Surgical Approaches to Isolated Zygomatic Arch Fractures

Two main approaches have been described for reducing isolated arch fractures: the temporal (Gillies) approach and the vestibular (Keen) approach.

Temporal (Gillies) Approach

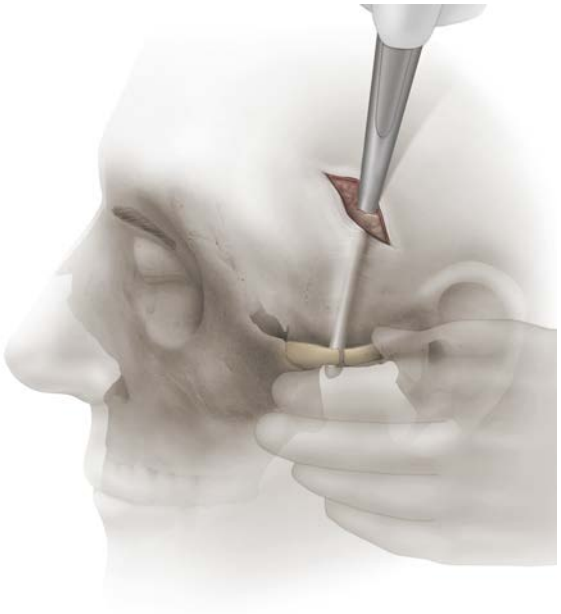
The bifurcation of the superficial temporal artery usually lies 2.5 cm above and anterior to the helix of the ear. The Gillies incision begins at this area, passing through the skin and subcutaneous tissue and running at an angle from anterosuperior to posteroinferior, thereby avoiding this artery and its parietal and frontal branches. Sometimes the middle temporal vein may be encountered. The temporalis fascia is exposed above this bifurcation, and the dissection is continued to the layer deep to the temporalis fascia and superficial

to the muscle. An elevator is inserted into this plane, and the area is swept medial to the zygomatic arch and the infratemporal portion of the zygoma. Finally, the blade of a Rowe zygoma elevator is inserted, and pressure is exerted anteriorly and laterally until the fracture is reduced; often an audible click is heard when the zygoma locks into place. Care must be taken to ensure that the blade is not situated medial to the coronoid process. A sweeping action of the blade along the medial aspect of the zygomatic arch and onto and including the lateral aspect of the zygoma ensures a satisfactory reduction, which is confirmed by concomitant palpation of the reduction site by the nonoperating hand. The procedure is completed by closure of the incision in two layers. Most medially or inferiorly displaced zygomas respond to this maneuver (Figure 9-17).

Vestibular (Keen) Approach

The main advantage of this approach is that the procedure is carried out through an intraoral approach, thus sparing a skin incision. The approach is also more direct: less dissection is necessary, there is no risk to vessels during the dissection, and the angle of reduction is superior and lateral, a more ideal reduction vector for zygomas that lie medially and inferiorly.

When used for an isolated arch fracture, a limited incision of approximately 2 cm is made in the maxillary vestibule approximately 5 mm superior to the mucogingival junction but inferior to the zygomatic buttress (at the first molar). A periosteal elevator is introduced through the incision, and intimate contact with the lateral antral wall is maintained. This technique creates a subperiosteal dissection that exposes the infratemporal surfaces of the maxilla and zygoma. The medial surface of the zygomatic arch is dissected free, and the location of the coronoid process is ascertained. The flat blade of the Rowe elevator is gently introduced into the incision site and placed under the infratemporal surface of the zygomatic bone. With the surgeon's free hand placed over the operative site, the elevator is pulled superiorly and laterally. The blade is then swept laterally, medial to the zygomatic arch and lateral to the coronoid process. With a lateral pull along the fracture portion of the arch, followed by a sweeping and lateral force, the zygomatic arch component is reduced. A click can sometimes be heard as the zygoma, the arch, or both are reduced. The incision is closed with chromic or Vicryl suture.



• **Figure 9-17** Gillies approach to the zygomatic arch.

Complications of Zygoma Injuries

Complications of fractures to the zygoma or the zygomatic arch are rare, but recognizing their signs and symptoms is important. These adverse events may occur early in the post-traumatic course or may manifest themselves late in the postoperative recovery period.

Infraorbital Paresthesia

After zygomatic injury, acute loss of sensory function of the infraorbital nerve is common and is the most frequently reported neurologic complication of zygomatic trauma.[23] The reason for this high incidence is its close proximity to the orbitozygomatic complex as it passes through the infraorbital fissure in the floor of the orbit to exit through the infraorbital foramen. Traumatic injury to the infraorbital nerve may be due to compression, edema, ischemia, or laceration.

During the immediate post-traumatic period, the incidence of sensory disturbances in association with fractures of the ZMC ranges from 18% to 94%.[9, 23-30] However, most patients with ZMC fractures will probably initially experience neurosensory deficits of the infraorbital nerve due to swelling or because the infraorbital foramen is in the fracture line.

Fractures whose repair requires open reduction and internal fixation are associated with a higher incidence of neurologic dysfunction. At the same time, however, recovery is faster when fractures are opened and fixated rather than reduced and not fixated.[23,28] The reason for this difference is presumably that anatomic reduction of the fracture relieves the pressure placed on the nerve, and fixation minimizes the potential for recurrence by keeping the bones in the correct anatomic position.

Because the infraorbital nerve can be damaged as it courses the floor of the orbit or, more commonly, as it exits from the infraorbital foramen, inspection during reduction is crucial. The surgeon should ensure that the nerve is not compressed during immobilization of the fractures and that the nerve is not compressed during reconstruction of the orbital floor.

Vriens and colleagues determined that certain fracture types are associated with a higher incidence of sensory

disturbance and thus with a different rate of return to normal sensation.[23] Overall, the long-term rate of complete sensory recovery of the infraorbital nerve is 64%; the return to normal sensation occurs on average within 15 weeks.

Once infraorbital nerve dysesthesia has been identified preoperatively, clinical neurosensory testing should be performed for establishing a baseline and should be repeated at each postoperative visit. The development of neuropathic pain warrants further investigation and intervention. Localization of nerve injury should be attempted. Infiltration of local anesthesia at the infraorbital foramen can help differentiate between neuroma formation within the infraorbital canal and neuroma formation distal to the foramen. Options for treatment include medications (e.g., amitriptyline, gabapentin), removal of bone plates, and nerve exploration.

Soft Tissue Complications

General complications that arise from the manipulation of soft tissue are numerous and can include dehiscence, hematoma or seroma, lymphedema, and scarring. With respect to the surgical approaches to the zygoma through the lower lid, other, more specific complications can arise, including vertical shortening of the lower lid, ectropion, and entropion.

If they become large enough, hematomas and seromas can be managed by decompression with a needle and a syringe. Lymphedema subsides over time, especially if the lower lid is supported in its proper position. Dehiscence of a wound may require nothing more than observation unless the defect becomes very large; in such cases the wound may require packing or, if indicated, resuturing.

Vertical shortening of the lower lid may occur when the scar contracts between the tarsal plate and the periosteum, thereby shortening the orbital septum. This complication can be prevented by providing superior support of the lower lid for several days (or until gross edema has resolved) after surgery. The simplest preventative method is the Frost suture.[31] This technique closes the eye, supports the lower lid, aids in the dissipation of lid edema, and allows postoperative examination of the globe and measurement of vision. Splinting of the lower eyelid by suturing antibiotic-laden, lubricated gauze to the lower eyelid after surgery has also been described.[32]

Ectropion and entropion are distressing problems, although most cases are self-limited. Ectropion is defined as the eversion of an edge or margin. Lower eyelid malpositions are graded mild when there is slight eversion of the cilia inferiorly with or without scleral show, moderate when the lid margin is everted with lower eyelid descent and scleral show, and severe when frank ectropion is present. Mild and moderate ectropion usually resolve over time with gentle massage of the lid. However, severe ectropion may require surgical correction.[33]

Specialized structures of the eyelids protect the eyes from exposure to the elements. Numerous oils, mucus, and tear glands are present within the tarsal-conjunctival mucous lining of the upper and lower eyelids. Blinking distributes this complex three-layer tear film over the surfaces of the eyes to protect them. Thus, chronic ectropion can result in exposure keratinization of the conjunctiva, which can contribute to ocular irritation and eventually lead to vision loss.

The incidence of ectropion in association with a transconjunctival approach to the infraorbital rim has been reported to range from zero to 6.7%.[34,35] When a subciliary approach is used, the incidence of ectropion ranges from 12% to 42%.[34,36-38]

Entropion is defined as an inversion or turning inward of an edge. It is usually symptomatic, with eye discomfort to the point of pain, tearing, photophobia, discharge, secondary infection, and various degrees of corneal surface breakdown (with visual loss). Occasionally, the lid is inverted so much that the lashes are tucked down into the fornix, but the eye is not particularly uncomfortable. Entropion that does not resolve spontaneously may require surgical correction.[33] However, frequent use of lubricating eye ointment and taping the lid into a relatively normal position may serve as effective temporary palliation.

Persistent Diplopia

Binocular diplopia is a common complication of zygoma fractures involving the orbit.[39] This complication may be temporary or may become permanent if not treated. When binocular diplopia is present initially after a zygomatic fracture, it is most likely due to edema or hematoma of one or more extraocular muscles or their nerves, as well as to intraorbital edema or hematoma. In such cases, resolution of diplopia after fracture treatment (if necessary) usually occurs spontaneously within 5 to 7 days (i.e., the time required for the initial edema or bleeding to disappear and resorb).

Diplopia can also be caused by muscle entrapment, but this cause is usually evident on clinical examination with a forced duction test or by simple examination of extraocular movements (Table 9-1). The forced duction test involves placing a drop of local anesthetic in the cul-de-sac of the lower lid, using a pair of toothed forceps to grasp the tendons of the appropriate rectus muscles and attempting to passively rotate the globe away from the restriction (Figure 9-18). Limitation of motion is not invariably an indication of entrapment; it can also be caused by orbital edema or hemorrhage. Conversely, the absence of resistance can indicate a neurologic deficit or a large nonrestrictive defect in the orbital floor. However, positive test results are much more likely with a "trap-door" injury. This cause of diplopia necessitates immediate exploration and reduction of herniated orbital tissue.

The cause of persistent diplopia is not known, but it has been postulated that post-traumatic fibrosis of the extraocular muscles results in residual diplopia after therapy.[40] The timing of treatment for diplopia is controversial. There is no debate that a displaced zygoma causing diplopia should be treated, nor is there controversy surrounding the need to reconstruct a large orbital floor defect with damage to the Lockwood ligament, which results in an inferior

TABLE 9-1 Eye Muscles with Their Actions and Innervation

Muscle	Origination	Insertion	Innervation	Function
Medial rectus	Margin of optic foramen	Sclera	CN III	Medial
Inferior rectus	Margin of optic foramen	Sclera	CN III	Inferior and medial rotation
Lateral rectus	Margin of optic foramen	Sclera	CN VI	Lateral
Superior rectus	Margin of optic foramen	Sclera	CN III	Upward and medial rotation of the eye
Superior oblique	Margin of optic foramen	Lateral/posterior globe	CN IV	Downward and lateral
Inferior oblique	Medial aspect of orbital floor	Inferior to the lateral rectus	CN III	Upward and lateral

repositioning of the globe. It is also commonly accepted that a trap-door injury or any physical restriction of movement should be corrected as early as possible.

The issue is whether to perform surgery on marginal cases when diplopia resolves slowly with simultaneous evidence of a cosmetic deformity. The possible resolution of diplopia can be hastened by the administration of steroids for 5 to 7 days; the use of this method can indicate whether the diplopia is caused by edema or by hemorrhage of the orbital muscle or fat.[41]

CT scans using 2-mm coronal cuts of the orbit demonstrate entrapment of the inferior rectus muscle and can aid in differentiating between contused and entrapped extraocular muscles. A contused muscle appears round on the scan; the normal muscle appears flat. In the case of possible muscle entrapment, the results of a forced duction test provide evidence of the need to explore the orbital floor.

Once the decision has been made to manage diplopia surgically, the goals are to prevent herniation of orbital contents, to provide a smooth orbital floor with or without an implant, and to reconstruct the floor or wall to mirror the contralateral side as closely as possible.

Traumatic Optic Neuropathy

Traumatic optic neuropathy is a rare but devastating cause of partial or complete loss of visual function after head injury. The incidence of traumatic optic neuropathy ranges from 2% to 20%.[6,12,39,42-49] It may manifest itself as conditions ra

ass
caused by projectiles, stab wounds, or bone fragments. The prognosis for this type of injury is poor. Indirect injuries result from deforming forces applied to the bony orbit, or by motion of the globe, in which the optic nerve absorbs energy concentrated at the orbital apex. This type of injury occurs when there is no evidence of a penetrating wound and the patient has suffered blunt frontal trauma. The most common site of indirect injury is believed to be the intracanalicular segment of the nerve.[50] Recovery of vision following traumatic optic neuropathy resulting from indirect injury is more likely than for that resulting from direct injury, and visual recovery can occur with or without treatment.[51]

Assessment for traumatic optic neuropathy involves a detailed ocular examination, including pupillary size and response to light, visual acuity, and fundoscopic examination. The presence of a Marcus Gunn pupil (afferent pupillary defect) with normal results from a fundoscopic examination is diagnostic for afferent optic nerve injury.[52] The sluggish pupil in reaction to light is often characteristic of progressive optic nerve injury. Identifying malfunctioning pupils is important because the initial measurement of the relative afferent pupillary defect predicts the final visual outcome.[53,54] When the patient cannot perceive light, the visual prognosis is poor.[51,54,55]

In addition to the clinical examination, computed tomography is crucial in demarcating the location of the injury; it enables assessment of the optic nerve, the optic canal, and any intracranial lesions that may cause a deficit in vision.[56]

The appropriate treatment for patients with traumatic optic neuropathy remains controversial. Options include observation, corticosteroids administered at various doses, and decompression of the optic canal.[52,57-62] The International Optic Nerve Trauma Study found that 57% of patients receiving no treatment experienced improvement by three or more lines of visual acuity.[54] The occurrence of spontaneous improvement in many patients makes it difficult to assess the effectiveness of any treatment method, and some authors have reported no statistically significant improvement in outcome with steroid use.[63] Optic nerve decompression has been performed when no improvement is seen after medical management, if radiographic evidence of canal impingement exists, or if the patient has very poor vision.[64-66]

Malunion of Zygomatic Fractures

A malunion of the zygoma will often result in cosmetic deformity from a malposition of the malar eminence, as well as diplopia secondary to malposition of the globe (Figure 9-19). Correction of these problems can be attempted by either augmentation or osteotomy. The most commonly used materials



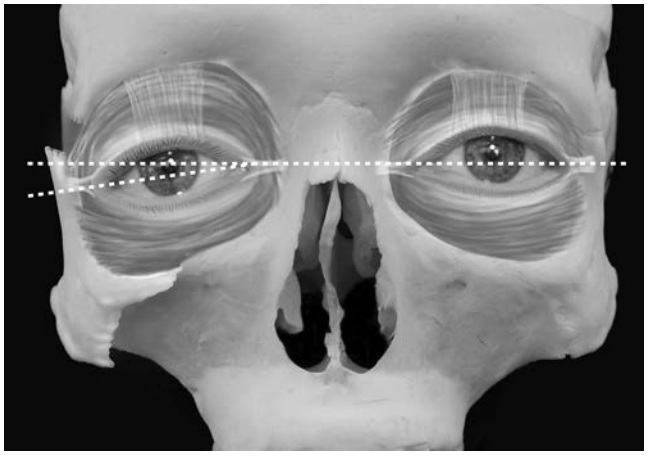
• **Figure 9-18** **A-B,** Forceps grasping the sclera above the inferior rectus attachment. **C-D,** Forced duction test showing unrestricted superior movement of the patient's eye.

for augmentation are Silastic, porous polyethylene, autogenous bone (calvarial), and hydroxyapatite-based materials. A corrective osteotomy should be performed as early as possible, before the fracture sites have healed and obscured the proper position of the fractured segments.

Two principal considerations are involved in addressing a malunion. If a functional deformity exists, a corrective osteotomy should be considered. An example of such a case is a malposed zygoma resulting in enophthalmos, diplopia, or both, or obstruction of the normal excursion of the coronoid process. If the deformity results in a cosmetic defect without a functional deficit, camouflaging the defect may be prudent. For example, if a malposed zygoma results in minimal zygomatic projection, an onlay graft using alloplastic or autogenous materials may be preferable to a corrective osteotomy.

Late-Onset Post-traumatic Enophthalmos

Enophthalmos is defined as recession of the globe within the orbit. Enophthalmos can result from an absolute reduction



• **Figure 9-19** Illustration of orbital dystopia and malar eminence malposition related to zygoma position.

of orbital tissue, a relative reduction of tissue, or both. Factors such as scarring and atrophy of orbital soft tissue (i.e., fat) are considered absolute reductions of orbital tissue, whereas bony displacement resulting in displacement of orbital soft tissue is considered a relative reduction of tissue. Specifically, post-traumatic enophthalmos has been attributed to atrophy of orbital intermuscular fat, enlargement of the bony orbit, dislocation of the trochlea, cicatricial contraction of the retrobulbar tissues, unrepaired fractures of the orbital wall, and displacement of the orbital tissue.

Whitehouse and others have found that fat atrophy is not responsible for any alteration in orbital volume and is unchanged after trauma.[67,68] Rather, it has been determined that fat loss rather than fat atrophy plays the predominant role in traumatic enophthalmos. Orbital floor disruption in the face of an intact orbital periosteum (Lockwood ligament) does not result in displacement of the globe. Failure to reconstruct the orbital walls results in disruption of the orbital ligaments; such disruption causes the anterior support of the globe to be weakened and results in enophthalmos. Maxillofacial trauma resulting in enlargement of the orbital cavity, in combination with disruption of ligaments and intraconal compartments, is considered to be the principal cause of enophthalmos.[67,69-72] In summary, three basic mechanisms occur singly or in combination to cause post-traumatic enophthalmos: an increase in the size of the orbit, a decrease in orbital contents, and a disruption of the ligamentous structures of the globe.

Post-traumatic enophthalmos is relatively uncommon; it occurs in only 4% to 9% of patients with midfacial fractures. Patients with pure orbital blowout fractures or those who have residual enophthalmos after surgical reduction of simple fractures of the zygomatic complex are normally seen 3 to 4 weeks after the injury or the procedure, when the edema masking the enophthalmos has resolved and the residual defect has become apparent.[6,73] Enophthalmos may have functional consequences, including gaze-evoked diplopia, eyelid retraction, lagophthalmos, and exposure keratitis.

Physical findings suggestive of enophthalmos include a deeper eyelid sulcus, eyelid position, eyelid asymmetry, or smaller eye. Complete examination of the globe for gross injuries, changes in visual acuity, and decreases in extraocular muscle function with a forced duction test are essential. A exophthalmometer is used to determine the degree of enophthalmos. A measurable difference of 2 mm or less in the relative position of the globes is normal; a difference of 3 mm is usually detectable by others and is considered abnormal.[74,75] In addition, patients with measurements of less than 3 mm have been shown to be satisfied with their appearance.[76] Therefore, enophthalmos with a measurement of 3 mm or more is an indication for surgical repair.

Many researchers have attempted to relate the amount of enophthalmos to the degree of bony displacement.[77,78] Manson and associates carried out extensive studies evaluating globe position as determined by the content and relationship of intracoronal and extracoronal orbital fat.[69] They found that intracoronal fat found intramuscularly was separated from extracoronal fat by fine ligaments. Intracoronal fat is found almost exclusively posterior and proximal to the orbital wall, because that is the location of the extraocular muscles. Extracoronal fat is primarily found anteriorly. Most of the fat along the orbital floor is extracoronal and anterior to this axis. Its removal results in a supratarsal deficiency but no posterior displacement of the globe. However, because most of the lateral orbital wall is behind this axis, displacement of this osseous segment increases the orbital volume exponentially and creates excessive volume expansion within the orbit and resultant enophthalmos, as well as loss of intracoronal fat. Comminuted fractures of the lamina papyracea on the posterior floor also lie behind the global axis, which extends from the lateral orbital rim to the anterior portion of the lacrimal bone. Intracoronal fat is found primarily behind the axis, and its loss is also crucial to the development of enophthalmos. Therefore, enophthalmos results from an increase in bony orbital volume by displacement of the medial orbital wall, posterior floor, or lateral orbital wall and is less likely to be related to defects in the inferior orbital floor.

Enophthalmos is treated by decreasing the orbital volume with osteotomies, or increasing the volume of orbital tissue with bone grafts, cartilage grafts, or alloplastic implants. If the degree of enophthalmos is severe, a combination of these methods can be used.[79-85]

Retrobulbar Hemorrhage

Retrobulbar hemorrhage is an ophthalmologic emergency resulting in increased intraocular pressure with ophthalmic artery compromise and loss of vision due to retinal ischemia. The cause of retrobulbar hematoma is trauma, either iatrogenic or trauma in general.[86-91]

The anatomic boundaries of the orbit, its rigid bony walls, and its inflexible anterior limit (orbital septum and eyelids), combined with hemorrhage into the retrobulbar space, result in soft tissue expansion leading to anterior displacement of the globe and septum. As the elastic limits of the septum are reached and bleeding continues, the orbit

becomes a closed, nonyielding space. The orbital and intraocular pressures increase, and these pressures cause compression of orbital structures and ischemia of the globe and optic nerve; the ultimate result can be blindness.[86] This condition is known as orbital compartment syndrome.

When the orbital intraocular pressure is not dangerously high, the condition can be managed medically with topical treatments, systemic carbonic anhydrase inhibitors, and oral or intravenous osmotic agents. Intravenous acetazolamide 500 mg and hydrocortisone 100 mg can be administered; alternatively, a rapid infusion of 20% mannitol can be used. If vision does not improve rapidly, within 30 to 45 minutes, surgical measures should be considered.[86]

However, when orbital pressures are extremely high and profound visual compromise is obvious, medical measures are not sufficient to rapidly reduce the orbital pressure. In this situation, an emergent canthotomy and cantholysis are necessary. If decompression is carried out within 2 hours of the onset of symptoms, it is likely to be successful in avoiding permanent damage.[92,93] Ophthalmology consultation is strongly recommended.

Three-Dimensional Computerized Navigation

In recent years the imaging precision of three-dimensional (3D) computerized scans combined with advancements in computer software have allowed for more anatomic reduction of mid-face and orbital fractures. These 3D navigation and planning platforms have allowed for more accurate restoration of orbital volume, and the subsequent mitigation of complications such as enophthalmos, diplopia, and limitations on extraocular movements.[94]

Construction of a computerized 3D model is derived from thin slice (1-2 mm) CT or magnetic resonance images that are loaded in the computer software system.[94] The software then allows examination of the traumatic defect and planning of the surgical reduction. The goal of preoperative planning is to simulate the modifications that will take place operatively and provide the desired anatomically correct outcome.

The software allows for creation of a template for reconstructing the affected side by mirroring the contralateral side (if proper skeletal anatomic positioning is unaffected by the traumatic incident), thus aiding not only in preoperative virtual surgical planning, but also with intraoperative assessment of the reduction. In the case of bilaterally affected patients, more complex segmental manipulation of the model or subvolume CT reference file insertion must be used to achieve the desired template.[94]

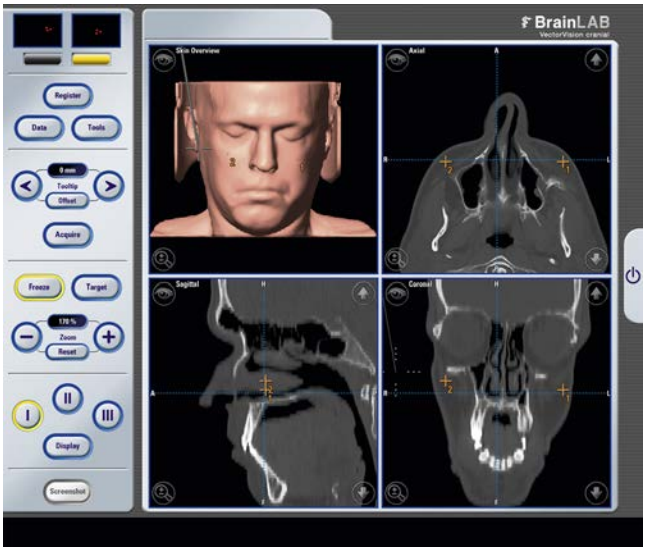
Intraoperative navigation is accomplished by having the 3D computer model registered and calibrated such that the position of the patient on the operating table and the surgical instruments match in their positions displayed on the computer model in real time. This registration can be accomplished by establishing reference points on the CT scan, instruments, and patient (Figures 9-20 through 9-22).



• **Figure 9-20** Navigational system setup.



• **Figure 9-21** Navigational system locator and wand.



• **Figure 9-22** Screen shot of navigational display.

3D computerized navigation can be helpful in avoiding non-anatomic reductions, which can limit the need for secondary reconstructions and associated complications.[91] Although 3D computerized navigation is still in its infancy, excellent results are being produced with satisfactory reconstruction rates approaching 100% with navigation-guided procedures and 85.7% with computer-assisted 3D models, versus 74.3% with traditional surgery.[92]

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10

Diagnosis and Management of Midface Fractures

MOHAMMED AL-OBAIDI, PAUL S. TIWANA

Introduction

The midface is the part of the facial skeleton spanning from the cranial base to the maxillary occlusal plane. This anatomic unit is important both functionally and cosmetically, as it provides support to the globes, sinuses, muscles of mastication and facial expression, and upper dentition. It therefore serves a supporting role in the physiologic function of the ocular, olfactory, respiratory, and digestive systems. Last, the human face remains our window to the world and is how others perceive us. Significant alterations of the form and function of the face secondary to trauma can leave a devastating impact on the daily life of the afflicted patient. Meticulous reduction and stabilization of these fractures is therefore a critical component of successful repair.

Although the epidemiology of facial fractures varies in the literature depending on the institution and population studied, general trends can be noted. Midface fractures occur related trauma.[1-6] There is also a generally higher reported proportion of male patients.[2,4-7] Because of their centralized location within the facial skeleton, midface fractures often present in combination with other facial fractures or as part of panfacial injuries.

This chapter will discuss the diagnosis and management of midface fractures that affect the occlusion, that is, Le Fort type fractures, as well as naso-orbital-ethmoid (NOE) fractures. For the management of injuries such as isolated nasal fractures, zygomatic fractures, and orbital fractures, please see the relevant chapters in this text.

The authors wish to acknowledge Drs. Likith V. Reddy and Matthew Pagnotto for their previous contributions to this chapter.

Midface Anatomy

The midfacial skeleton is centered on the maxilla and its complex articulations with surrounding structures including the palatine, zygomatic, nasal, sphenoid, and ethmoid bones. The maxilla houses the bilateral maxillary sinuses, which expand in size from birth to adulthood and contribute to the inherent structural weakness of the region. The maxillary bones are integral in formation of the superior aspect of the oral cavity, the inferior and lateral walls of the nasal cavity, and the inferomedial aspects of the orbits. Therefore, most midface fractures involve the maxilla to some extent.

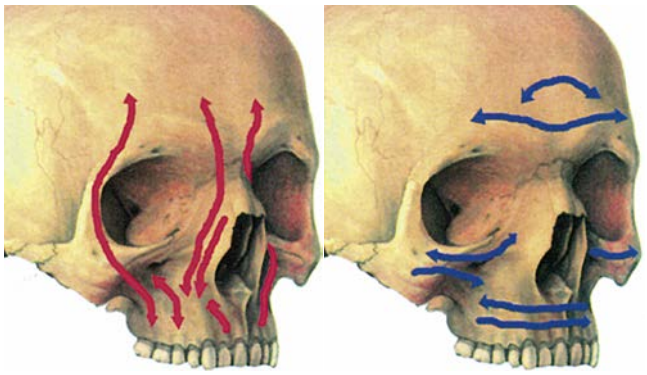
Critical to the management of injuries to the midface is understanding of the skeletal buttresses, vertical and horizontal pillars that provide support and protect vital structures from external forces[8-10] (Figure 10-1). The vertical support of the face is provided by the nasomaxillary (medial), the zygomaticomaxillary (lateral), and the pterygomaxillary (posterior) buttresses, which are most resistant to vertically directed forces. The horizontal buttresses—the supraorbital/frontal bar, infraorbital rims, the zygomas, and maxillary alveolus—are weaker but provide some resistance to horizontally directed forces. The weakest protection is available from the thin sagittal buttresses provided by the maxillary walls, palate, lateral nasal walls, and the nasal septum.[11] Areas of thin bone between this framework, as well as the paranasal sinuses, create anatomic sites of weakness that result in reasonably predictable fracture patterns.

Although the buttresses, just described, have been given varying names and definitions in the literature, it is critical to recognize their significance, as outlined in Box 10-1.[12]

Classification of Midface Fractures

Midface or middle third fractures include nasal fractures, orbital fractures, naso-orbital-ethmoid fractures, zygomatic and zygomaticomaxillary complex fractures, Le Fort fractures, palatal fractures, and maxillary dentoalveolar fractures.

Many classification schemes have been suggested for different midface fractures. The classic Le Fort system for maxillary fractures, first published in 1901, categorized fractures based on common patterns.[13] Rene Le Fort originally



• **Figure 10-1** Classically depicted vertical *(left image)* and horizontal *(right image)* buttresses of the facial skeleton.

• Box 10-1 Buttresses of the Facial Skeleton: General Concepts

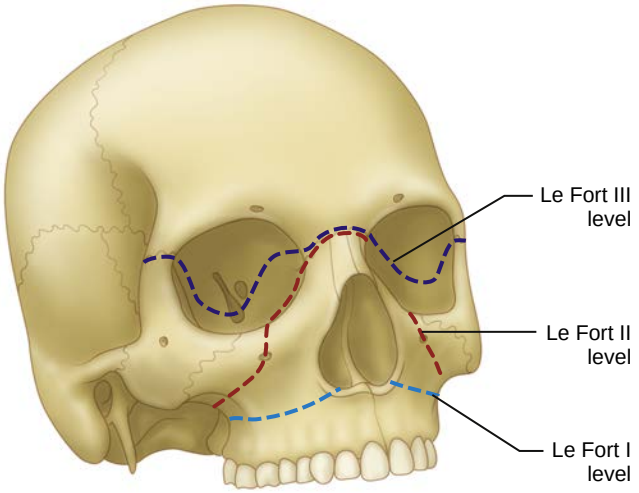
The buttress concept allows improved appreciation of facial structure.
Buttresses provide sufficient bone thickness to accommodate metal screw fixation.
All buttresses are linked directly or indirectly to the cranial base as a stable reference point.
Reduction of transverse buttresses restores facial profile and width; reduction of vertical buttresses restores facial height.
Reduction of the buttresses restores functional support to the teeth and globes.

Hopper RA, Salemy JD, Sze RW: Diagnosis of midface fractures with CT: what the surgeon needs to know, *RadioGraphics* 26:783-793, 2006.

studied these patterns on cadaver skulls subjected to external frontal forces and described three lines of least resistance or the "linea minoros resistentiae." These were subsequently adopted as the Le Fort I fracture, the Le Fort II fracture, and the Le Fort III fracture (Figure 10-2). Although this scheme has been prized as a simple and systematic method to diagnose and treat midface fractures, it is well recognized that most high-energy injuries today do not follow these patterns.

The Le Fort type I fracture pattern results from a force directed above the maxillary teeth, resulting in a separation of the palate. The Le Fort type II fracture pattern results from a force delivered at the level of the nasal bone, resulting in mobility and separation of the midface "pyramid." The Le Fort type III fracture pattern results from a force directed at the orbital level, resulting in a craniofacial dysjunction or separation of the entire middle third of the craniomaxillofacial skeleton from the skull base.

Other classification systems have been suggested to better describe midface fractures, citing the inadequacies of the Le Fort system. The system of Donat and colleagues is based on the facial vertical buttresses and horizontal beams and uses clinical and radiographic findings to describe the fracture pattern along 11 unilateral and 22 bilateral sites.[14] Although they have shown that this system can improve accurate diagnosis and communication, many surgeons find



• **Figure 10-2** Le Fort classification of midface fractures. (From Baghe ri S: *Current therapy in oral and maxillofacial surgery*, St Louis, Mosby, 2012.)

it to be too complicated. Manson elaborated on the Le Fort classification by defining the level of highest fracture, the pattern of the segment of the maxilla carrying the dentition, and associated fractures.[15] Nevertheless, the original Le Fort classification system has to date remained the most popular and is discussed, along with palatal and naso-orbital-ethmoid fractures, in the following respective sections. Classification of other facial fractures is discussed in their respective chapters.

Diagnosis of Midface Fractures

Physical Examination

Initial evaluation of the severely injured midface begins with applying the principles of advanced trauma life support (ATLS). In assessing midfacial injuries in the emergency setting, the airway and cervical spine deserve particular attention. If the airway is compromised, a definitive airway must be established with intubation or surgical intervention. Care must be taken if endotracheal intubation is attempted, as cervical spine injuries occur in as many as 9.6% of patients with facial fractures.[16] Surgical tracheostomy or cricothyroidotomy is preferred if intubation cannot be achieved with in-line immobilization of the cervical spine.[17]

Once the patient is stabilized, assessment of the midface is carried out as part of the comprehensive facial examination. The complete facial examination is a systematic evaluation of all structures from the dura to the pleura and is beyond the scope of this chapter.

Thorough inspection of the face should be carried out and any areas of edema, ecchymosis, abrasions, lacerations, hemorrhage, and gross deformities noted and documented (Figure 10-3). Otorrhea or rhinorrhea should raise suspicion of cerebrospinal fluid (CSF) leakage, and packing should be avoided initially to prevent retrograde infection resulting in meningitis.

Palpation of the entire craniomaxillofacial skeleton is performed in a systematic manner to assess for step-offs,



• **Figure 10-3** Patient presenting after a motor vehicle crash. After the airway has been secured and the patient is stabilized, a full maxillofacial examination is completed. Note diffuse edema, ecchymoses, a large laceration, and a flat, rounded appearance, all suggestive of a severe midface fracture.

mobility, crepitus, or irregular segments. The surgeon begins palpation at the frontal bone and supraorbital rims and progresses downward along the facial skeleton, to evaluate the zygomas, maxilla, and mandible.

Attention should be paid to the periorbital regions, and a full ocular examination is performed. Extensive periorbital edema and ecchymosis are the first signs of orbital trauma. The globes should be evaluated for proptosis, extraocular muscle movement, and pupillary size and reactivity to light. Visual acuity and fundoscopic examination are also warranted. Ocular injury is commonly present in midface trauma patients. In one study of midface fractures with orbital injury, 90% of patients were found to have an ocular injury to some degree.[18] Patients with naso-orbital-ethmoid fractures are at significant risk of concomitant ocular injury and subsequent loss of vision, reported in 30% of patients in one series.[19] It is therefore prudent that all patients with facial fractures involving the orbit receive ophthalmologic evaluation.[18,19]

Evaluation of the lacrimal drainage apparatus and the medial canthal tendon are important parts of the evaluation for naso-orbital-ethmoid fractures. Detailed description of the bimanual examination and traction tests for the medial canthal tendon are presented in the NOE section below. Measuring the intercanthal distance is also an important part of assessing for naso-orbital-ethmoid fractures.

Evaluation of the maxilla for midface fractures is assessed by firmly grasping the pre-maxilla and attempting to displace it in three dimensions. Ecchymosis and laceration of the vestibule or palate are common findings with fractures of the maxilla. A malocclusion may be noted, and widening of the maxilla may be indicative of a palatal fracture.

Imaging

Prior to advancements in radiologic modalities, plain radiography was employed for assessing the midface. However, with current technology there is no longer a role for plain radiography in the evaluation of midface fractures. Computed tomography (CT) has become the modality of choice for evaluation of these injuries, and current multidetector CT techniques allow for excellent detection of fractures and patterns of injury[20] (Figure 10-4). Multiplanar high-resolution images are easily and quickly obtained and often can be reformatted to generate three-dimensional (3D) images. Thin cuts of 1.0 to 2.0 mm show adequate anatomic detail to demonstrate most facial fractures. Conversely, caution is advised when interpreting 5 mm or higher cut CTs, as fractures can be missed.

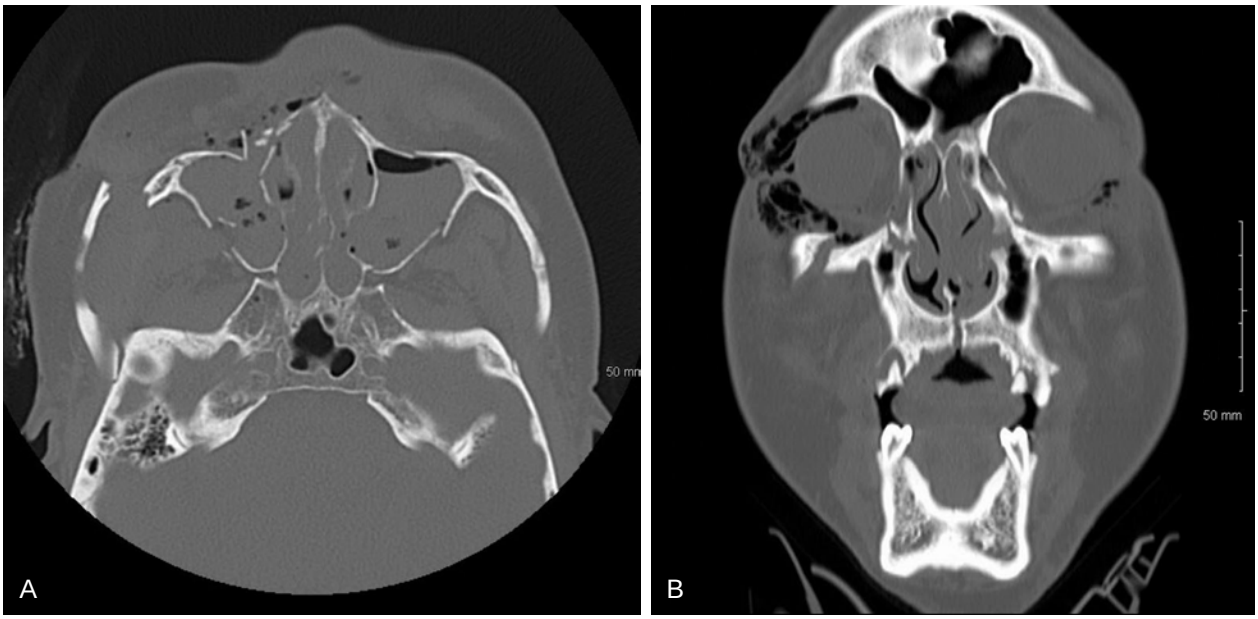
The role of 3D reformatted CT has been investigated. Previously it was reported to be inferior to 2D CT but useful in severe complex fractures.[21,22] With continued improvement in availability and technology, 3D CT is being used more often and is commonly employed in combination with 2D CT (Figure 10-5). However, because of artifact during the reformatting process, 3D CTs have decreased ability to detect nondisplaced fractures, inadequate soft tissue evaluation, and difficulty detecting deeper fractures.[23] Therefore, the authors recommend against relying solely on 3D CT images for diagnosis and treatment of midface fractures.

The use of magnetic resonance imaging (MRI) for the evaluation of facial fractures is not common, as bony trauma is better examined with CT. MRI can be used as an adjunctive modality when intracranial injury or unusual soft tissue injuries are suspected. MRI is also helpful for evaluation of cranial nerve deficits.[23] Similarly, ultrasound has not gained popularity in the acute facial trauma evaluation. Although it is noninvasive, inexpensive, safe, and fast, ultrasound will fail to demonstrate facial fractures with adequate accuracy. It has been employed, however, in certain clinical situations as an adjunct.[24]

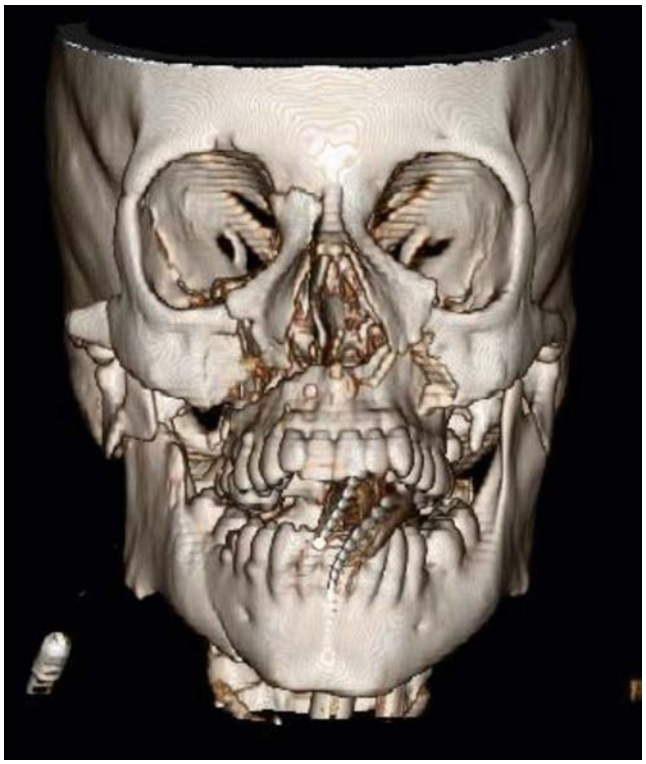
Le Fort Fractures

Introduction

The Le Fort classification of midface fractures has been in use for over a century. Several additional attempts have been made to describe and classify midface fractures since that time.[14,15,25,26] However, this system remains the simplest and most widely recognized classification.



• **Figure 10-4** Two-dimensional computed tomographic images in **(A)** axial and **(B)** coronal views allow for accurate diagnosis of complex fractures. **A** is consistent with a left Le Fort II and right Le Fort III with a posteriorly impacted maxilla. **B** demonstrates a bilateral Le Fort II fracture with a concomitant sagittal palate fracture.



• **Figure 10-5** 3D CT reformatting shows excellent visualization of the pattern of injury and degree of displacement. This image depicts a complex midface fracture pattern with Le Fort I, II, and III levels.

Knowledge of the skeletal buttresses previously described and their involvement is a necessary part of the management of these fractures. Accurate diagnosis and identification of all fracture lines is important for the determination of stable and unstable bony landmarks. Furthermore, all Le Fort fractures affect the position of the maxillary alveolar ridge and thus affect the occlusion. Therefore, adequate management of Le Fort fractures centers around reestablishing the skeletal buttresses and the pre-injury occlusion.

Anatomy

Le Fort fractures involve several of the bones that make up the midface skeleton, including the maxilla, palatine bones, pterygoid plates of the sphenoid, zygomas, nasal bones, frontal bone, ethmoid, and vomer. As has been discussed earlier, the skeletal buttresses of the midface are often fractured and are key to achieving satisfactory results. These include the nasomaxillary, pterygomaxillary, and zygomaticomaxillary vertical buttresses, and the infraorbital rim, zygomas, and maxillary alveolar horizontal buttresses. Failure to reestablish these buttresses will invariably lead to inadequate midface height, width, and projection, resulting in a short, wide face.

rior and posterior ethmoidal arteries. Branches of the maxillary artery include the descending palatine, sphenopalatine, infraorbital, and superior alveolar arteries.

Neurosensory supply is via the second division of the trigeminal nerve. This nerve exits the infraorbital foramen and supplies the lateral nasal, superior labial, and inferior palpebral regions as well as the labial mucosa and anterior teeth. The infraorbital neurovascular bundle is often encountered with adequate exposure and should be protected.

Classification

patients often present with fractures of different levels, asymmetries, comminution, and additional facial fractures. Patients with more complex fractures are more likely to have coexisting secondary facial fractures and other traumatic injuries.

The Le Fort I fracture is a horizontal fracture caused by a force delivered above the apices of the maxillary teeth. It extends through the pyriform aperture of the nose anteriorly and the pterygoid plates posteriorly. It involves the lateral nasal wall (medial maxillary sinus wall) and the anterior and lateral maxillary sinus walls. Simply stated, a Le Fort I fracture is the separation of the palate from the rest of the maxilla (Figure 10-6).

The Le Fort II fracture is a pyramidal fracture that involves separation of the central midface from the cranial base. It extends from the pterygoid plates and zygomaticomaxillary suture through the infraorbital rims and ends at the nasofrontal suture (Figure 10-7). The zygomas and lateral aspects of the orbits are intact with Le Fort II fractures. Le Fort II fractures are usually indicative of a more severe injury and have been found to be significantly associated with intracranial injuries and increased mortality.[27]

The Le Fort III fracture is described as full craniofacial dysjunction, in which the entire midface is separated from the cranial base. Superiorly the fracture extends across the nasofrontal suture, the medial and lateral orbital walls, and the zygomaticofrontal sutures. Posteriorly it extends across the pterygoid plates and the posterior maxilla. Laterally it extends through the zygomatic arches (Figure 10-8). A pure Le Fort III fracture represented approximately 9% of midface fractures in one series.[28] Generally, the majority of Le Fort III fractures are a combination of Le Fort I, II, zygomaticomaxillary complex, and naso-orbital-ethmoid fractures. Additionally, Le Fort III fractures are also associated with serious intracranial injuries.[27]

For all Le Fort fractures, the nasal septum and palate may additionally be fractured. Palatal fractures have been classified by Hendrickson and colleagues as six types of fractures based on fracture pattern[29] (Figure 10-9):

Type I: alveolar
Type II: sagittal
Type III: parasagittal
Type IV: para-alveolar
Type V: comminuted/complex
Type VI: transverse

Type III fractures are the most encountered pattern as the parasagittal bone of the palate is thinner than the midsagittal buttress. Park and Ock presented an alternative scheme for classification of palatal fractures based on the required treatment plan.[30]



• **Figure 10-6** Le Fort I fracture. Note the fracture of the palate from the midface.



• **Figure 10-7** Le Fort II fracture. Note the pyramidal shape of the fractured maxillary segment.

Diagnosis

As with all facial traumatic injuries, a thorough clinical and radiographic examination is required. A systematic clinical evaluation of all portions of the face is carried out, with inspection and palpation of the facial skeleton and supportive structures. Edema, ecchymosis, abrasions, and lacerations should be noted. All bony projections and articulations should be palpated for any steps, mobility, or crepitus, which may indicate a fracture. An

ocular examination should assess visual acuity, pupil size and reactivity, and extraocular muscle movement. Extraocular muscle limitation and binocular diplopia may be indicative of an orbital fracture. Additional concomitant ocular injuries should be sought for, and findings such as monocular diplopia, hyphema, or anisocoria should raise suspicion for a globe injury. Most agree that patients with orbital trauma should have an ophthalmologic evaluation when possible.

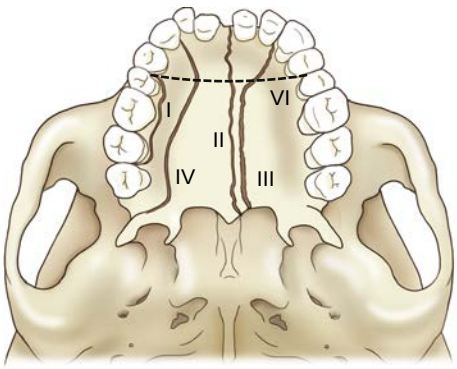
Le Fort I fractures often have subtle clinical findings. Malocclusion and maxillary mobility are the most consistent findings. Muscle pull from the lateral and medial pterygoid muscles displaces the fractured maxilla backward and downward, which is clinically evident as an anterior open bite (Figure 10-10). Manual assessment of mobility involves placing an index finger and thumb posteriorly on the bony segment of the maxillary arch and attempting movement in three dimensions. Alternately, the thumb and index finger may grasp the anterior palate to attempt movement. Eliciting pain on palpation and on occlusion are also consistent findings. Palatal fractures can be assessed with manual attempts to transversely widen or collapse the maxillary arch. Palatal ecchymosis can also be indicative of a sagittal or parasagittal palatal fracture.

A Le Fort II fracture will usually be associated with more extensive soft tissue edema. Attention should be paid to the nasal bridge, the orbital rims, and the maxilla. Intraoral findings are similar to evaluation for a Le Fort I fracture. Additionally, mobility and step-offs may be encountered at the infraorbital rims and the nasal bridge, with overlying edema and ecchymosis. Bilateral periorbital edema and ecchymosis, known as "raccoon eye sign," is concerning for orbital fractures. Manipulation of the maxilla may elicit palpable mobility at the nasofrontal junction and infraorbital rims. Epistaxis is very common, and CSF rhinorrhea may be present when a dural tear at the skull base is involved. Hypoesthesia of the infraorbital nerve is also very common because of edema and direct trauma to the nerve.

Le Fort III fractures require a greater amount of force and therefore will be associated with additional cranial, orbital, and facial injuries. In addition to the findings described for Le Fort II fractures, Le Fort III fractures will elicit mobility at the zygomaticofrontal and nasofrontal sutures on manipulation of the maxilla. However, because of the frequent comminution and additional fracture patterns, this may not be present. Cranial base injury with CSF leakage from the nose (rhinorrhea) or ears (otorrhea) is assessed clinically, and any suspicious drainage should be tested with a simple halo test at bedside. This involves the use of a white paper towel to assess the spread of the dropped fluid. The more viscous blood will remain in the center, and CSF will spread more widely, creating a positive halo sign. Additional signs indicative of skull base fractures include "raccoon eyes" and Battle sign, which is ecchymosis overlying the mastoid process.



• **Figure 10-8** Le Fort III fracture. Note complete disarticulation of the facial skeleton from the skull base.



• **Figure 10-9** Hendrickson classification of palatal fractures.



• **Figure 10-10** Classic anterior open bite associated with a Le Fort fracture. Traumatic impaction of the maxilla and backward and downward pull of the pterygoid muscles contribute to this finding.

Radiographic examination for midface fractures is best accomplished with thin-cut (1.0 to 2.0 mm) CT with a minimum of axial and coronal sections. Additional information can sometimes be obtained from 3D CT reconstruction, which may aid in treatment planning. Attention should be paid to the skeletal buttresses and the posterior region of the maxilla and pterygoid plates (Figure 10-11).

A systematic clinical and radiographic evaluation of the facial skeleton allows the clinician to accurately diagnose Le Fort fractures. Often the patient has multiple fracture patterns and different fracture levels bilaterally. Treatment should not begin without adequate knowledge of the fracture diagnosis and classification.



• **Figure 10-11** Axial CT scan of a Le Fort III fracture demonstrating fractures through the pterygoid plates and the zygomatic arches bilaterally. All Le Fort fractures will demonstrate fractures at the posterior buttress through the posterior maxilla or pterygoid plates.

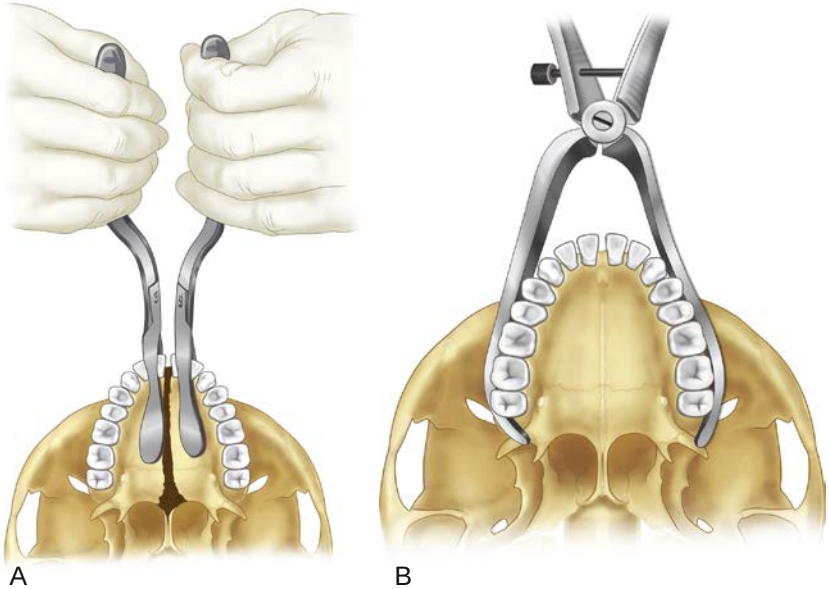
Treatment

General Considerations

Timing of repair of Le Fort fractures is somewhat controversial. Some surgeons have previously advocated early or immediate treatment. However, concomitant neurosurgical trauma and other injuries may come into play, and treatment is recommended once the patient is stabilized and edema from the initial insult has subsided. Nevertheless, ideal management is best performed within 10 to 14 days.[31,32] After this time period it may become exceedingly more difficult to adequately disimpact the maxilla and achieve optimal soft tissue drape.

Le Fort I Fractures

Treatment of an isolated Le Fort I fracture begins with adequate exposure via a maxillary vestibular incision and dissection of the fracture segments. Mobilization of the maxilla may be necessary, especially in the case of a delayed treatment. A Rowe maxillary disimpaction forceps or a Hayton-Williams forceps may be used to achieve adequate mobilization and reduction (Figure 10-12). A word of caution must be noted when using forceps to reduce midface fractures; the injudicious use of force when using these instruments can cause further fractures of the maxilla and skull base as well palatal and nasal mucosal tearing. Alternative instruments include Tessier maxillary mobilizers or a towel clamp in the anterior nasal spine region. The patient's occlusion is then reestablished by applying maxillomandibular fixation. At this point the maxillomandibular complex is positioned for fixation, with care taken to ensure the condyles are seated in the glenoid fossae and the vertical dimension of the face is correct. Once adequate position is achieved with the condyles seated, four-point rigid internal fixation is used to maintain the maxilla in a position to



• **Figure 10-12** Disimpaction of the maxilla: **A,** Rowe maxilla disimpaction forceps. **B,** Hayton-Williams forceps. (From Fonseca RJ, Barber HD: *Oral and maxillofacial trauma*, ed 4, St Louis, Saunders, 2013.)

resist translational and rotational movement in all dimensions. Typically, miniplates are placed onto the zygomaticomaxillary buttresses and along the pyriform rim bilaterally (Figure 10-13). Maxillomandibular fixation can be released and the occlusion rechecked.

Although closed reduction with maxillomandibular fixation remains a viable treatment option, its postoperative

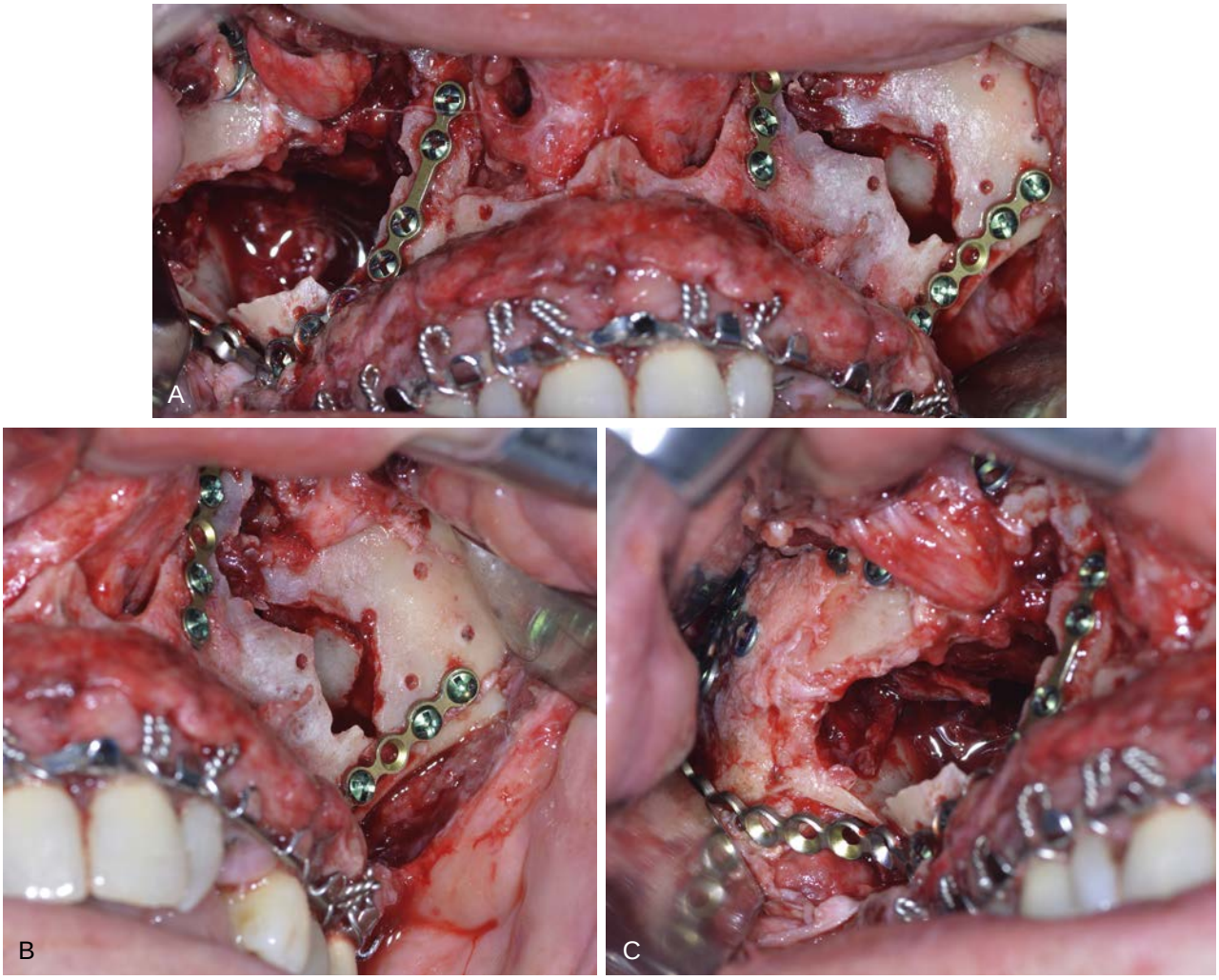
Le Fort II Fractures

oral vestibular incision. However, for the majority of these fractures, displacement of fractures at the infraorbital rim, nasofrontal region, or orbital walls requires additional exposure through other incisions. A coronal incision is a viable option in cases where multiple sites of fixation are required, and provides the additional advantage of exposure of the cranial vault for graft harvest. Commonly access through the infraorbital rim is needed, and exposure can be achieved with any of several incisions including transconjunctival, subciliary, subtarsal or "mid-lid," and infraorbital incisions.

Once adequate exposure of the fracture lines is achieved, the maxilla is mobilized and maxillomandibular fixation is (Figure 10-14). Additional points of fixation are needed based on the fracture pattern and comminution. When comminution limits the ability to reestablish vertical facial height using anatomic bony reduction, the surgeon fixates the maxilla at a position that allows approximately 2 mm of incisor show at repose.

Le Fort III Fractures

Le Fort III fractures require a more complicated surgical treatment. As stated previously, they are often found to coexist with other facial fractures and varying patterns of complexity and comminution. A Le Fort III fracture can be thought of

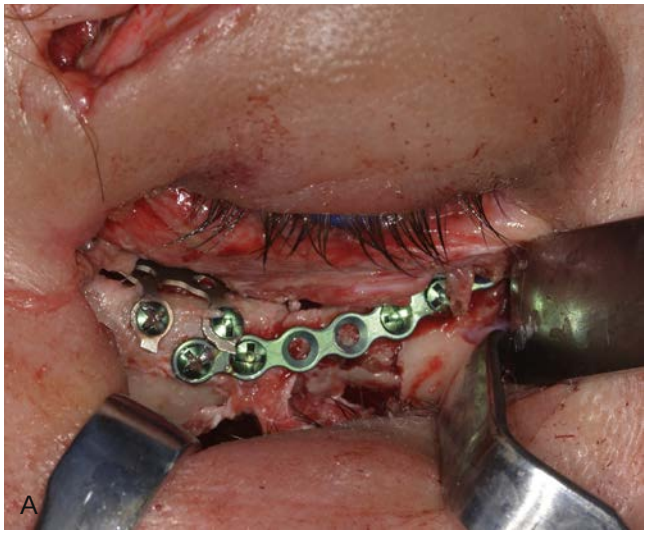


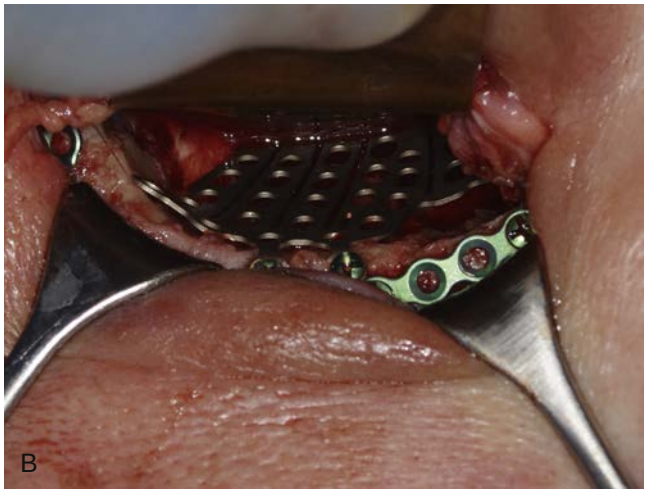
maxillary and nasomaxillary buttresses. Note significant comminution of the right maxillary sinus. **B,** Close-up of left side. **C,** Close-up of right side.

as a combination of bilateral Le Fort I/II, zygomatic, and naso-orbital-ethmoid fractures.[33] As such, the same principles apply to management of these fractures. Marciani and Gonty summarized the four factors contributing to successful management of complex craniomaxillofacial fractures. These are early definitive treatment; anatomic and functional repair of naso-orbital-ethmoid injuries; wide exposure of fractured segments; and anatomic repositioning and stable fixation in all planes.[34] A coronal incision is almost always necessary for adequate exposure for Le Fort III fractures (Figure 10-15).

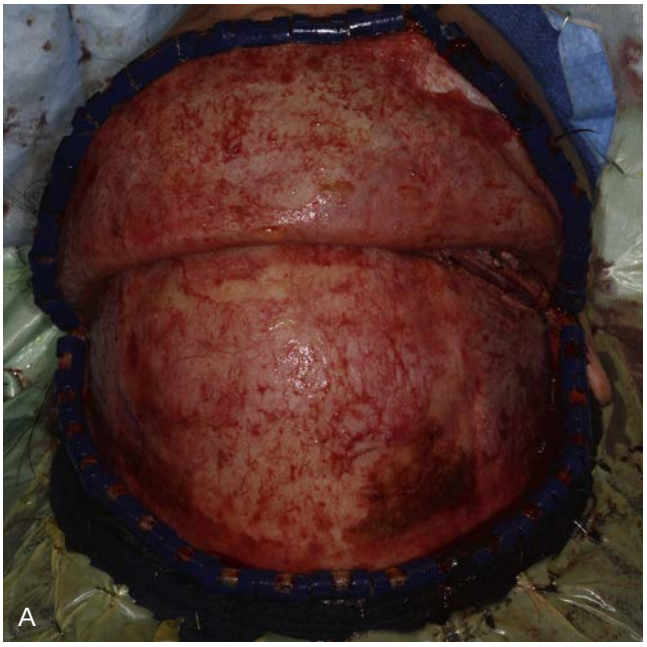
Multiple treatment algorithms and sequences have been suggested for the treatment of complex panfacial fractures. Two main schools of thought are followed for the management of these injuries. The first was described by Gruss and colleagues, in which reconstruction proceeds from stable to unstable segments, that is, from the outer to the inner facial frame.[35,36] In this method, mandibular fractures are fixated last, obviating the need for open reduction and fixation of condylar process fractures. Fixation of the zygomatic (the "outer facial frame") fractures then proceeds from lateral to medial. The frontozygomatic and frontotemporal fractures are reduced and rigidly fixated, followed by the nasofrontal fractures. The maxilla is secured to the mandible with maxillomandibular fixation. This is followed by reconstruction of the nasal frame, the NOE segments, and the anterior maxillary buttresses. Finally, open reduction and fixation of symphyseal, body, and angle fractures of the mandible goes forward. Treatment is tailored for the individual patient and is based on a systematic evaluation of all fracture sites and wide exposure.

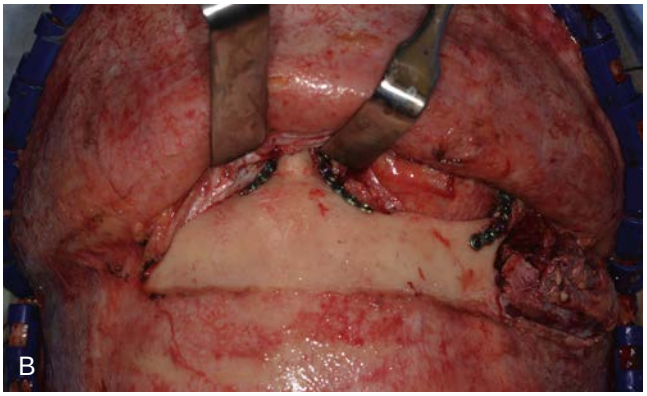
The second school of thought was introduced by Markowitz and expanded upon by Kelly and Manson.[37,38] They described a method whereby the width of the midface is first established at the NOE region, followed by an outward sequence of fixation ("inside-out"). The mandible was fixated, including open reduction of condyle fractures, before the final reduction of the midface was completed ("bottom-up"). The advances in rigid fixation over the past few decades have enabled surgeons to follow different methods and treatment sequences to achieve satisfactory results. It is





In this patient, a concomitant orbital floor blowout fracture required reconstruction with an orbital implant (**B**).





• **Figure 10-15** Coronal approach to the supraorbital rims, the zygomaticofrontal sutures, and the nasofrontal region. **A,** Elevation of the flap. **B,** Fixation of the bilateral nasofrontal and right zygomaticofrontal fractures. Note that the amount of exposure is dictated by the fracture pattern, and in this patient the left zygomaticofrontal suture was not exposed.

critical that the surgeon formulate a systematic treatment plan with the goals of reestablishing facial width, height, and projection, as well as the pre-injury occlusion.

With more severe fracture patterns and increased comminution, it is often necessary to use bone grafting procedures to reestablish the skeletal buttresses. Autogenous bone grafts remain the best option for facial reconstruction in trauma patients. Bone can be harvested from the calvarium, ribs, ilium, and intraorally from the mandible. Calvarial bone grafts are an excellent option as they are usually immediately available when a coronal flap has been elevated and can be used for various reconstruction purposes.

Palatal Fractures

Isolated palatal fractures are rare, and the presence of a sagittal palatal fracture usually indicates that a Le Fort fracture exists. Eight to 13% of Le Fort fractures are complicated [29,30]

in oral and maxillofacial trauma surgery. Arguments against the use of rigid plate fixation include, first, the significant compromise in blood supply effected with mucosal stripping leading to bony necrosis; second, a substantial increase in the likelihood of an oral-nasal fistula; and last, the inability to simultaneously fixate the palate while maintaining maxillomandibular fixation, thereby automatically inducing

Occlusal splints can be extremely useful in reduction of palatal fractures. Preoperative impressions are taken and dental models are fabricated, with the splint fabricated after appropriate model surgery to reestablish the occlusion (Figure 10-16). If no mandibular fractures exist, the palatal fracture is reduced with the application of the occlusal

sible, as in the rare case of the edentulous maxilla, anatomic reduction must be achieved, and consideration should be

thus decreasing the risk of vascular compromise.[39]

Naso-Orbital-Ethmoid Fractures

Introduction

Injury to the naso-orbital-ethmoid region, referred to as the NOE fracture, poses a significant challenge in diagnosis and treatment.[31,40] It often involves comminuted segments and is associated with important anatomic landmarks, including the medial canthal tendon and the lacrimal apparatus. Furthermore, it is commonly associated with additional fractures as well as other traumatic injuries, including central nervous system injuries and CSF drainage.[19]

Mechanism and velocity of injury affect the variable patterns of NOE fractures seen, and these often occur with other midface fractures.[41] Ellis reported a 65% rate of concomitant Le Fort or frontal sinus fractures in his series of 26 patients with NOE injuries.[31] In order to achieve a satisfactory outcome, adequate surgical exposure and attention



• **Figure 10-16** Models taken for a patient with a sagittal palatal fracture. The left side model shows the posttraumatic dental arch. The maxillary model was cut at the site of fracture and the occlusion reestablished using an articulator and the mandibular cast. A surgical splint is fabricated from the postsurgical model on the right.

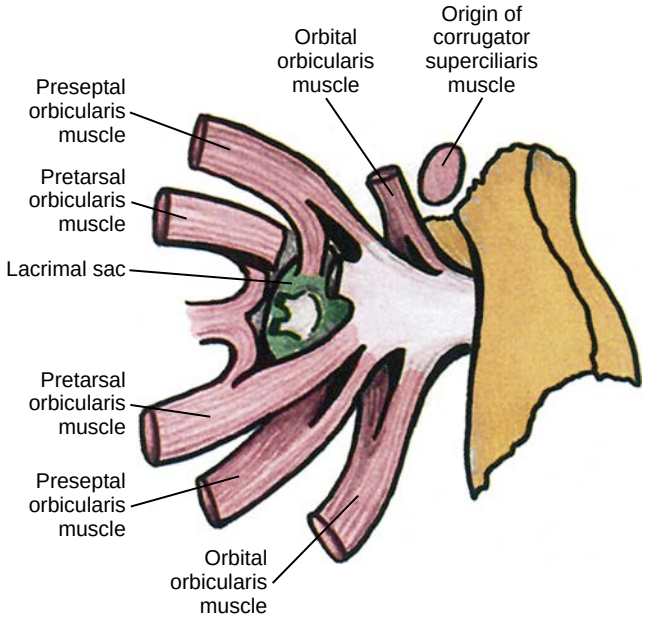
to the regional anatomy is required. Early repair is recommended, as poor cosmetic and functional results can ensue, including midface retrusion, blunted palpebral fissures, telecanthus, ocular dystopia, epiphora, nasal deformities, and cerebrospinal fistula formation.

Anatomy

The naso-orbital-ethmoid region is a complex intersection of the cranium, nose, orbit, and maxilla. The primary vertilla, the lacrimal bone, and the ethmoid lamina papyracea bilaterally. This area is fragile and prone to comminution and displacement.[42] Two buttresses provide horizontal support to the region: the superior frontal bar along with the supraorbital rims, and inferiorly the infraorbital rims and zygomas.

The proximity of the cribriform plate of the ethmoid bone to these structures means that associated injury resulting in CSF leakage, pneumocephalus, or olfactory dysfunction is possible with these fractures. Two additional anatomic regions deserve mention, as they are especially important for the accurate diagnosis and management of NOE fractures: the medial canthal tendon and the nasolacrimal apparatus.

The medial canthal tendon is a complex fibrous extension of the tarsal plates and orbicularis oculi muscles (Figure 10-17). The tendon divides into anterior and posterior limbs, which each supply fibers to a third superior limb, which surrounds the lacrimal sac. The anterior limb attaches to the anterior lacrimal crest of the frontal process of the maxilla; it is fan-shaped, stronger, and functions to pull the medial commissure of the eyelid forward and downward.[43] The posterior limb attaches to the posterior lacrimal crest of the lacrimal bone; it is thinner and functions to maintain the eyelid position tangent to the globe.



• **Figure 10-17** Anatomy of the medial canthal tendon.

to pull the eyelid in a posterior and superior direction. The tensor tarsi, or Horner, muscle is intimately associated with posterior limb of the medial canthal tendon, functions to support the lacrimal apparatus, and plays an important role in tear flow.

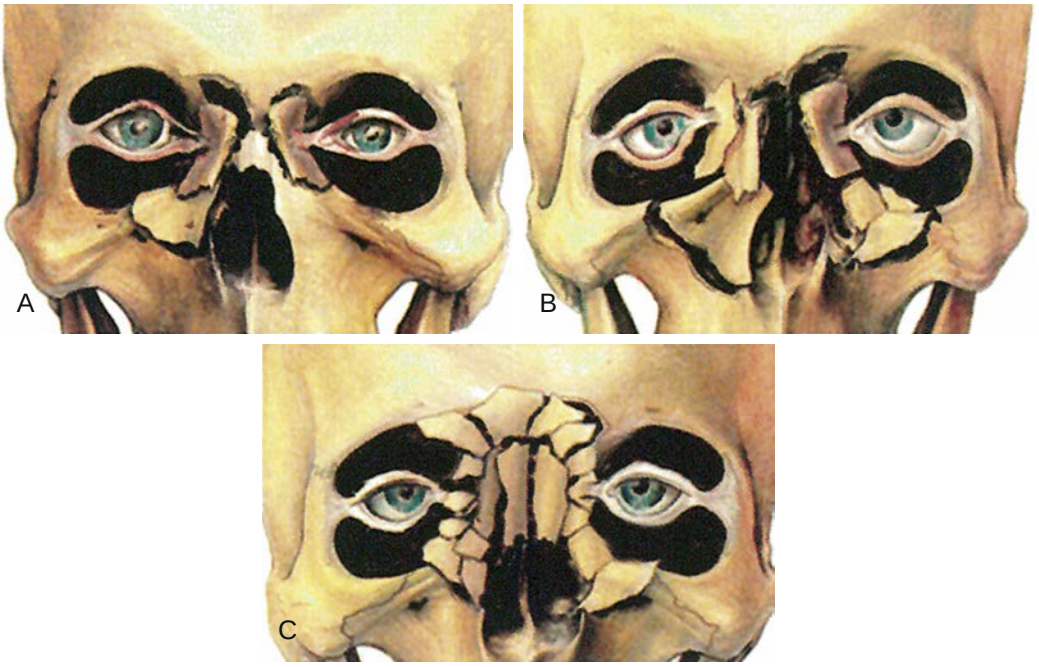
Normal intercanthal distance, the distance spanning between the two medial canthal tendons, is 28 to 35 mm.[44,45] Disruption of the medial canthal tendon results in unopposed muscle pull of the orbicularis oculi muscle, which results in narrowing of the palpebral fissure and widening of the intercanthal distance, known as telecanthus. The presence and degree of medial canthal tendon displacement, whether from avulsion of attachment or mobility of a fractured bony segment, is paramount to accurate diagnosis and treatment of NOE fractures. Adequate reattachment and/or stabilization of the medial canthal tendon is necessary to prevent telecanthus, enophthalmos, and lacrimal system dysfunction.[45] Secondary, delayed reconstruction is extremely difficult.

The lacrimal apparatus is composed of the lacrimal gland in the superolateral aspect of the orbit and the drainage system medially. The lacrimal drainage apparatus consists of an upper and lower lacrimal canaliculus, which begins as a lacrimal punctum at the medial aspect of the eyelid margins, the lacrimal sac, and nasolacrimal duct. The upper and lower canaliculi join to form the common canaliculus prior to draining into the lacrimal sac located in the lacrimal fossa of the lacrimal bone. Tears drain into the lacrimal sac with the aid of the orbicularis oculi and Horner muscle function, and the nasolacrimal duct carries this flow from the sac to the inferior meatus of the nasal cavity. Dysfunction of the lacrimal drainage apparatus, whether from trauma or surgery, results in epiphora and must be evaluated perioperatively.

Classification

NOE fractures can be unilateral or bilateral, and their classification was classically described by Markowitz and colleagues in 1991.[46] This classification is based on the description of the central fragment, which is essentially the lower two thirds of the medial orbital rim, to which the medial canthal tendon attaches superiorly. Sargent more recently advocated the simplification of this previous scheme by classifying fractures as unilateral or bilateral, and as simple or complex/comminuted.[47]

A Markowitz type I NOE fracture involves the central fragment as a single segment, with the medial canthal tendon attached (Figure 10-18, *A*). This is the simplest form of the NOE fracture and may be unilateral or bilateral, with varying levels of displacement. If the fracture involves a single bilateral segment across the nasal bridge,



• **Figure 10-18** Markowitz classification of naso-orbital-ethmoid fractures. **A,** Type I; **B,** type II; **C,** type III.

telecanthus is not expected, and the fractures need only be fixated.

A Markowitz type II NOE fracture implies comminution of the central fragment with the medial canthal tendon remaining attached to a single osseous segment that is large enough to be reduced and fixated (see Figure 10-18, *B*).

A Markowitz type III NOE fracture is the most complex form of the fracture, which is defined as severe comminution of the central fragment with the medial canthal tendon being avulsed or remaining attached to a small osseous segment that cannot be fixated (see Figure 10-18, *C*). This dictates that transnasal wiring and possibly medial canthopexy be performed.

Diagnosis

Identification of NOE fractures is made by clinical and radiographic examinations. A thorough systematic maxillofacial trauma evaluation is carried out with visual inspection and manual palpation. Edema, ecchymosis, and lacerations are evaluated. Nasal projection, height, and mobility are evaluated. Flattening of the nasal dorsum, retrusion, and gross mobility are indicative of fractures in the region. The orbital rims are also palpated for any step-offs that would indicate fracture segments.

The intercanthal and interpupillary distance is measured to evaluate for telecanthus, taking into account the amount of edema present (Figure 10-19). An intercanthal distance of greater than 35 mm should raise suspicion of medial canthal tendon displacement, and greater than 40 mm is considered diagnostic.[48] Rounding of the medial canthal lake and epiphora are also supportive. Often it is helpful to obtain pre-injury photographs to compare to the clinical findings.[44]



• **Figure 10-19** Presentation of naso-orbital-ethmoid (NOE) injuries. This patient demonstrates the classic findings with NOE fractures, including telecanthus, flattening and widening of the nasal base, edema, ecchymosis, and signs of ocular injury such as subconjunctival hemorrhage.

The medial canthal tendon attachment can be evaluated externally with the "bowstring" or traction test. This is performed by applying lateral traction to the eyelids while palpating the medial canthal tendon attachment, with a positive test elicited with a palpable bowing of the fractured

segment. This can be difficult to assess in the acute setting when edema is present. The bimanual exam has been suggested to be a more sensitive test, using a Kelly clamp intranasally and a finger placed externally at the region of the medial canthal tendon. Lateral displacement of a fractured segment with the clamp will be palpated by the overlying finger.[49]

An intranasal examination is also necessary to evaluate the nasal septum, turbinates, and nasal mucosa. Any lacerations, hematomas, or active bleeding is evaluated. Clear rhinorrhea concerning for CSF leakage is indicative of involvement of the cribriform plate and skull base.

Radiographic evaluation for NOE fractures requires axial and coronal CT scans.[41] The extent of injury and comminution is best evaluated with 1.0- to 2.0-mm cuts (Figure 10-20). Three-dimensional CT reconstruction can be a valuable additional tool for assessment of comminution and fracture segments.

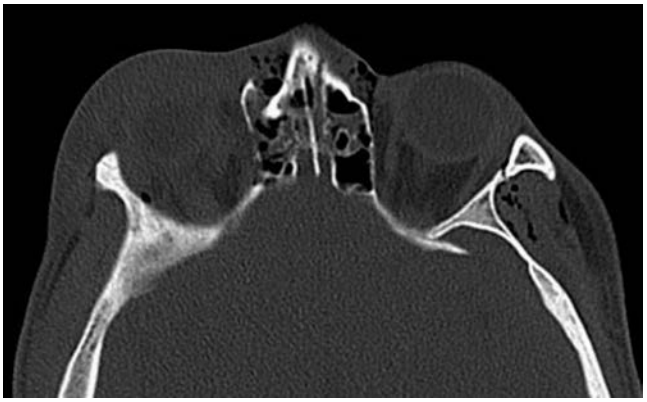
Clinical and radiographic examinations are used to make the diagnosis and further classify the fractures along with associated injuries, which directly dictate the type and extent of treatment.

Treatment

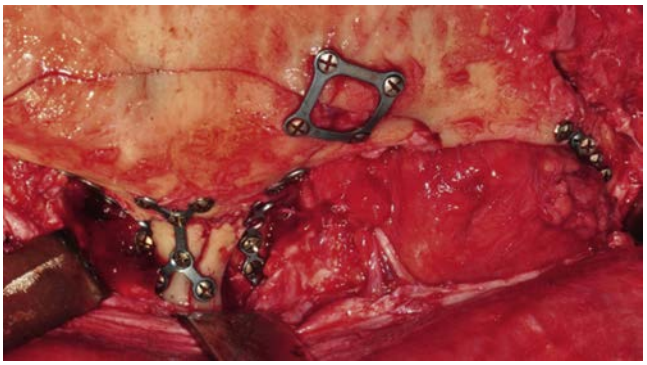
A systematic approach to the treatment of NOE fractures is recommended to avoid omitting any crucial steps in their management. This comprehensive treatment is best described as a series of eight steps first presented by Ellis: exposure, identifying the medial canthal tendon/tendon-bearing bone, reconstruction of the medial orbital rim, reconstruction of the medial orbital wall, transnasal canthopexy, reduction of septal fractures, nasal dorsum reconstruction/augmentation, and soft tissue readaptation.[31] Not all these steps are required for every fracture, but the surgeon should be cognizant of the importance of each one when needed. Most authorities recommend early treatment, as there is evidence that delayed primary treatment (later than 10-14 days) results in greater incidence of telecanthus and epiphora.[32,45,50]

Markowitz type I fractures are usually sufficiently managed by three-point rigid fixation of the central fragment (Figure 10-21). This is accomplished by reducing the segment and reestablishing the relationships of the nasofrontal junction to the nasal complex, the nasal complex to the maxillary buttress, and the nasal complex to the infraorbital rim. Medial canthal tendon disruption is rare in this type of fracture, and canthopexy is not usually indicated.

Markowitz type II fractures will involve more extensive comminution, but the medial canthal tendon will still be attached to a sizeable bony segment. Treatment here requires anatomic reduction of the comminuted bony fragments with intraosseous wiring or miniplates. This is followed by rigid fixation at the buttresses as described earlier. If the tendon-bearing osseous segment is rigidly fixated, no canthopexy is required.



• **Figure 10-20** Axial computed tomography of a naso-orbital-ethmoid fracture demonstrates posteriorly impacted and comminuted nasal radix.



• **Figure 10-21** Three-point rigid fixation of bilateral single-segment naso-orbital-ethmoid fractures via a coronal incision. (From Fonseca RJ, Barber HD: *Oral and maxillofacial trauma*, ed 4, St Louis, Saunders, 2013.)

The type III Markowitz NOE fracture is the most difficult to treat because of the level of comminution and disruption of the medial canthal tendon. Transnasal wiring and canthopexy is usually necessary, as is nasal dorsum reconstruction. The principles of access and repair otherwise are similar, and close adherence to the eight steps presented here becomes more important in achieving a predictable outcome.

Exposure

Wide surgical exposure is required for adequate treatment of NOE fractures. Esthetic incisions are preferred, and therefore the coronal incision is used most frequently because of the combination of good cosmesis and wide exposure of the superior aspects of the fractures. Previously described incisions such as the gull-wing, open sky, or frontoethmoid (Lynch) incisions are avoided when possible because of the conspicuous location of their scars. Inferiorly, exposure of the central fragment is achieved with a lower eyelid incision. Finally, a maxillary vestibular incision is also often needed to expose the lower part of the nasomaxillary buttress for fixation. Another esthetic option that has been suggested for NOE fractures is the maxillary degloving approach.[51] A combination of a coronal incision, lower eyelid incision, and vestibular incision

is typically adequate for treatment of NOE fractures. The coronal flap should be dissected subperiosteally to expose the entire supraorbital rim from the frontozygomatic suture to the nasal bone. The supraorbital neurovascular bundle should be released from its notch or foramen to improve the ability to reflect the flap. Care should be taken to limit disruption of the lacrimal drainage system or strip any remaining medial canthal attachment from bone.

Identifying the Medial Canthal Tendon/ Tendon-bearing Bone

The medial canthal tendon must be identified in order to achieve a cosmetic result. This can be performed through the coronal flap exposure, or if necessary, through a separate skin stab incision placed 3 mm medial to the canthus. The medial canthal tendon is evaluated for complete avulsion or attachment to a bony segment. Regardless, it should be tagged with a braided suture or wire for later use in canthopexy.

Reduction/Reconstruction of the Medial Orbital Rim

Reconstructing the medial orbital rim and the central fragment is crucial to achieving adequate fixation and avoiding postoperative telecanthus. Rigid fixation with miniplates is used when the level of comminution allows for it. Transnasal wiring is used to medially reduce the canthal tendon-bearing bone segment. This is achieved by passing a 26- or 28-gauge wire through two holes drilled in the medial orbital wall, with at least one hole being posterior and superior to the lacrimal crest. This posterior vector is critical in preventing splaying or rotation of the osseous segment, with subsequent telecanthus (Figure 10-22). The wire is passed in a horizontal mattress fashion, and effort should be made to "over reduce" the medial orbital rims to reestablish the normal intercanthal distance and prevent a broad nasal dorsum.[48]

Reconstruction of the Medial Orbital Wall

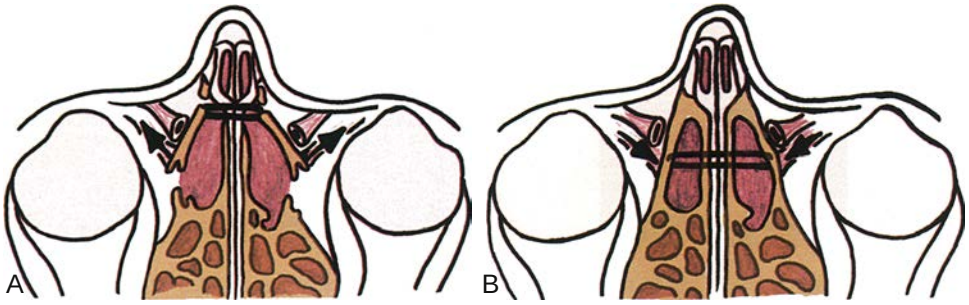
Bony medial wall defects should be assessed preoperatively using CT images. If a significant medial orbital wall or orbital floor blowout fracture exists, this should be reconstructed to prevent postoperative sequelae such as enophthalmos, diplopia, and vertical dystopia.[52] The decision to reconstruct the medial orbital wall is guided by the surgeon's suspicion of a significant increase in orbital volume. The choice of reconstruction material is similar to uncomplicated orbital fractures and includes titanium mesh, alloplasts (such as porous polyethylene), and bone grafts harvested from the calvarium or ribs. Access is achieved through the previous surgical exposure, and the mesh or graft is secured to the orbital rim with rigid fixation.

Transnasal Canthopexy

Markowitz described a low 3% rate of medial canthal avulsion in patients with NOE fractures. Therefore, reduction and transnasal wiring of the tendon-bearing osseous segment is usually sufficient to prevent telecanthus when the tendon is intact. However, Merkx and colleagues reported a higher incidence of postoperative telecanthus when "indirect canthopexy" was performed through reduction and fixation of the tendon-bearing segment compared to a "direct technique" canthopexy.[45] If the medial canthal tendon is felt to be disrupted, or the comminution is too severe to reduce the tendon-bearing segment, then a transnasal medial canthopexy is indicated. This is accomplished by placing a 2- to 4-mm hole superior and posterior to the lacrimal crest along the medial orbital wall. The wire is passed transnasally with an awl and secured to the supraorbital rim on the contralateral side. It is important to achieve a superoposterior vector on the medial canthal tendon to prevent telecanthus and result in normal approximation of the lid to the globe. The position of the medial canthus must be evaluated often intraoperatively and compared to the contralateral canthus to ensure that symmetry and an adequate position are attained. If bilateral canthopexy is required, separate transnasal wires should be used, and the two should not be secured to each other. This avoids total loss of anatomic position if one side becomes loose postoperatively.[31]

Reduction of the Nasal Septum

The nasal septum is often fractured or displaced in NOE fractures. The goals of treatment should be to place the



• **Figure 10-22** Transnasal wiring technique for naso-orbital-ethmoid fracture reduction. When the wire is passed in a vector anterior to the lacrimal crest **(A),** splaying of the posterior segment occurs and results in telecanthus. Posterior wire fixation **(B)** prevents this complication.

septum back into a midline position to prevent nasal airway compromise. As the bony dorsum will be reconstructed at the next step, no major reconstruction of the septum is warranted. Simple manipulation and the use of an Asch forceps is sufficient to apply anterior and superior force and bring the septum back into midline alignment.

Reconstruction/Augmentation of the Nasal Dorsum

Because of the nature of the NOE fracture, the nasal dorsum usually loses critical support from the bony and cartilaginous septum and nasal radix. Additionally, a flattened and retruded nasal dorsum (the "saddle" nose) worsens the appearance of telecanthus, whereas an overprojected dorsum may help mask a high intercanthal distance. For these reasons it is often necessary to reconstruct the nasal dorsum with the use of a cantilever dorsal bone graft. This can be obtained from calvarial bone nearby, or from other sources such as ribs, iliac crest, or the mandible.[53] The bone graft is an elongated sheet of cortical bone and is shaped to taper the two ends, which has been described as a "surfboard shape." The width of the graft is tailored to the gender, race, and facial proportions of the patient. The graft is secured to the frontal bone with rigid fixation (Figure 10-23). Additional nasal augmentation procedures may be needed depending on the status of the nasal cartilages. A columellar strut graft is sometimes indicated to improve nasal tip projection when this has been compromised. Markowitz used a columellar strut graft in approximately 20% of NOE fracture patients.

Readaptation of Soft Tissues

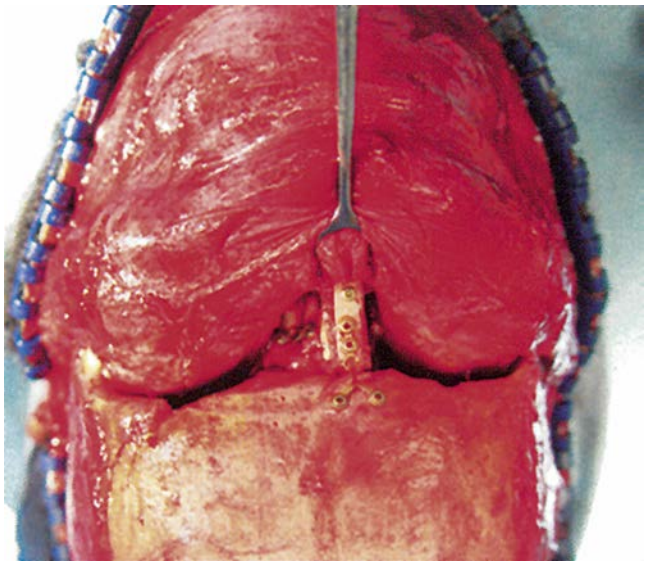
Poor adaption of the soft tissues into the medial naso-orbital "valley" region has been implicated in soft tissue thickening, which gives the appearance of increased intercanthal distance and widening of the nasal bridge. This can be ameliorated with meticulous draping of the soft tissues and adequate external splinting. A dorsal nasal splint such as a Denver splint may be used but often will not reach far enough posteriorly into the naso-orbital valley region. A thermoplastic splint (e.g., Aquaplast) is better suited, as it may be custom trimmed and molded down into these recesses. If severe comminution exists, external bolsters secured to each other with a transnasal wire are an excellent choice, with a variety of materials used and reported in the literature (Figure 10-24). Internal nasal splints such as Doyle splints are also used to support the nasal septum.

Complications

Complications associated with midface fractures increase with the severity and level of comminution of the injury. Before treatment, it is important to thoroughly document the concomitant injuries sustained from the traumatic event, such as nerve deficits, globe injuries, and hematomas.[2] Intraoperative complications may include excessive bleeding, nerve damage, and injuries to the cornea or globe. Postoperative complications are mainly related to inadequate reduction and fixation of fractures and associated structures. Resulting secondary deformities may be cosmetic, functional, or both and include facial asymmetry, enophthalmos, diplopia, telecanthus, epiphora, malocclusion, and mandibular hypomobility.[6,54] Additional postsurgical complications include infections, hematomas, and hypertrophic scarring.

Malunion

Malunion of a fracture occurs when it heals without reduction or with inadequate reduction. This creates a healed bone that is in incorrect anatomic alignment. The best way to avoid this complication is with timely treatment and



• **Figure 10-23** Nasal dorsum reconstruction with a dorsal bone graft via a coronal flap. (From Fonseca RJ, Marciani RD, Turvey TA: *Oral and maxillofacial surgery*, ed 2, St Louis, Saunders, 2008.)



• **Figure 10-24** Application of a rigid external nasal splint with transnasal wiring. (From Fonseca RJ, Marciani RD, Turvey TA: *Oral and maxillofacial surgery*, ed 2, St Louis, Saunders, 2008.)

meticulous surgical technique, as secondary correction of malunion becomes much more difficult.

Malunion of Le Fort fractures may result in malocclusion due to inadequate mobilization of the maxilla, inadequate intraoperative maxillomandibular fixation, and failure to seat the condyles in the glenoid fossae during fixation. It may also occur due to patient noncompliance with diet restrictions. Secondary corrections by performing a Le Fort I osteotomy and reestablishing the occlusion is usually sufficient. However, if a bony gap greater than 5 mm is noted after repositioning, placement of a bone graft should be considered.

Malunion of the zygoma or orbital walls may result in enophthalmos, hypophthalmos (hypoglobus), persistent diplopia, or cosmetic asymmetries.[54] The type of correction depends on the complication. Typically, functional problems are best treated with corrective osteotomies and bone grafting, whereas cosmetic deficiencies can be treated with augmentation with onlay autografts and alloplasts.

Enophthalmos

Several etiologies have been suggested for secondary deformities of the position of the globe, including fat atrophy, loss of suspensory ligament support, and increase in orbital volume due to inadequate reduction of fractures.[55] An early retrospective study concluded that the majority of orbital deformities were due to malposition of the zygoma.[56] The incidence of posttraumatic enophthalmos was reported to be 8% in one study.[18] Evaluation of secondary enophthalmos is best measured with CT scanning to assess the discrepancy between the volume of the orbital cavity and the orbital contents.[57] Treatment involves reconstruction of the orbit with implants or bone graft in order to restore the pre-injury orbital volume.

Telecanthus

Persistent telecanthus following NOE fracture repair is a difficult problem to correct. The incidence of postsurgical telecanthus was reported to be 14.1%.[5] In a study of 10 consecutive comminuted Markowitz type III NOE injuries, the mean postoperative intercanthal distance was 36 mm, and none of the patients had clinically detectable telecanthus. Merkx and colleagues reported on a series of 36 patients with NOE fractures, with significantly smaller intercanthal distance achieved with early primary repair of the fracture.[45] Furthermore, they noted better results when a "direct" technique using transnasal canthopexy was applied. Therefore it is clear that correct diagnosis and adequate reduction of the medial canthal tendons during the primary repair is critical to avoid this complication.

Epiphora

Epiphora, or tear overflow onto the face, can be caused by nasolacrimal drainage obstruction or ectropion of the lower eyelid. It is a known complication of nasolacrimal apparatus injury as it relates to midface fractures, especially naso-orbital-ethmoid fractures. Evaluation of the lacrimal canaliculi and nasolacrimal ducts with dyes and irrigation is controversial in the acute setting because of edema and inflammation, which increases the risk of iatrogenic injury.[50] An older study by Gruss and co-workers reported a low incidence of lacrimal dysfunction of 5% to 17.4%[58] and recommended deferring lacrimal apparatus repair initially.

In a more recent retrospective study of NOE fractures, posttraumatic epiphora due to dacryostenosis was noted in 27 of 58 patients (46.5%). Of those, 17 were permanent findings that required dacryocystorhinostomy to correct.[59] However, studies have demonstrated that early repair of NOE fractures significantly decreases the risk of developing epiphora.[45,58] The authors recommend treatment of the fracture and observation of the lacrimal apparatus in the postoperative period, with dacryocystorhinostomy reserved for persistent epiphora.

Ocular and Extraocular Muscle Complications

Complications related to globe injuries and extraocular muscle entrapments following midface fracture treatment have been reported. These can be related to isolated orbital fractures or more complex midface fracture patterns. Occasionally, reduction of the orbital components will entrap the extraocular muscles, and this can be avoided by fixating the orbital wall fracture after completed reduction and fixation of other fractures. Intraoperative forced duction examination before closing the soft tissues should confirm intact movements. Limitations in extraocular movements postoperatively are usually due to edema and local anesthesia. However, a forced duction test is required for persistent ophthalmoplegia to rule out true entrapment, and surgical exploration is performed to correct it.

Iatrogenic injuries to the globe, especially the cornea, are rare but have been reported. This is prevented by meticulous surgical technique and protection of the globe intraoperatively with corneal shields or suturing the eyelids. If an injury is suspected, urgent ophthalmologic evaluation is warranted. Common complaints include foreign body sensation and eye pain.

CSF Leakage

Cerebrospinal fluid rhinorrhea or otorrhea can be seen with high-impact injuries including Le Fort II, Le Fort III, and NOE fractures. The cribriform plate of the ethmoid bone is often fractured. Presence of CSF leakage is indicative of a dural tear. If suspected, diagnosis can be made with a bedside halo test or with formal laboratory testing with CSF-specific beta transferrin. Surgical repair of midface fractures can proceed, as reduction of the fractures will often assist in resolution of the leak. Herford and colleagues reported that 4 of 10 patients with severe NOE fractures had CSF

or otorrhea is persistent for more than 3 to 4 weeks, surgical repair should be considered.[60] Antibiotic prophylaxis for meningitis is controversial and has been recommended by some authors. Additional precautions should be taken, including elevating the head of bed and avoiding straining, sneezing, and nose blowing.

Endoscopic Repair of Midface Fractures

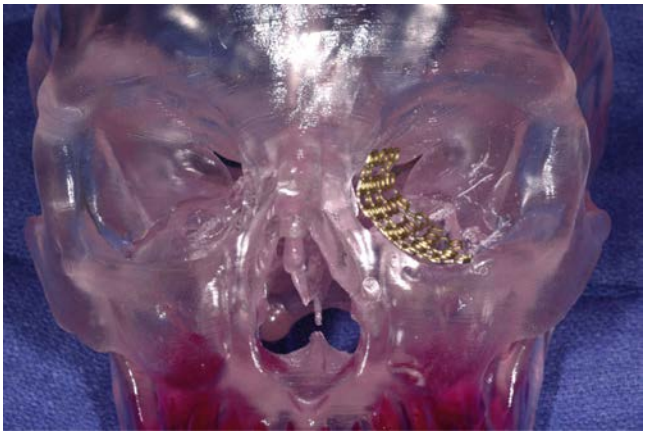
rally occurring optical cavities in the maxillofacial region and the learning curve required to adopt new surgical techniques and armamentarium had previously deterred surgeons. Newer endoscopic technology and an increasing desire for minimally invasive surgical approaches have led to some advances in the field. Proponents cite decreased surgical access morbidity, smaller dissections, less conspicuous scars, decreased blood loss, and fewer complications of wide surgical access.[61]

Reported case series in the literature have now shown endoscopic surgical repair to be viable treatment options for mandibular condylar fractures, frontal sinus fractures, orbital floor fractures, and zygomatic arch fractures,[62-67] with reported success rates comparable to those of previous methods. Nevertheless, limited exposure remains a challenge, and increased operative times decrease its cost effectiveness. Wide application for routine midface fractures has not been adopted, but this technique may prove to be a powerful adjunct in maxillofacial surgery.

Summary and Future Advancements

Injuries to the midfacial skeleton present significant challenges to the maxillofacial trauma surgeon. Fractures of the midface are often the result of high-energy injuries and are often seen in the polytrauma patient. Concomitant neurologic and ocular injuries are frequently encountered and may delay or alter management. The anatomy is complex, and fracture patterns are highly variable and often comminuted. Complications are common, including secondary deformities related to malunion, malocclusion, ocular and canthal disturbances, and contour abnormalities. These are difficult to treat secondarily, and primary surgical repair is the best opportunity for success.

The ability to provide predictable successful treatment of midface fractures is predicated on knowledge of the complex anatomy, systematic physical and radiographic examination, accurate diagnosis, comprehensive treatment planning, and meticulous surgical technique. Central to the management of complicated injuries is the restoration of facial height, width, and projection, which is achieved by reestablishing the vertical and horizontal buttresses of the face. Additionally, the restoration of normal occlusion is a primary aspect of management of Le Fort maxillary fractures. Bone grafting should be used judiciously when significant bone loss and comminution has occurred, and the maxillofacial surgeon should be adept at these procedures.



• **Figure 10-25** Stereolithographic model based on preoperative computed tomography, demonstrating the use of a preoperatively selected and bent reconstruction plate. (From Fonseca RJ, Barber HD: *Oral and maxillofacial trauma*, ed 4, St Louis, Saunders, 2013.)

Improvement in radiographic technology has increased the diagnostic capabilities of current CT imaging. More recent advancements have allowed for excellent 3D reconstruction of the facial skeleton, and the fabrication of stereolithographic models is steadily gaining popularity. These allow for excellent 3D treatment planning and are often used to fabricate pre-bent fixation plates prior to treatment, which decreases operative time (Figure 10-25). Virtual surgical planning is also being used more commonly for complex maxillofacial trauma and has promising applications.[68]

Finally, advancements in intraoperative stereotactic navigation systems and intraoperative CT imaging have become more commonplace. Navigation systems allow for precise manipulation and positioning of fracture segments into ideal alignment based on preoperative 3D scans.[69-71] Intraoperative CT and scanning is used to confirm adequate reduction and fixation immediately, allowing for corrections to take place and preventing the need for a second operation.[72] These techniques may prove to be especially important for secondary repair of posttraumatic deformities of the facial skeleton.

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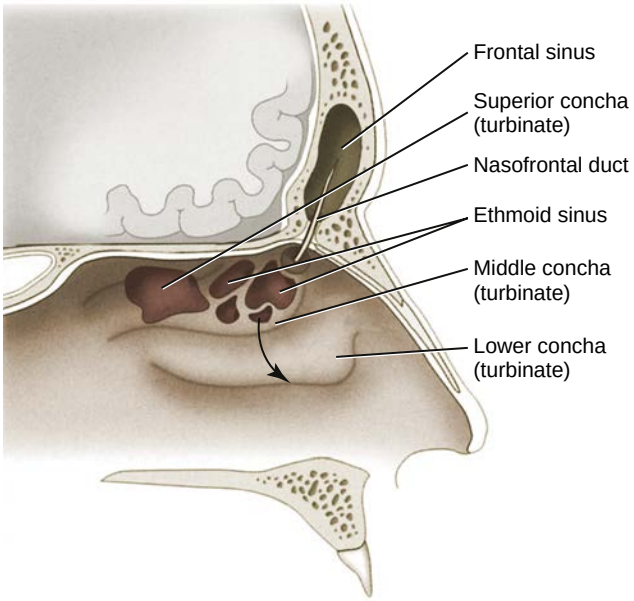
Diagnosis and Management of Frontal Bone Injuries

TIRBOD FATTAHI, DESMON BROWN

Introduction

Frontal bone injuries typically encompass frontal sinus injuries as well as supraorbital rim fractures. Often times, blunt or penetrating injures to the underlying brain are also encountered. The purpose of this chapter is to describe contemporary management of frontal sinus fractures and associated intracranial injuries.

Fractures of the frontal sinus or sinuses make up about 5% to 15% of all facial fractures in the adult patient.[1-3] This is a relatively low frequency of occurrence. However, there are a myriad short-term and long-term potential complications associated with this type of injury, which may involve not only the frontal sinuses, but more importantly the brain. Because of its potential for high morbidity and mortality, clinicians managing this type of injury must be able to address the acute injury appropriately as well as being cognizant of the potential complications and their inherent management.

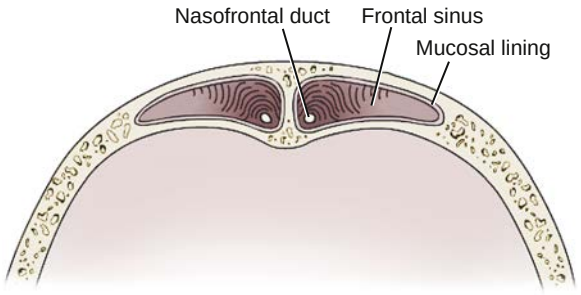


• **Figure 11-1** Sagittal view of the frontal sinus with the drainage pathway of the nasofrontal ducts.

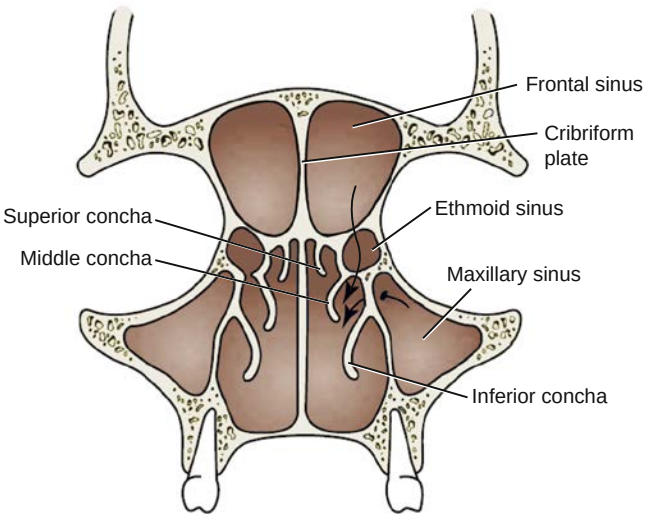
The purpose of this chapter is to discuss surgical anatomy, radiographic and clinical evaluation of patients, classification of injuries, management of fractures, and complications associated with frontal sinus fractures.

Surgical Anatomy

The frontal sinus or sinuses are single or usually paired paranasal sinuses embedded within the frontal bar of the frontal bone (Figures 11-1, 11-2, and 11-3). They are outpouchings



• **Figure 11-2** Axial view of the frontal sinus; note medial and posterior location of the nasofrontal ducts.



• **Figure 11-3** Coronal view of the frontal sinus.



• **Figure 11-4** **A,** Patient with blunt trauma to mid and upper face with deep laceration of the forehead. **B,** Further evaluation revealed displaced fracture of the left frontal sinus.

of the ethmoidal air cells with a typical size of 3.5 × 2.5 × 1.5 cm, although significant variations can occur. There usually exists a bony septum separating the right and left sinus. Initial pneumatization of the frontal sinus begins in the early stages of the second trimester, and radiographic evidence of the sinus can be seen by the age of 6 years.[4,5] The floor of the sinus forms a portion of the orbital roof; therefore, any medial orbital roof fractures may involve the frontal sinus. The posterior wall separates the anterior cranial fossa from the sinus. This wall is rather thin and can be fractured and displaced into the brain secondary to blunt trauma. Arterial blood supply to the sinus is via the supraorbital artery and the anterior ethmoidal arteries. The venous system mirrors that of the arterial system plus the diploic veins of the frontal bone, known as the veins of Breschet, and the superior sagittal sinuses. The physiology of the frontal sinus is similar to other paranasal sinuses of the face. Pseudostratified ciliated columnar respiratory epithelium lines the sinus. Mucin is cleared by the ciliary flow (rate of 250 cycles/min) and is drained from the sinus through the nasofrontal ducts (NFDs) located at the medial aspect of the floor into the middle meatus of the nose.[6,7] The location of the NFDs is clinically significant because trauma to the floor of the sinus or medial aspect of the sinus/orbital wall can injure the NFD.



• **Figure 11-5** Preoperative photograph of patient with frontal sinus trauma. Note periorbital edema and ecchymosis.

Clinical Evaluation

Patients with isolated frontal sinus fractures usually have periorbital ecchymosis and pain in the forehead region.[8] This finding in the presence of blunt trauma to the forehead along with lacerations in the region should raise the suspicion of frontal sinus fracture (Figures 11-4 and 11-5). Blunt or penetrating trauma to this region can also produce altered sensation of the forehead and scalp secondary to injury to the supraorbital and supratrochlear neurovascular bundles. If the patient is seen shortly after the injury, one might also appreciate a depression in the bony forehead. This finding is seldom seen because of soft tissue swelling. Crepitation might be palpable if evaluating such bony injuries. The

examiner should always be cognizant of other concomitant injuries such as intracranial bleeding and cervical injuries (Figures 11-6 and 11-7).

Evaluation of the nose for possible cerebrospinal fluid (CSF) is imperative in patients with frontal sinus fractures. If the posterior table of the sinus or the base of the skull in the region of the cribriform plate are fractured, the dura might be lacerated, causing leakage of CSF into the sinus and then into the middle meatus. Confirmation of the CSF is placed on a cotton sheet; if a red central ring (blood) surrounded a by clear halo (CSF) is observed, one should suspect. CSF will usually have high chloride and low glucose concentration compared to serum.[9-11] Testing for presence of β2 transferrin, a protein marker found exclusively in CSF, aqueous humor, and endolymph, in the nasal drainage can be done via electrophoresis. It is important to remember that patients with frontal sinus trauma may also have associated orbital and naso-ethmoidal injuries. These injuries and their managements are discussed elsewhere in this book.



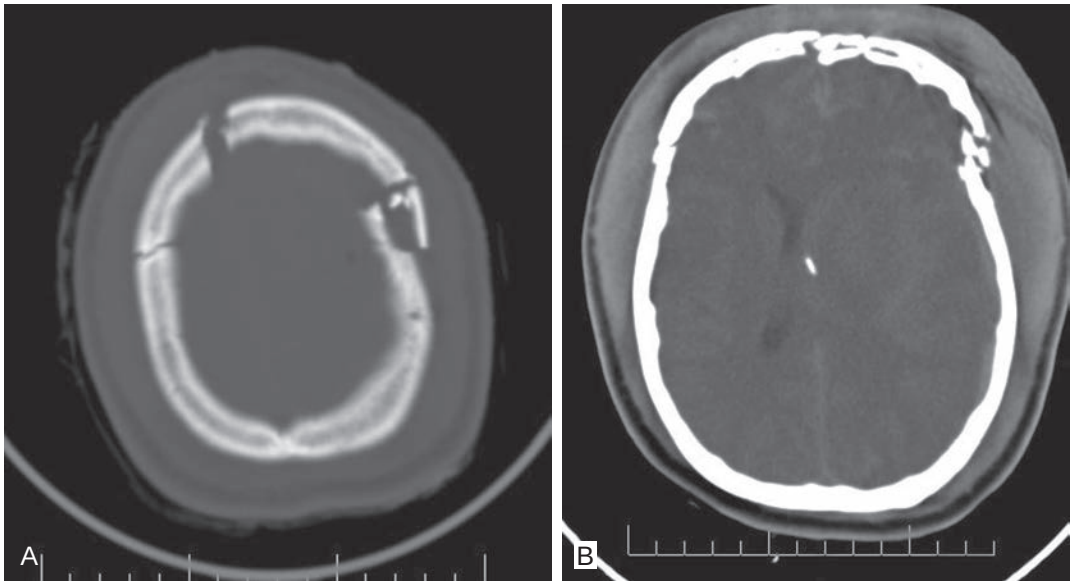
• **Figure 11-6** Significant frontal sinus trauma and simultaneous intracranial injury. Note intracranial bleed within the frontal lobe.

Radiologic Evaluation

The gold standard method of evaluation for frontal sinus fractures is computed tomography (CT).[12,13] This is also true of most mid and upper face trauma. Although multiple planes can be obtained, the two most useful planes of view are axial and coronal on a CT scan (Figures 11-9, 11-10, and 11-11). The ideal thickness of such a scan should be 1.0 mm. Generally no contrast is needed for evaluation of facial fractures, although intracranial bleeding usually requires addition of intravenous contrast to a CT scan. Axial views can give a clear view of the anterior and posterior table, as well as evidence of intracranial impingement. Coronal views can give clues to the status of the nasofrontal ducts, floor of the sinus, and involvement of other adjacent structures such as the orbital roofs. In cases of significant comminution, three-dimensional (3D) images can also be quite helpful (Figure 11-12).

Classification of Frontal Sinus Fractures

There have been numerous attempts at universal classification of fractures of the frontal sinus. For the most part, these



• **Figure 11-7** **A,** Significant skull fractures involving the frontal sinus and temporal regions. **B,** Note effacement of the lateral ventricle and intracranial contusion.

have added nothing other than confusion to the literature. The simplest and most basic classification of frontal sinus fractures is one that clearly describes three specific areas: the anterior table, the posterior table, and the status of the N [14-17]

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placement greater than the width of the anterior table, it is considered a displaced fracture, and consideration should be given to surgical repair in order to prevent a cosmetic deformity (Figure 11-13). If the fracture displacement is not



• **Figure 11-8** Cerebrospinal fluid (CSF) halo test; blood in the middle and CSF along the periphery.

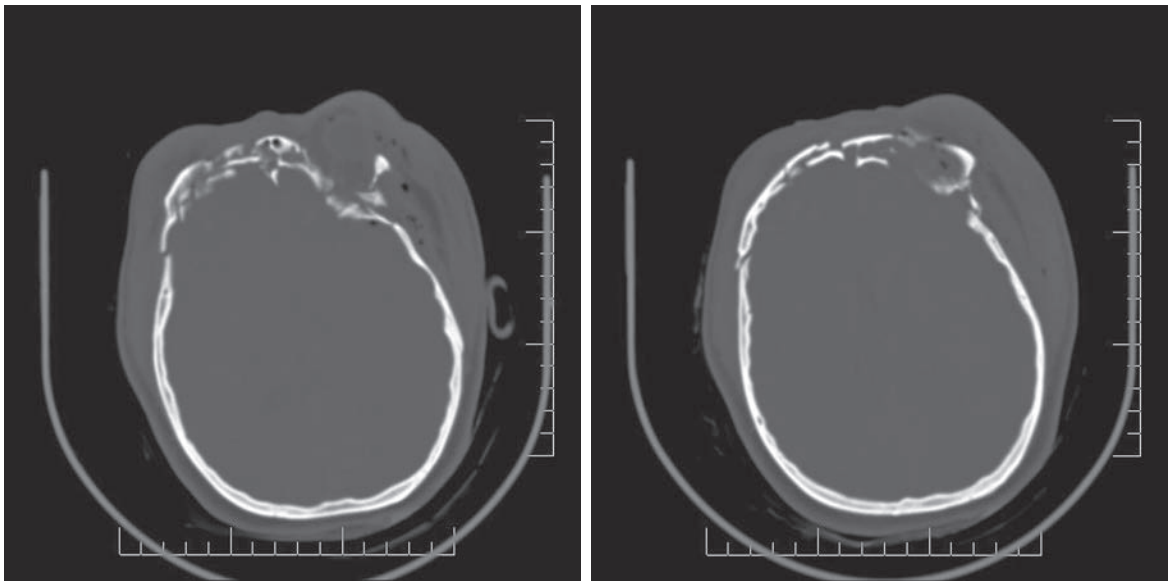
involvement of one or both frontal sinuses (if there are two distinct sinuses).

An *isolated* posterior table fracture, although not as common, can also occur. The most common presentation of posterior table fracture is one with a concomitant anterior table fracture (Figure 11-14). The concern with these types of injuries is the possible intracranial involvement of the fracture. A posterior wall fracture can be comminuted, nondisplaced, or displaced intracranially. The last can cause significant brain injury.

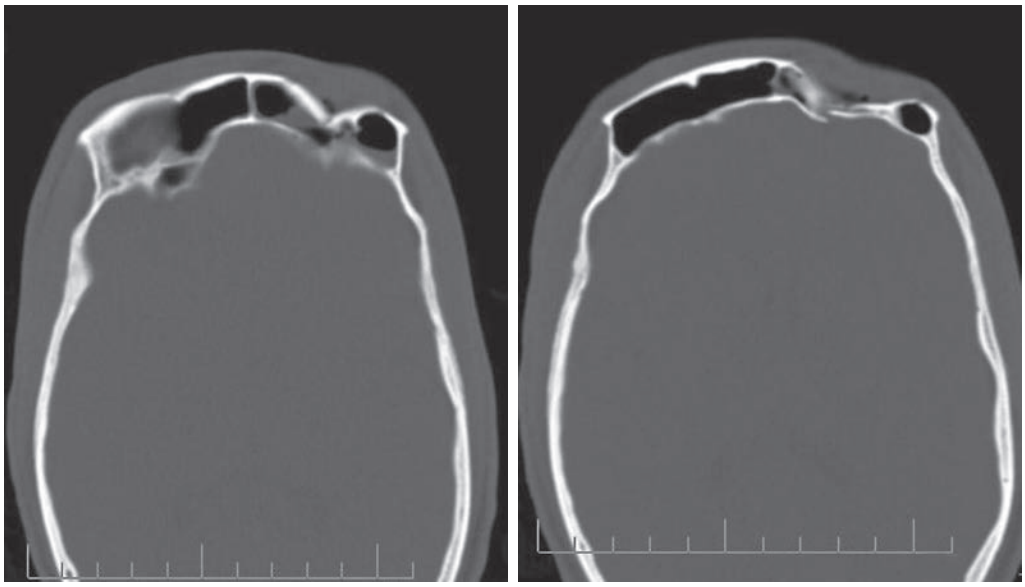
Nasofrontal ducts should be considered injured if there are fractures along the floor of the sinus or the medial aspect of the orbital roofs (Figure 11-15). Intraoperative correlation is required in such cases.

Surgical Management of Frontal Sinus Fractures

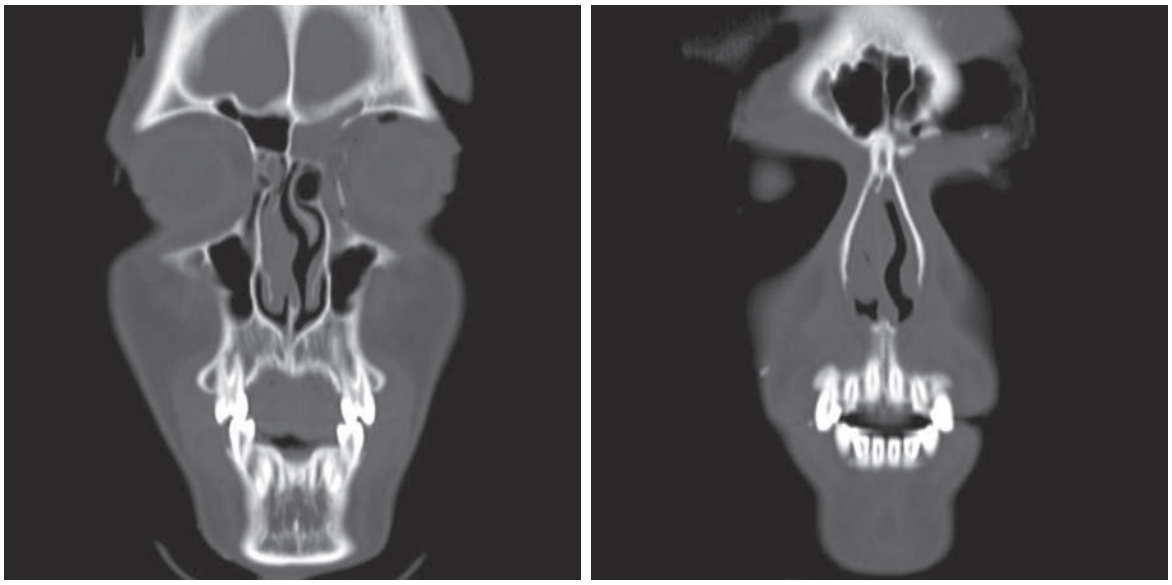
Access to the fractures is via a coronal (bitemporal) incision or through existing lacerations if long enough (Figures 11-16 and 11-17). Other incisions such as open sky and gull wing have been mentioned in the literature, although they are not aesthetically pleasing. The incision should extend between the preauricular regions in hair-bearing scalp in an irregular fashion (Figure 11-18). If there is receding hair, the incision can be moved posteriorly to ensure its placement within hair (Figure 11-19). The coronal flap is elevated in a subgaleal plane. The dissection can be carried in this plane until about 2 to 3 cm above the frontal sinus, at which point a subpericranial (subperiosteal) approach can be commenced.



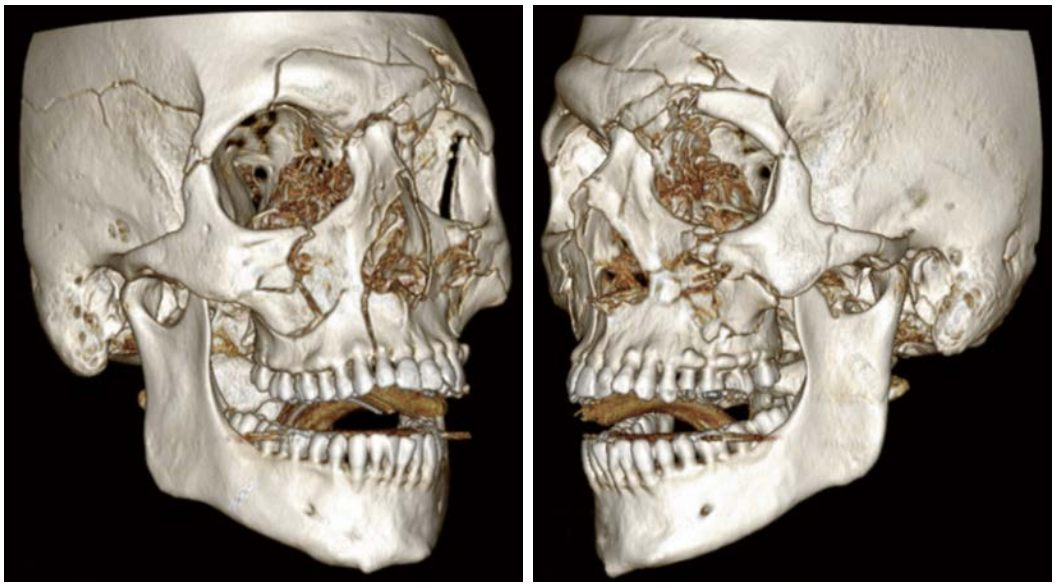
• **Figure 11-9** Axial computed tomography scan images depicting comminution of the anterior and posterior frontal sinus walls and lateral skull fracture.



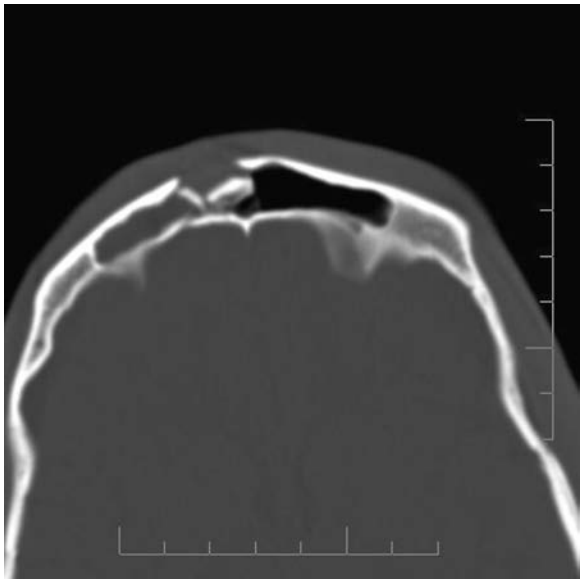
• **Figure 11-10** Axial computed tomography scan images demonstrating a displaced anterior and posterior table fracture of the left frontal sinus.



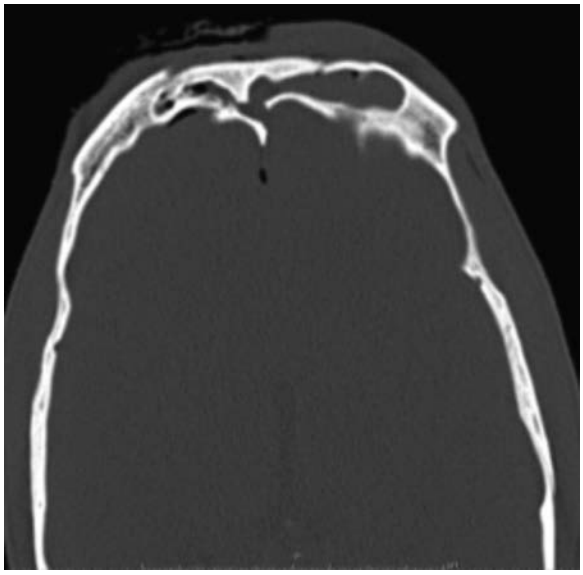
• **Figure 11-11** Coronal computed tomography scan images demonstrating left-sided frontal sinus fracture involving the floor of the sinus and orbital roof. This type of injury frequently involves the nasofrontal duct.



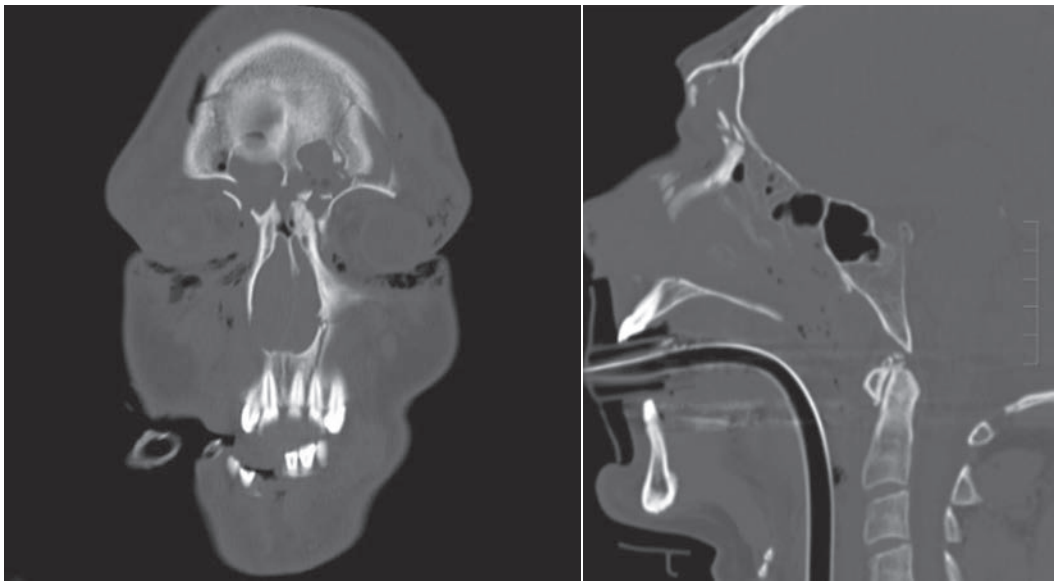
• **Figure 11-12** 3D reconstruction computed tomography depicting disruption of the frontal bar and midface trauma.



• **Figure 11-13** Axial image of a displaced anterior table fracture.



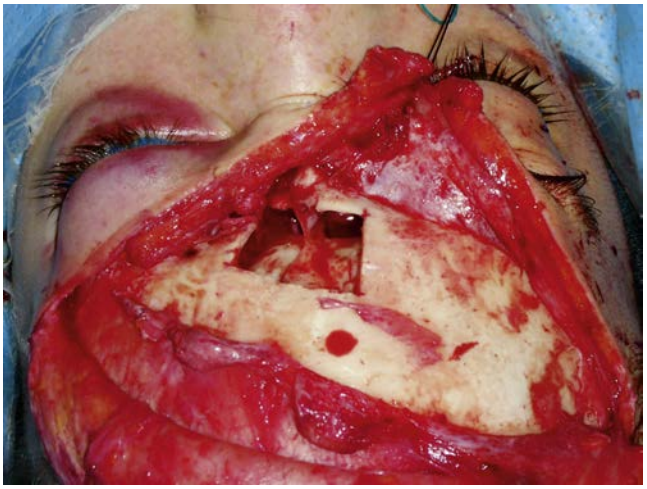
• **Figure 11-14** Axial image of fractures of anterior and posterior tables. This type of injury requires cranialization.



• **Figure 11-15** Coronal and sagittal views demonstrating high likelihood of injury to the nasofrontal ducts in the area of medial sinus floor.



• **Figure 11-16** Use of existing laceration to access left-sided frontal sinus fracture.



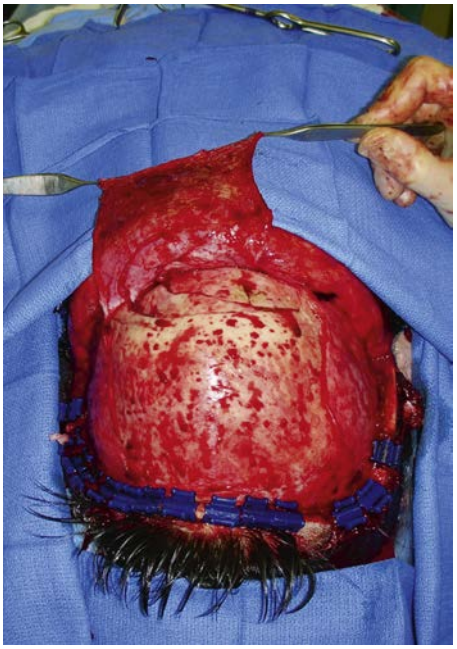
• **Figure 11-17** Extensive transverse laceration of the forehead with easy access to the frontal sinus. The fractured segments have been removed to gain access to the nasofrontal duct.



• **Figure 11-18** Irregular outline of a coronal incision in two different patients.



• **Figure 11-19** Note posteriorly placed incision *(arrows)* to ensure placement of the final scar within hair-bearing area in patients with receding hairline.

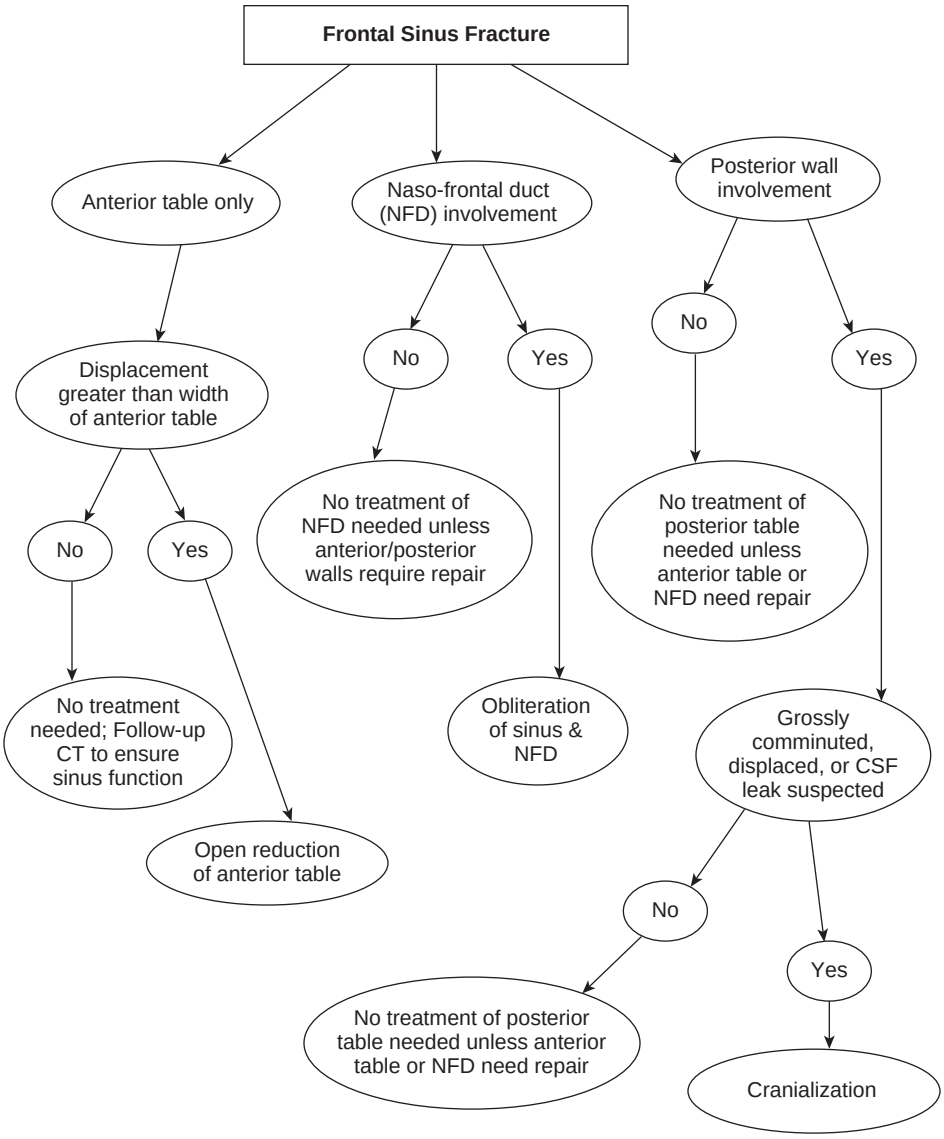


• **Figure 11-20** The coronal flap has been elevated in a subgaleal plane all the way anterior past the fractures. This allows elevation of a separate, pedicled vascularized pericranial flap (Adson pickups).

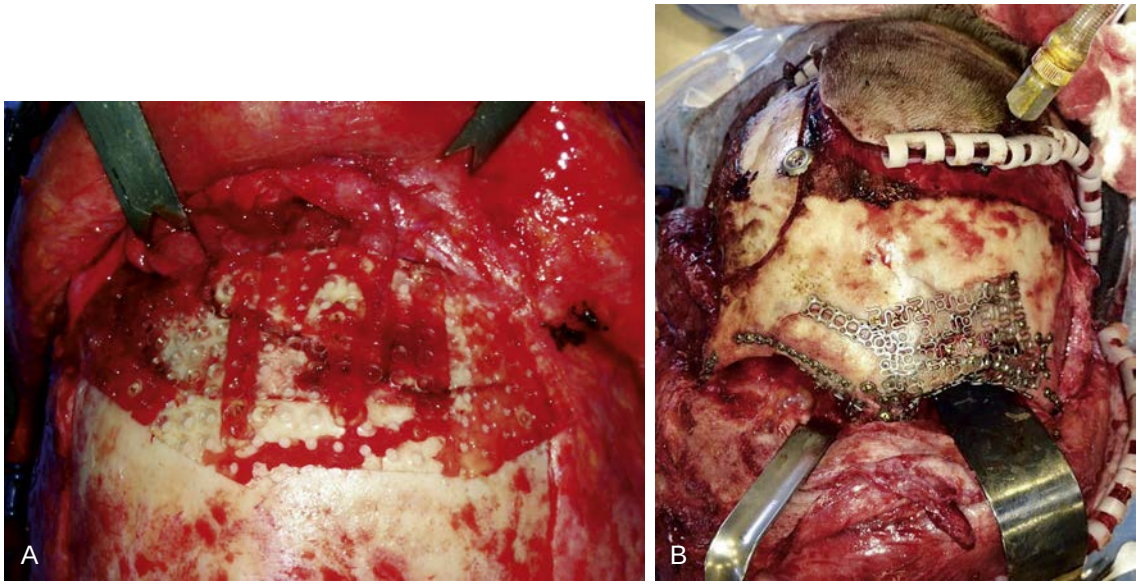
Alternatively, the dissection can be carried in a subgaleal plane all the way to the frontal bar; then a separate pericranial flap can be elevated which can be used as a vascular, pedicled flap to line the posterior wall or be used to obliterate the sinus (Figure 11-20).[18]

Once the fractures are visualized, treatment algorithms dictate how they should be addressed. Management of frontal sinus fractures is predicated on three anatomic structures: anterior table, posterior table, and NFDs (Figure 11-21). If the fracture is isolated to the anterior wall only without involvement of the NFDs or the posterior wall, but the displacement is greater than the width of the anterior table, the depressed segment is carefully reduced, and the fracture is fixated with titanium miniplates or resorbable plates (Figure 11-22). No further intervention is required. Nondisplaced or minimally displaced isolated anterior table fractures (less than the width of the anterior table) typically do not require surgical repair.

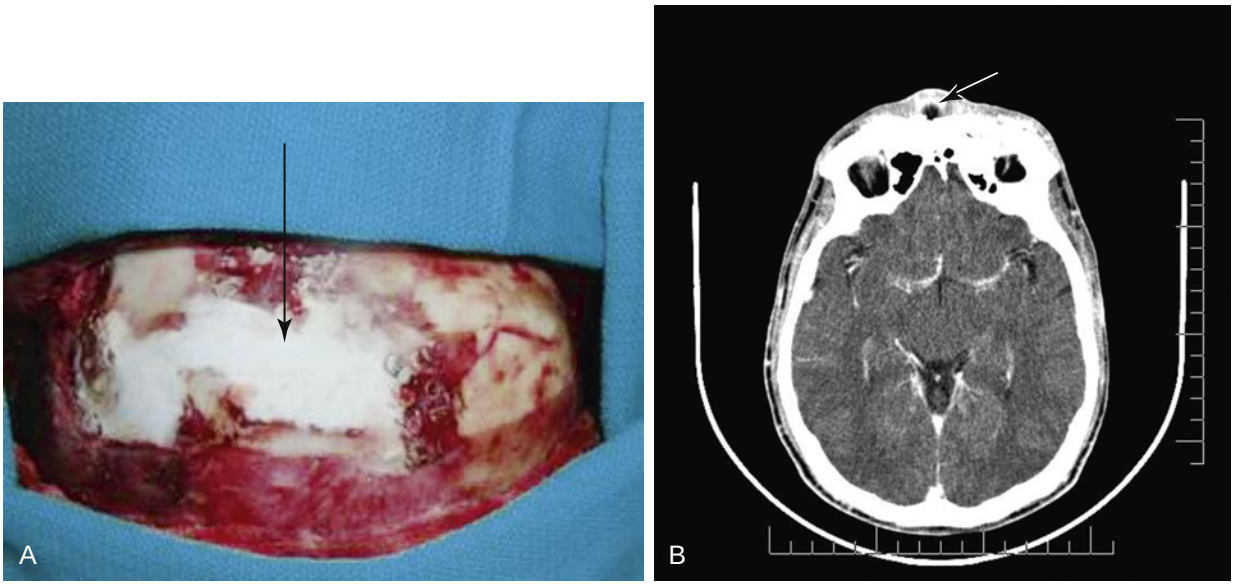
If the anterior wall and the NFDs are involved in the injury, then the decision must be made based on the health of the NFDs. The fractured anterior wall segments must be carefully removed and saved. If the status of the NFDs is uncertain, the patency of the ducts can then be confirmed by injecting a dye (methylene blue, fluorescein, or sterile milk) directly into the ducts at the base of the



• **Figure 11-21** Simple algorithm for management of frontal sinus fractures.



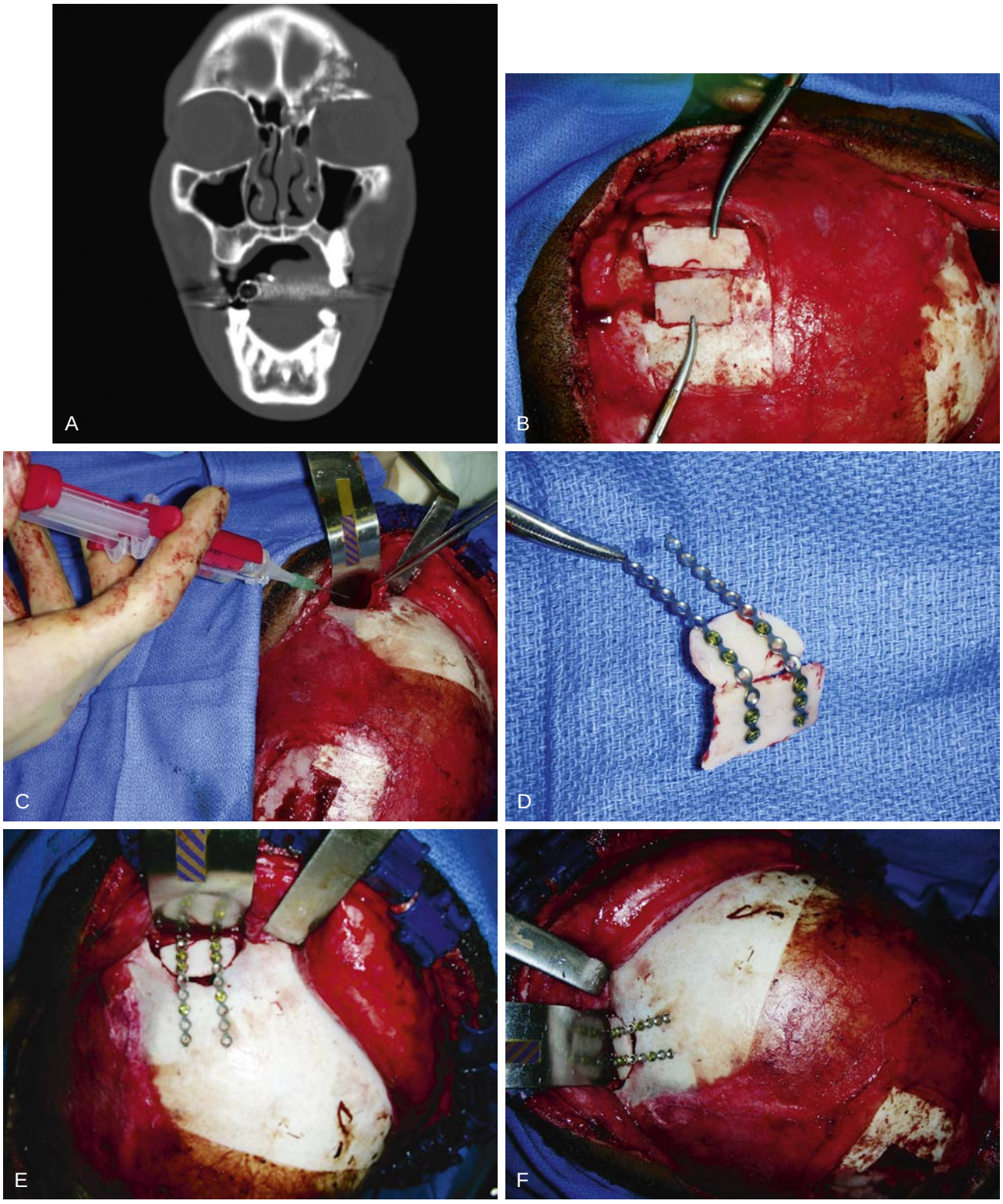
• **Figure 11-22** Reconstruction of the anterior table with resorbable mesh **(A)** and titanium **(B).**



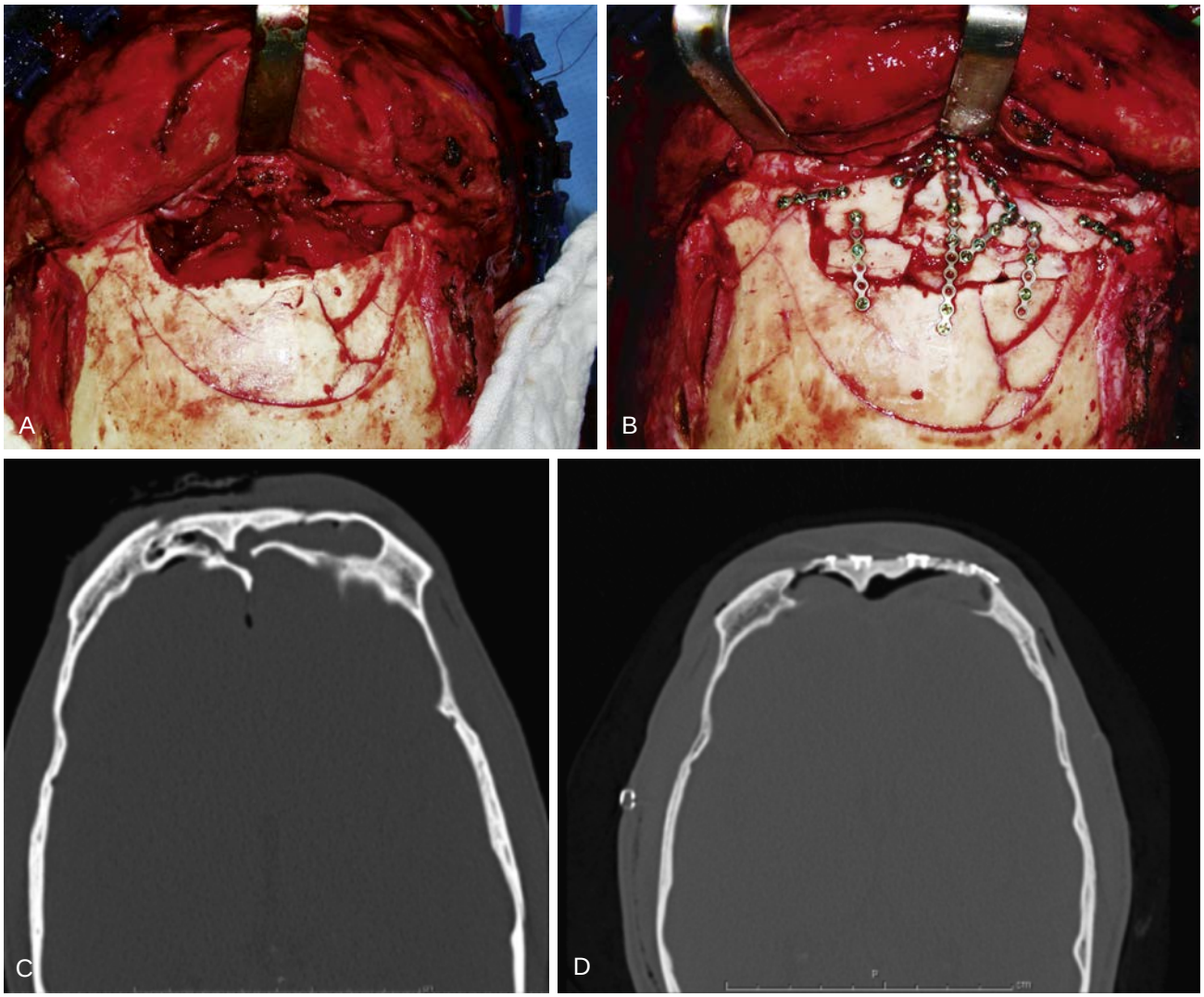
• **Figure 11-23** **A**, Intraoperative photo of patient with synthetic bone cement used for frontal sinus obliteration *(arrow)*. Two months later, the patient presented with a forehead abscess. **B**, Note abscess anterior to the sinus *(arrow)*. Patient required multiple debridements to remove necrotic bone and cement.

frontal sinus. If the dye is visualized in the middle meatus or in the nasopharynx, the NFDs are intact and do not require obliteration. If the NFDs are grossly involved in the fracture, or the results of dye injection are equivocal, the NFDs should be obliterated. [19,20] Obliteration of the NFDs renders the frontal sinus nonfunctional; therefore, the nasal cavity must be sealed from the sinus and the brain. This is done by removing any sinus lining from the opening of the NFDs and plugging the ducts with autogenous material such as fat, pericranium, temporalis muscle, fascia, or bone.[2,21] The sinus lining is removed with rotary instruments or sinus curettes. Oftentimes, sinus obliteration is done at the same time of NFD obliteration. Sinus obliteration is performed by removing all remnants of respiratory epithelium from the injured sinus. If the fractured anterior wall has been removed to facilitate access into the sinus, all sinus epithelium should be removed from it as well. The purpose of sinus obliteration is to close the dead space created by occluding the NFDs. It also offers one more layer of protection against retrograde nasal contaminants. Common materials used for sinus obliteration include abdominal fat, bone, and pedicled pericranial flap. Synthetic hydroxyapatite or bony cements should not be used to obliterate the entire sinus because of the high risk of infection secondary to lack of adequate vascularization (Figure 11-23).[2] The use of synthetic fibrin sealants has gained popularity in recent years in maxillofacial surgery.[22] Fibrin sealants essentially mimic the final two steps in the clotting cascade, forming a thin, sticky, gelatinous fibrin layer that can be sprayed onto an area. Fibrin sealants have been used in the management of frontal sinus fractures for occluding NFDs, for sinus obliteration, and in cases of posterior wall fractures by sealing the sinus from the dura and brain (Figure 11-24). Abdominal fat is, however, the most widely used material and is harvested from an infraumbilical, midline transverse incision 3 to 4 cm in length; alternatively, fat can be harvested from a 1-cm incision at the inferior portion of the umbilicus for a more aesthetic result. Blunt dissection superficial to the rectus fascia allows access to superficial abdominal fat, which can then be transplanted into the sinus. More than 60% of the transferred fat may be resorbed with time, so overfilling and gentle harvesting of the fat is important.[23-25] The authors' preferred method of obliteration is elevation of an extended pericranial flap; not only can this flap be used in obliteration of the sinus cavity, it can also be used to provide a layer of protection over dura in cases where cranialization is necessary.

Management of the posterior wall fractures probably poses the greatest risk of complications because of the potential for brain injury.[23-26] If a posterior wall fracture is present, irrespective of the presence of an anterior wall or NFD injury, the first question to ascertain is the determination of dural tears and CSF leaks. Most nondisplaced posterior wall fractures will not cause injury to the dura. On the other hand, grossly comminuted and displaced fragments of the posterior wall can in fact cause dural tears in the frontal lobe and initiate a CSF leak. If there is a nondisplaced posterior wall fracture, intraoperative evaluation is necessary to ensure absence of CSF leakage. CSF can be seen as a clear fluid leaving through the fractured segments of the posterior wall. If there is no CSF leakage, one can proceed as stated previously with any NFD injuries or anterior wall injuries. Fibrin sealants are an excellent option to seal any small fractures in the posterior wall. In cases of posterior wall displacement or gross comminution, significant dural tears can occur. Management of frontal sinus fractures with displaced or grossly comminuted posterior wall fractures requires a cranialization



• **Figure 11-24** **A,** Comminution of the sinus floor with involvement of the anterior table and nasofrontal duct (NFD). **B,** Due to severe comminution, cranial struts were harvested to reconstruct the orbital roof and anterior sinus table. **C**, Application of fibrin sealant into the NFD and posterior wall. **D,** The harvested struts were plated to recreate an orbital roof and anterior sinus wall. **E-F,** Reconstructed area following securing of bone graft to the adjacent area.



• **Figure 11-25** **A,** Anterior table and posterior table have been removed. Nasofrontal ducts are occluded. Sinus is cranialized. **B,** The anterior table has been reconstructed using plates and screws. **C-D,** Note removal of posterior wall and anterior movement of the frontal lobe following cranialization.

procedure. In this procedure, the entire damaged posterior wall is removed, all dural tears are repaired, and the frontal lobe is allowed to expand into the sinus (Figure 11-25). A formal frontal craniotomy may be required depending on the extent of dural injury (Figure 11-26).[27] In this procedure, the anterior cranial fossa is essentially increased. If cranialization is undertaken, the NFDs and the sinus must be obliterated as previously described. It is paramount to occlude the NFDs and completely separate the nasal cavity from the newly cranialized frontal sinus. Again, as previously mentioned, pericranial flaps can be quite useful in this mode of therapy.

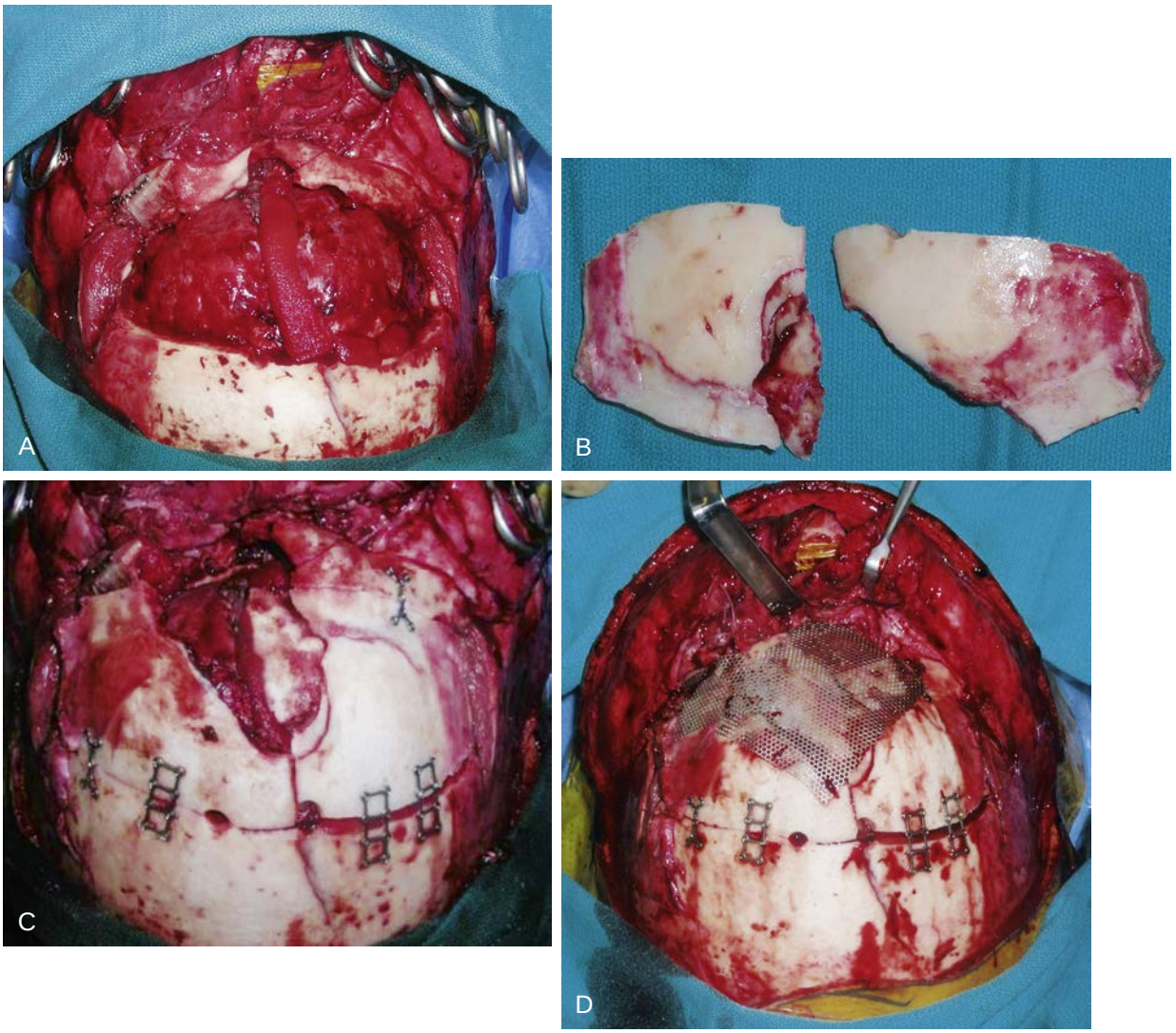
In cases where gross comminution of the anterior wall renders its reconstruction difficult, one can use a large titanium mesh or obtain split calvarial bone to reconstruct the anterior wall.[28]

There are instances where the patient has two separate frontal sinuses separated by a thin bony septum. If only one side is injured, and there is no radiographic or clinical evidence of involvement of the other sinus, surgical repair should only be done to the injured sinus; the noninvolved sinus can continue to function as a normal paranasal sinus.

Endoscopic Repair

Newer technologic advances also play a role in the management of frontal sinus fractures. Isolated anterior table fractures can be treated with endoscopic assistance.[29-31] This technique is rather limited because it will not offer access into the sinus

This is a useful technique where elevation of *large* bony fragments of the anterior wall is needed. Although it might be somewhat time consuming, it certainly obviates the need for a coronal incision and can reduce length of hospital stay postoperatively (Figure 11-27).



• **Figure 11-26** **A,** A frontal craniotomy to access large dural injury and intracranial bleed. The frontal sinus is fractured. **B,** Frontal bone is split into two pieces. **C,** Replacement of the frontal bone. The sinus has been cranialized. **D,** Large titanium mesh is placed to cover bony irregularities.

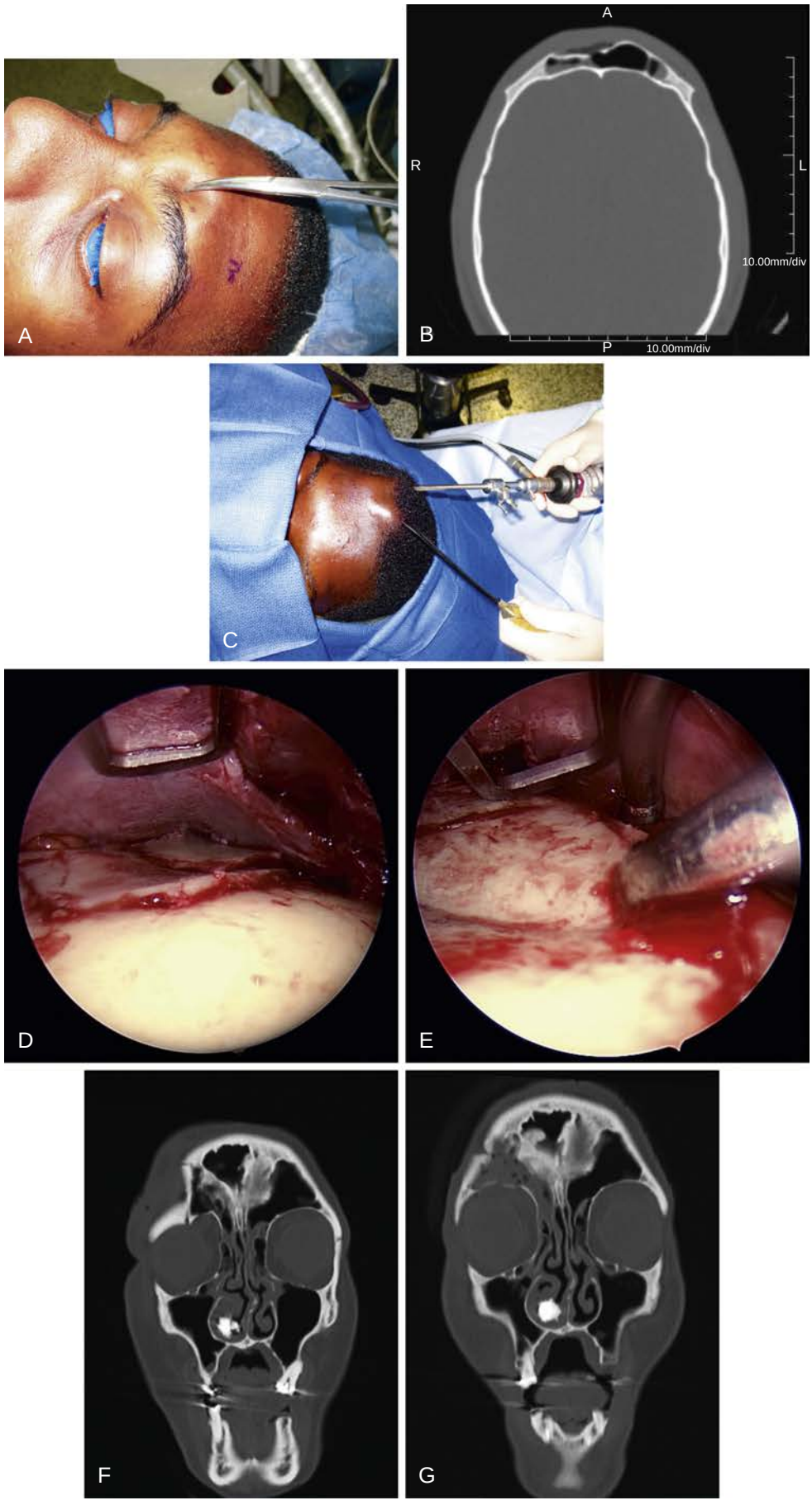
Postoperative Care

Patients with repaired frontal sinus fractures should receive perioperative antibiotics and be placed on sinus precautions. Length and choice of antibiotic therapy varies from institution to institution and is surgeon dependent. At least 24 hours of antibiotic therapy should be rendered to the patient. Sinus precautions should be continued for approximately 10 days. Physical activity should be avoided. Forehead sutures (if a forehead laceration was used during repair) should be removed in 5 days. Scalp sutures or staples should be removed in 10 to 14 days. A postoperative CT scan is recommended to assess the reconstruction of the sinus and to serve as a reference for future use. In cases where no surgery was rendered (e.g., nondisplaced fractures), a follow-up CT at 6 weeks is recommended to ensure proper aeration of the sinus.[32] Because certain postoperative complications can occur up to years later, frequent follow-up visits are recommended. This can be challenging at times because of the generally low compliance rate of patients with facial injuries.

Complications

There are two types of complications following frontal sinus fracture repair: acute and chronic.[4-6,33,34] Acute complications can occur within the first several weeks postoperatively and may include the following:

1. *Wound infection associated with the incision.* This may require local wound care, antibiotic therapy, and local debridement.
2. *Infection associated with the sinus (frontal bone osteomyelitis) and its new contents (abdominal fat, pericranial flap, etc.).* This more serious complication can be due to retrograde infection from the nose or formation of a blood clot within the sinus, which can foster an abscess. This is a serious matter and requires radiologic evaluation and



• **Figure 11-27** Anterior wall fracture.



• **Figure 11-28** Patient with postoperative cellulitis of the forehead 14 days following obliteration of the frontal sinus. Note areas of redness.



• **Figure 11-29** Hematoma formation following harvest of abdominal fat. Arrow points to umbilicus.

surgical intervention and debridement to prevent intracranial spread of infection (Figure 11-28).

3. *Complications associated with the donor site (abdomen).* If abdominal fat has been harvested, care must be taken to ensure a completely hemostatic donor site. Hematoma formation following abdominal fat harvest is rare, but must be treated with formal incision and drainage (Figure 11-29).
4. *Intracranial events such as meningitis and brain abscess.* This can be a direct extension of an abscess from within the sinus cavity with intracranial spread. It requires urgent medical and surgical intervention.
5. *CSF leaks.* Most CSF leaks associated with facial fractures cease following repair of the fracture. However, persistent CSF leaks following repair of frontal sinus fracture may require bed rest, elevation of the head, sinus precautions, or more invasive interventions such as lumbar drain or skull base surgery.

Chronic complications can occur up to years or decades the NFDs or the sinus. Because the sinus may not be functioning (depending on the treatment rendered at enlarge, erode through adjacent bone, and spread intracranially.

2. *Cosmetic deformity.* If the anterior wall is not reconstructed properly or if the hardware is palpable, contour irregularities may occur. This usually necessitates a cranioplasty to augment and camouflage the contour deficit, or removal of the hardware. Contour irregularities can also occur following osteomyelitis of the frontal bone, which requires surgical debridement.
3. *Chronic headache and neurologic deficits.* Blunt trauma to the head may lead to posttraumatic concussion syndrome.[35] This can cause long-term headaches with no residual focal deficits. Other neurologic deformities include altered sensation of the forehead and scalp from the supratrochlear and supraorbital nerves, which might have been injured during the initial insult and/or surgery.

Management of postoperative complications, acute and chronic, requires a team approach including the surgeon, neurologist, and neurosurgeons. This ensures proper communication between practitioners and prompt management of potentially serious sequelae.

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12

Assessment and Management of the Injured Child

BRUCE B. HORSWELL, DAMIAN MAXWELL

Epidemiology, Assessment, and Management of Pediatric Trauma

Introduction

Surgical care of infants and children has improved dramatically in the past four decades. One area of concern, however, remains in the area of pediatric trauma care. Worldwide, childhood injury remains a growing and costly problem. Every year approximately 875,000 children die from trauma, and nonfatal injuries directly and indirectly affect tens of millions of children globally.[1] As access to food and potable water improves and infectious diseases are more effectively controlled, injury remains a prolific killer and major cause of death in children. Trauma is the leading cause of morbidity and mortality among U.S. children, surpassing that of all other major causes combined.[1,2] On average, 12,000 children 0 to 18 years of age die each year in the United States from an unintentional injury.[3]

Mechanisms of Injury

The highest injury mortality rates for all death in children are due to unintentional injuries. Children aged 5 to 19 years die primarily from motor vehicle–related injuries, which peak during adolescence.[4,5] Bicycle-related accidents, inclusive of those involving motor vehicles, are still a significant problem for young and school-aged children.

Blunt injuries are more common than penetrating injuries in children, but penetrating injuries are more lethal. Despite a relative decline in penetrating injuries over the past 20 years, firearm-related deaths continue as one of the top three causes of death in American youth.[6-8] The reduction in injuries may be related to a concerted push by many health care organizations (American College of Surgeons, American Academy of Pediatrics, American Pediatric Surgery Association) to improve awareness and promote change in policy toward firearm possession and use. Similarly, education and environmental changes to promote behavior modification and ensure safety for children have all contributed to the reduction in firearm-related injury. Non-accidental trauma (child abuse) accounts for 5% to 10% of trauma-related injuries.[7] In summary, the leading cause of pediatric trauma mortality is from falls, and second is related to motor vehicle collisions.[8]

Gender

The death rate from injury for males is nearly twice that for

ence in incidence.[9] Boys are also more prone to participate in contact sports and personal violence.

Outcomes

Data on outcomes for pediatric patients treated at dedicated pediatric trauma center versus non-dedicated centers have been conflicting. Both historical studies and contemporary investigations indicate that survivability and recovery is enhanced in hospitals that specialize in pediatric trauma rather than in non-specialized hospitals. Recent studies have shown that pediatric injury mortality is inversely proportional to the number of level 1 (highest designation by the ACS) pediatric trauma centers that regionally serve a population.[10-13] Conversely, injury-related mortality does not appear to differ when treating adolescents at adult trauma centers when compared to pediatric trauma centers.[14] Generally, outcomes improve at ACS-designated trauma centers, whether adult or pediatric, but verified level 1 pediatric trauma centers appear to have increased survivability and improved functional outcomes for infants and children.[10]

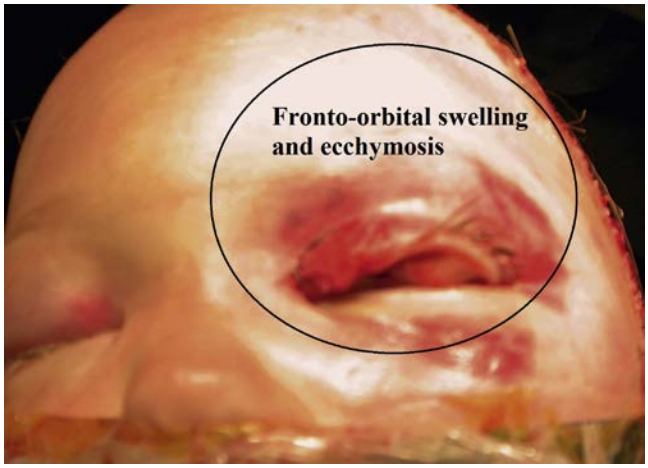
Costs

The financial burden related to childhood trauma is difficult to assess. One has to consider acute care medical costs, rehabilitation efforts, the loss of work or production, and the combination of these factors over a projected life span. The estimates, as depicted in Figure 12-1, are in the billions of dollars. These estimates take into account the loss of manpower in the workforce as well as the immediate and long-term costs to the individual and family/caregivers. Although children do tend to recover from injury faster than adults, their functional outcomes, if initially poor, are worse in the long term.[6] The indirect costs are immeasurable when considering the loss or chronic impairment of a child in the family or community.

Initial Evaluation

Assessment of the injured child differs from the care of adults in their unique injury patterns, physiologic responses, and management. Compared to adults, children have a smaller body mass to body surface area ratio and a less rigid skeleton protecting abdominal and thoracic structures. Energy transmitted through the body per unit volume, therefore, is much greater, leading to multi-system injury. The higher ratio of surface area to body mass also accounts for increased susceptibility of the pediatric patient to insensible fluid and heat loss, compounding the physiologic derangement in traumatic injury.[11]

Immediate action, whether in the field or at a medical facility, requires a systematic approach so that subtle, treatable injuries do not progress and become life-threatening. In 1979, Crowley defined the "Golden Hour," the first hour after a traumatic injury, as being critical for treatment to ensure optimal care for injured patients.[12] Dr. Alex, took it one step further when in 1994 at the Scudder Oration on Trauma of the American College of Surgeons (ACS), he referred to this early resuscitation period in young children as the "Platinum Half Hour."[13]



• **Figure 12-1** Child with head trauma and obvious peri-orbital bruising *(circle)*.

Several questions need to be answered during this critical time when confronted with these unknowns:

1. Is there an immediate threat to life?
2. Is this a single or multiple organ injury?
3. What is the most effective way to facilitate stabilization, workup, diagnosis, and therapy?

This approach involves the primary survey, a resuscitative phase, a secondary survey and definitive care as described by Advanced Trauma Life Support (ATLS) as advanced by the ACS.[14] The primary survey involves the identification of injuries related to control of the *airway*, ensuring adequate *breathing*, maintenance of *circulation*, assessing neurologic *disabilities*, and complete *exposure (ABCDEs)*, in that order but often simultaneously. This systematic progression addresses and corrects immediate threats to life *(ABCDs)* and assists in appropriate triage of the injured child. Adjunctive measures including urinary and naso-orogastric catheters should be placed where indicated and additional diagnostic measures that complete the initial evaluation include pulse oximetry measurement, intravenous (IV) access, electrocardiogram (ECG), radiographs, and focused assessment by sonography for trauma (FAST).[14-16]

Primary Survey—*ABCDEs*

- ***A***irway: clear, maintain and secure, protect cervical spine
- ***B***reathing: ventilate and oxygenate
- ***C***irculation: control bleeding, restore volume
- ***D***isability: Pediatric Glasgow Coma Scale (PGCS) and pupils
- ***E***xposure: disrobe, logroll, avoid hypothermia
- Foley catheter unless contraindicated
- Gastric tube unless contraindicated

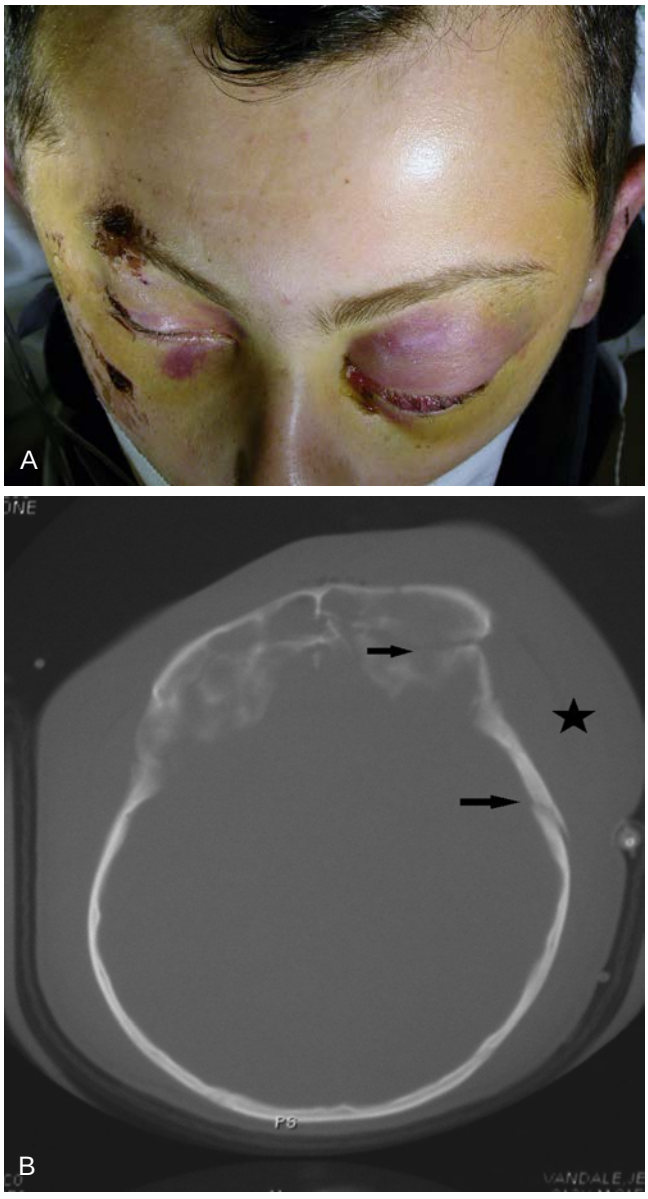
Studies

Although a lateral c-spine, chest x-ray, and pelvic x-ray are still commonly ordered, their sensitivity to identify such injuries as pelvic fractures and cervical spine injuries are limited. The clinician should be cognizant that children's x-rays are not interpreted in the same manner as adult studies. Children may have significant spinal cord injury without radiographic abnormality (SCIWORA) or other bony injuries with what may appear to be normal x-rays.[11]

FAST is the evaluation of choice for the determination of significant amounts of fluid in the pediatric abdomen. It is especially useful in the hypotensive patient in whom the clinician wants to rule out intra-abdominal cavitary fluid. Its yield is often user dependent, but when performed by a trained surgeon, FAST is indispensable.[17]

Suspicion of traumatic brain injury should prompt the use of emergent non-contrasted computed tomography (CT) scan of the head. Children are at significant risk for intracranial injury and therefore should undergo imaging, particularly those children with signs of somnolence and decreased or changing mental status and/or irritability, focal neurologic findings, depressed skull fracture, bulging fontanel, seizure, worsening vomiting, and loss of consciousness

(LOC) for longer than 1 minute (see Figure 12-1).[15] Identifying reliably sensitive and specific clinical indicators has been difficult, however, because studies have found conflicting evidence regarding the significance of LOC, vomiting, seizures, and headache. Children younger than 2 years should be considered as a separate entity. Younger children are more difficult to assess clinically, are more easily injured even from short falls, have a higher incidence of asymptomatic or occult injuries, and more often are victims of non-accidental injury.[14,15] In addition to the predictors of intracranial injury found in older children, nonfrontal scalp hematomas (surrogate markers for skull fracture) were found to be predictors of intracranial injury, with larger hematomas in younger children of greater concern.[15] If the index of suspicion remains high for intracranial injuries, then CT should be performed (Figure 12-2).



• **Figure 12-2** **A,** Child with large fronto-orbital hematoma and periorbital ecchymosis. **B,** Overlying scalp hematoma *(star)* and underlying cranial fractures *(arrows)* on computed tomography.

Indications for CT Head[11,14]

- Uncertain LOC or prolonged LOC
- Changing neurologic exam
- Bradycardia
- Signs of skull fracture
- Focal trauma, penetrating injury
- Bulging fontanel
- Signs of upper facial trauma
- Sedated or unreliable exam
- Seizures

Do not get CT in unstable, deteriorating child!

Criteria for Patients Who Can Reliably Forego Computed Tomography Imaging[14,16]

- Normal neurologic examination
- Normal mental status
- Normal behavior per caregiver
- No loss of consciousness (LOC)
- No vomiting
- No severe headache
- No evidence of skull fracture (for children <2 years, no nonfrontal scalp hematoma)
- No signs of basilar skull fracture (absent Battle, raccoon signs)
- No high-risk mechanism (fall greater than 3 feet in children <2 years, fall greater than 5 feet in older children, struck by high-impact object, ejection from motor vehicle, motor vehicle crash or auto pedestrian with death of another, auto-bike without helmet)
- No concern for non-accidental injury

Neurologic Status

Responsiveness is assessed with the alert, verbal, pain, unresponsive (AVPU) system and with the Glasgow Coma Scale (GCS) and its pediatric modification, the Pediatric Glasgow Coma Scale (PGCS) (Tables 12-1, 12-2, and 12-3).[17] The PGCS was developed for children younger than 5 years who have more limited communication skills. A total PGCS score of 13 to 15 represents minor injury, a score of 9 to 12 represents moderate injury, and a score lower than 8 represents severe injury.

Even with modifications, the GCS score has limitations in its use for infants and very young children. To date, however,

TABLE 12-1 Pediatric Glasgow Coma Scale: Eye Opening

Score	≥1 Year	0-1 Years
4	Opens eyes spontaneously	Opens eyes spontaneously
3	Opens eyes to a verbal command	Opens eyes to a shout
2	Opens eyes in response to pain	Opens eyes in response to pain
1	No response	No response

TABLE 12-2 Pediatric Glasgow Coma Scale: Best Motor Response

Score	≥1 Year	0-1 Years
6	Obeys command	N/A
5	Localizes pain	Localizes or withdraws to pain
4	Flexion withdrawal	Flexion withdrawal
3	Flexion abnormal (decorticate)	Flexion abnormal (decorticate)
2	Extension (decerebrate)	Extension (decerebrate)
1	No response	No response

TABLE 12-3 Pediatric Glasgow Coma Scale: Best Verbal Response

Score	>5 Years	2-5 Years	0-2 Years
5	Oriented, converses	Appropriate words	Cries appropriately
4	Disoriented but converses	Inappropriate words	Cries
3	Inappropriate words	Cries and/or screams	Cries and/or screams inappropriately
2	Incomprehensible sounds	Grunts	Grunts
1	No response	No response	No response

this is the best tool to facilitate communication between physicians and assess the neurologically injured child.[6,11,14]

Neurologic Disability

- Pupils: symmetry, reaction
- LOC: PGCS
- Track and trend PGCS as a vital sign
- Intubate for coma, PGCS ≤8
- Motor: strength, symmetry
- Abnormality/deterioration: call neurosurgeon
- Mild (PGCS 13-15): observe, consider CT for history of LOC
- Moderate (PGCS 9-12): admit, obtain CT, repeat CT 12-24 hr
- Severe (PGCS < 8): intubate, ventilate, obtain CT, repeat CT 12 to 24 hr

Resuscitation

Table 12-4 refers to some of the anatomic features that must be taken into consideration in the resuscitation of an injured child.

TABLE 12-4 Pediatric Anatomical and Clinical Relevance

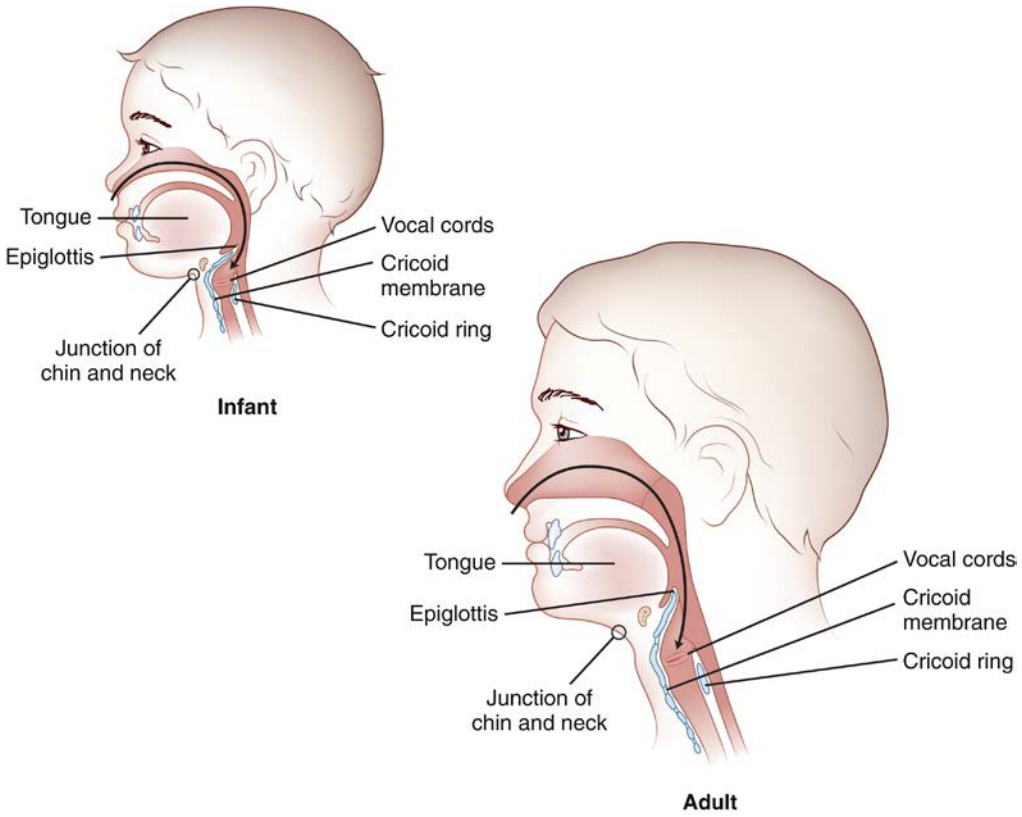
Anatomical Distinctive	Clinical Relevance
Large body surface area, small body size	Greater forces of injury dealt to a small body and more organ exposure to injury
Large cranium to body proportion	Head trauma and increased cervical strain
Elastic skeleton	Less external trauma (i.e., fractures) with concealed
Short pliable neck, large tongue	Difficult airway (uncuffed endotracheal tubes in very young)
Larynx anterior, short and cephalad with narrowest portion at cricoid	Increased risk of right bronchus intubation
Increased peripheral resistance and reflex tachycardia, less reserve	Rapid response to hypovolemia initially but also rapid cardiovascular decline with continued blood loss

At any point in the primary survey that a change occurs, the ABCDEs should be repeated to assess for deterioration. The evaluation of the injured child is a constant interplay between assessment and management as a dynamic process. Any child presenting after a major trauma should have supplemental oxygen and breathing supported. Respiratory distress and altered mental status are often the first signs of significant injury. In contrast to adult patients, tachycardia and hypotension are late signs of shock in the injured child.[11]

Airway

The pediatric airway has unique characteristics that must be considered to ensure a secure airway and optimize gas exchange. Because injured children do not usually present with preexisting pulmonary disease, serum oxygen saturation greater than 90% on room air is the objective hallmark of effective air exchange. Whenever this objective cannot be reached, one must consider parenchymal injury, pneumothorax, or aspiration. The most common reason to intubate an injured child is often to facilitate resuscitation from shock and/or coma.[6,16,18] Current trauma guidelines recommend immediate endotracheal intubation for patients with a PGCS <9 based on the high probability that such an altered level of consciousness is indicative of a brain injury of such severity that progressive cerebral edema is likely to occur.[18,19]

Airway management is complicated by a number of factors, including the urgency of situation with upper airway obstruction or preexisting hypoxia; uncertainty of cervical spine status; uncertainty regarding the airway because of the presence of blood, vomitus, or debris in the oral cavity or laryngopharyngeal injuries; a full stomach; intracranial hypertension; and uncertain volume status.[19]



• **Figure 12-3** Diagram of adult and pediatric airways and distinctions. (From Auerbach PS, Cushing TA, Harris NS: *Auerbach's wilderness medicine,* ed 7, Philadelphia, 2016, Elsevier.)

The pediatric airway is small, short, and funnel shaped (Figure 12-3).[20] Its small diameter is the most important determinant of gas exchange, because small changes in diameter from edema or deformity can result in significant alterations in gas exchange. Children have large tongues relative to their oral cavities, which can easily occlude the oropharynx. Therefore, one should "align" the oral, pharyngeal, and laryngeal introits as much as possible to facilitate movement of air.[14] The disproportion between the cranium and the midface is inversely related to the age of the child. The larger occiput results in a tendency for the neck to flex, forcing the tongue posteriorly into the pharynx. The larynx is more anterior in the young child, and orienting the mid-face slightly superiorly and anteriorly (the "sniffing position") will protect the airway from collapse.[20] Once this is performed, simple bag-mask ventilation often allows for adequate gas exchange. If the decision is made to intubate the patient, a roll should also be placed under the shoulders to assist in maintaining this alignment while protecting the cervical spine at all times. When preparing to intubate a child with a severely compromised airway from head or neck trauma, neuromuscular blockade should be avoided unless immediate surgical airway personnel and equipment are on standby.[18,19] Surgical airways can be established first by cricothyroidotomy with a 14-gauge needle followed by a formal tracheostomy once the patient is stable.

Breathing

Normal respiratory rate in children is age dependent. Whereas an infant will breathe 60 times per minute, an older child will breathe 20 times per minute. It must be stressed that *hypoventilation and the associated respiratory acidosis is the most common etiology of cardiac arrest in children.* Adequate ventilation, combined with fluid resuscitation to maintain perfusion, remains the basis for resuscitation in the pediatric trauma patient.[14,20,21]

Tension pneumothorax is a clinical diagnosis based on the findings of respiratory distress, tachycardia, hypotension, tracheal deviation, absence of breath sounds, jugular venous distention, and cyanosis (Figure 12-4).[14] Treatment should not be delayed for radiographic confirmation. When tension pneumothorax is suspected, immediate needle decompression is required. This can be accomplished by percutaneously inserting a large-bore needle at the second intercostal space in the midclavicular line. Definitive chest tube placement can then be performed in the fifth intercostal space at the anterior axillary line.

Circulation

Children often maintain a normal blood pressure and heart rate until there is significant cardiovascular collapse due to their excellent physiologic reserve. The diagnosis of shock therefore is not always straightforward. The accepted ranges

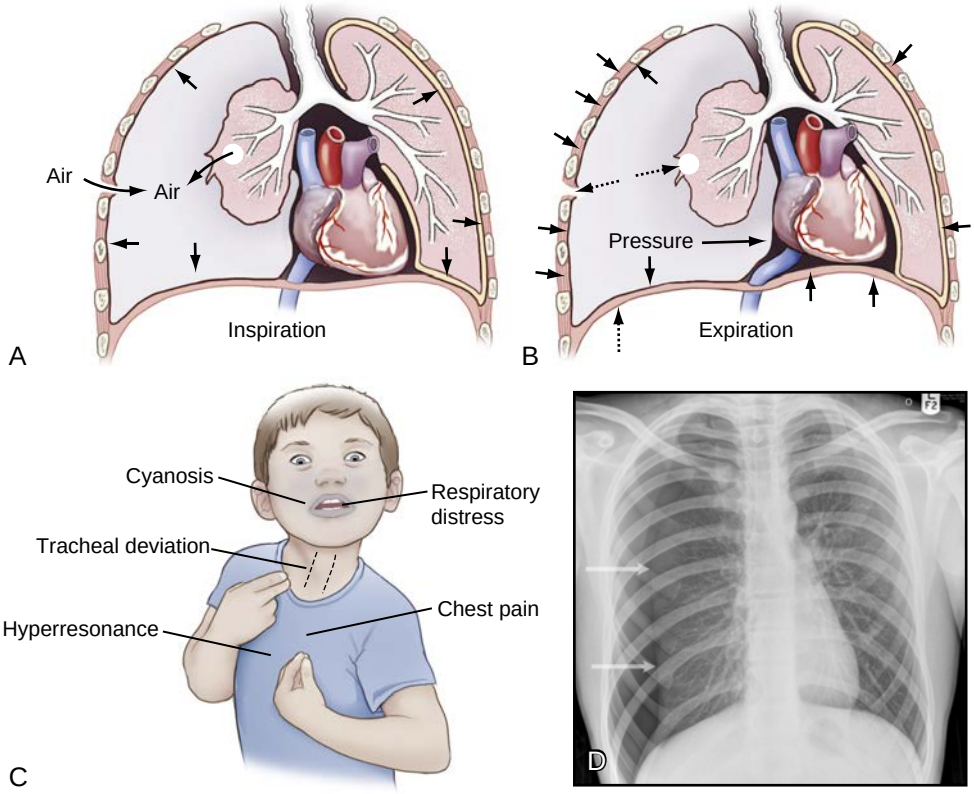
of normal for vital signs vary with age. A normal heart rate for an infant can be as high as180 beats/minute, while a heart rate of >100 beats/minute for an adolescent would be considered tachycardia.[22] Less obvious signs of hypovolemia, such as decreased pulse pressure, mottled skin, cool extremities, and lethargy, can be clues of shock in the eyes of the experienced clinician.[14,21]

The first step in establishing circulation is to control any obvious bleeding with direct pressure. Blind clamping and application of tourniquets are discouraged. Initial intravenous access can usually be obtained by percutaneous methods in an upper extremity vein. This can often be technically challenging in the hypovolemic patient. If percutaneous access is unattainable, placement of a femoral vein line is often the next most appropriate step. If access cannot be gained, then surgical cut-down to the greater saphenous vein above the ankle is commonly used. When all else fails, intra-osseous access and infusion is required. Cannulation can often be facilitated by patented drills designed for this purpose and should be directed into the medullary cavity in the anteromedial aspect of the tibia, 2 to 3 cm distal to the tuberosity (away from the plateau), under sterile techniques. All medications that can be administered by IV for resuscitation can also be given through an intraosseous line but require saline flush.[1]

The child with significant trauma will require volume resuscitation, which begins with 20 to 40 mL/kg *warmed crystalloid* solution. Systolic blood pressure less than 70 mm Hg plus twice the age in years requires 40 to 60 mL/kg of crystalloids followed by 10 to 20 mL/kg warmed type-specific or O-negative packed red blood cells. This degree of instability usually results from greater than 30% to 35% loss of circulation blood volume, estimated at 80 to 90 mL/kg for children. The most likely site of such hemorrhage is the peritoneal cavity, and this can be confirmed quickly by surgeon-performed FAST examination and a chest x-ray.[6,11] Restoration of blood volume is most commonly achieved with type-specific blood, but in dire emergency O-negative blood may be used. One must continue to use O-negative blood for resuscitation if this was initially given. Because significant volumes of anti-A and anti-B antibody may be present in massive transfusions, it is not appropriate to change to type-specific blood after massive transfusion of O-negative blood.[6,16]

Neurologic

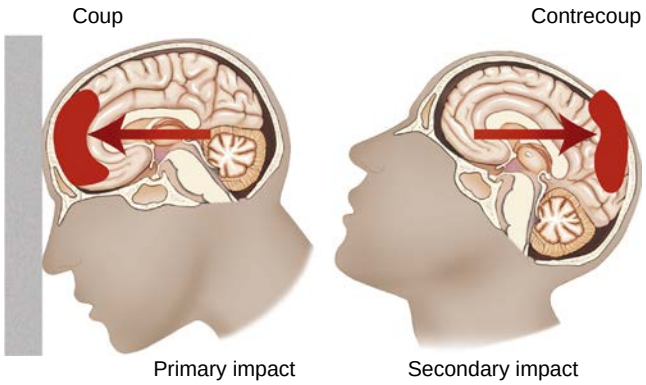
Traumatic brain injury (TBI) is an important cause of injury-related death and disability in children, accounting for over half of deaths. There is a bimodal distribution of TBI in children aged 0 to 4 years and adolescents.[4,23] TBI disproportionately affects males, accounting for the majority of hospital-related



• **Figure 12-4** Tension pneumothorax with absent breath sounds, tracheal deviation away from injury, jugular distention, and cyanosis. (**D** From Kumar Thakur R, Mahomed A: Correlating radiology with thoracoscopic findings in a case of primary spontaneous pneumothorax in a child? *J Minim Invasive Surg Sci* 2(3):31-34, 2013.)

encounters and deaths from TBI in boys.[23] Non-accidental trauma (shaken baby syndrome or child abuse) should always be in the differential diagnosis in infants and young children.[24] Blunt or non-penetrating trauma occurs as the result of a direct impact on the brain and skull. These injuries often occur after a motor vehicle collision or fall and account for the vast majority of TBI in the United States.

Blunt head injury patterns vary, but regardless of classification, they typically result in damage to the underlying brain by either *coup or contrecoup forces* (Figure 12-5). Focal damage to the ipsilateral side of contact is termed coup and damage to the opposite side of the brain is termed contrecoup. The predominant contrecoup damage occurs on the side opposite the impact and is commonly accompanied by subdural hemorrhages and cortical contusion. The brain "bounces" off the skull, causing disruption of the overlying and very fine lattice-like surface meningeal vessels.[24]



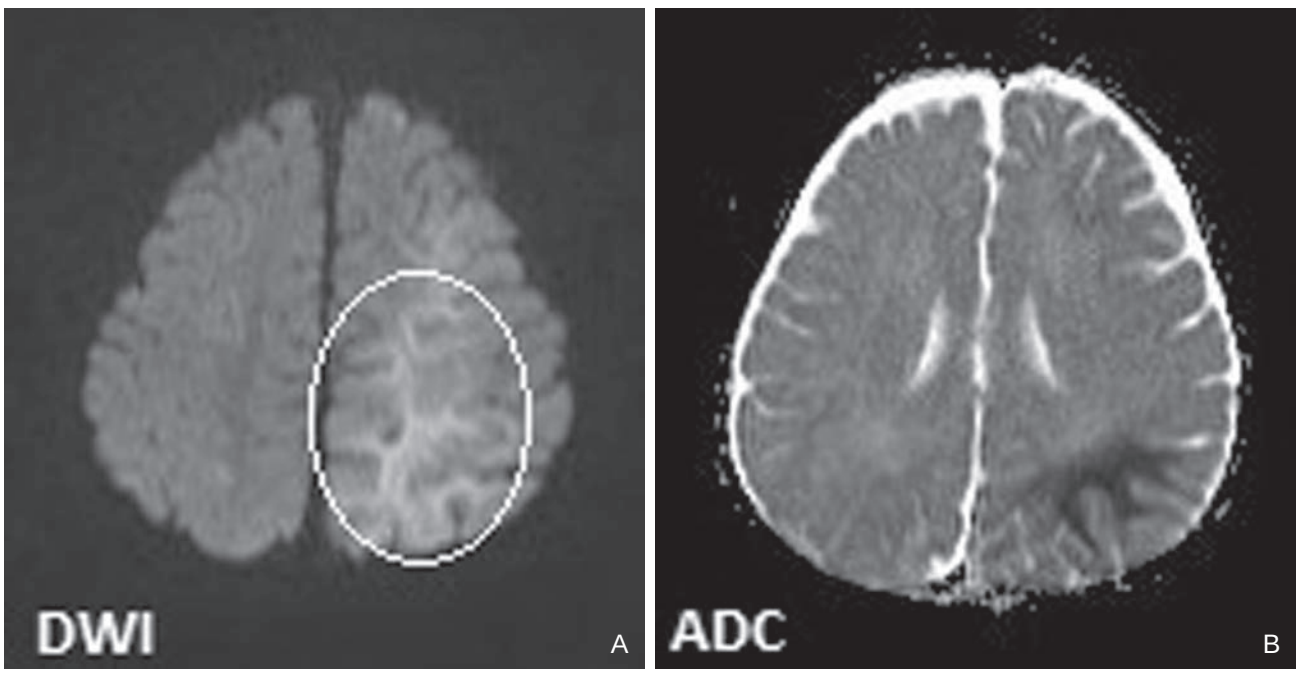
• **Figure 12-5** Whiplash and coup-contrecoup intracranial forces. The primary site of injury results from the brain thrust against the frontal area from sudden whiplash and/or striking an object forcefully. The secondary site of injury results from the brain being thrust backward after impact in a recoil motion. (Lewis SL, Dirksen SR, Heitkemper MM, Bucher L, Camera I: *Medical-surgical nursing: assessment and management of clinical problems,* ed 8, 2011, Elsevier.)

Penetrating injuries result in direct cerebral disruption of the underlying neuronal and vascular connections and indirect blast effect, especially in gunshot wounds. Penetrating injuries also carry a risk of increased infection due to the introduction of foreign material.

Axonal Injury

Axonal injury results from acceleration and deceleration forces or sudden rotation of the head and its "shearing" effects on the underlying neuronal structures. Axonal injury is often coupled with vascular injury. After several hours, physical separation of the axons occurs into proximal and distal segments. Mechanisms include blunt force, whiplash, and violent shaking. This shearing injury is classically observed as petechial hemorrhages in white matter and commonly referred to as diffuse axonal injury (DAI).[25] CT findings, although less sensitive than magnetic resonance imaging (MRI), may show punctate lesions <2 mm in the white matter, corpus callosum, and brainstem or vascular defects in diffusion-weighted images (Figure 12-6). Patients with DAI may spontaneously recover with transient loss of consciousness, or if severe, may be left with permanent neurologic defects or succumb to this potentially lethal injury. To date there are no effective treatments for DAI.

The benefit of routine *repeat* head CT scans in all brain-injured children admitted to the intensive care unit is of questionable value. One study of 173 patients demonstrated a 27% rate of CT-identified new lesions after initial CT, though no patients required operative intervention or



• **Figure 12-6** Magnetic resonance imaging diffusion-weighted image **(A)** with evidence of parenchymal edema and vascular flow defects **(B)** indicative of diffuse axonal injury.

change in care.[26] Another study of 63 children who had sustained TBI and were re-scanned 24 hours after their initial CT found a highly significant correlation between the children's GCS status and CT findings. The authors concluded that most patients with an unchanging or improving neurologic examination did not justify routine repeat head CT.[27]

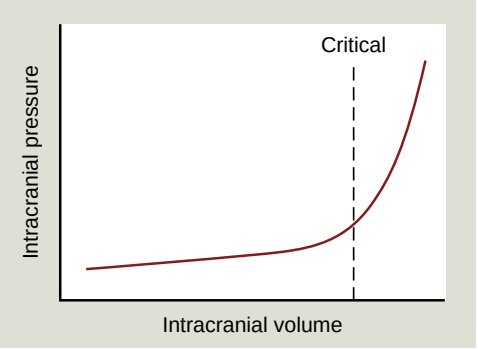
Concussion

Concussion is often used to label the constellation of symptoms that occur after mild to moderate TBI when no pathologic lesion or process is identified. Generally speaking, concussion is a head injury resulting in altered mental status, with or without loss of consciousness. Classic symptoms include headache, nausea, vomiting, difficulty concentrating, retrograde and/or anterograde amnesia, and personality changes.[28] Complete recovery after concussion is common though unpredictable. Long-term consequences include impaired attention, cognition, depression, mood disorders, and emotional lability.[27,28]

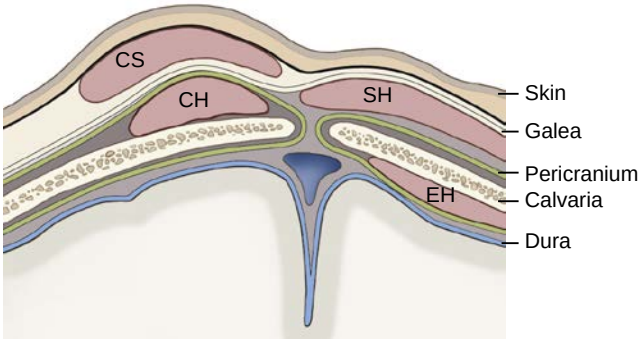
The developing brain of a child has some structural differences when compared to the adult. The disproportionately large skull of an infant has to account for the rapid increase in size of the brain that takes place in the first 3 years of life.[28] The developing brain has incomplete synapse formation and neural arborization, which account for the impressive developmental cognition of a child as they mature. The subarachnoid space around the brain adds little protection from blunt trauma or applied shear forces. Studies have indicated that the smaller neural axis of infants and young children results in a less compliant pressure-volume relationship with an increased risk of intracranial hypertension, despite the space for expansion afforded by open sutures and fontanels.[29-31]

Monroe-Kellie Doctrine

Given that the cranium is a rigid, non-expansile container, the Monroe-Kellie doctrine states that the total volume of the intracranial contents will remain constant and any increase in the volume of one component must be at the expense of another.[32] Therefore, once a space-occupying lesion expands beyond the compliance of the other structures, the intracranial pressure (ICP) will begin to rise.[30-32] Expanding intracranial hemorrhages are classic examples of this phenomenon. Figure 12-7 demonstrates this intracranial phenomenon.



• **Figure 12-7** Intracranial volume (constant) = Brain + CSF + Blood + Mass lesion volumes Intracranial components are noncompressible; thus, once the cranial vault is filled, pressure (ICP) rises dramatically. Increasing ICP eventually leads to decreased cerebral blood flow. Expansile lesions or edematous brain will push CSF into the spinal canal or vascular spaces and herniation shortly follows.



• **Figure 12-8** Diagram of subtypes of hematomas in traumatic brain injury in children. *CH,* Cephalohematoma; *CS,* caput succedaneum; *EH,* epidural hematoma; SH,subgaleal hematoma.

Intracranial Hemorrhage

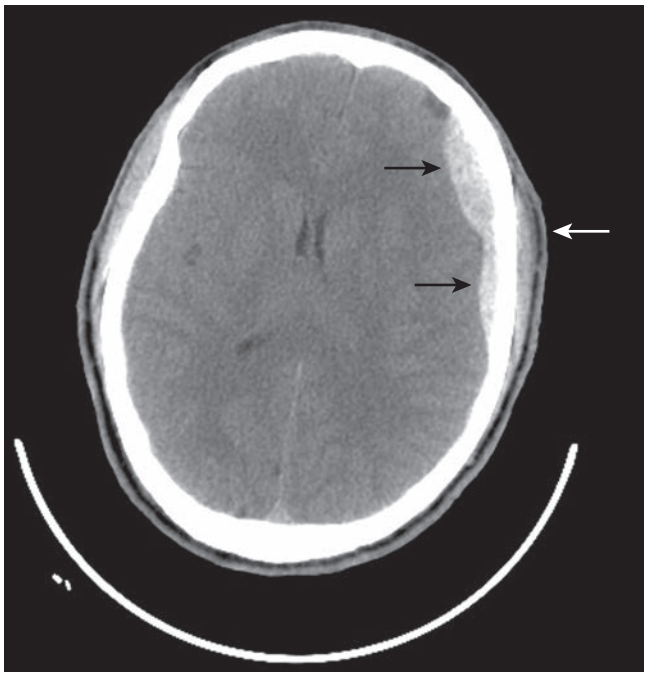
Head trauma in children may result in both extra- and intra-cranial bleeding. Some overt presentations with obvious swelling, such as caput succedaneum or cephalohematomas from traumatic birth, are fairly benign, require no interventions and usually clear within days to weeks. Caput swellings are edematous scalp accumulations which cross the sutures, whereas cephalohematomas accumulate below the pericranium and are therefore confined by the sutural margins. Cephalohematomas are true hemorrhages and take longer to resolve. These are typified in Figure 12-8.

Subgaleal hemorrhages are superficial to the skull, confined between the galea and pericranium, and generally are flatter and broader. More significant hemorrhages are those which occur intracranially from direct trauma to the head. Epidural hematomas are *extra*dural, and result from a disrupted artery with progressive expansion and a clear demarcation on CT imaging. Subdural hematomas are blood accumulatio

du
grammatically illustrates these particular lesions in TBI.

Epidural

Epidural hematoma typically results from disruption of the middle meningeal artery and is classically seen on CT as a lenticular or biconcave hypodense lesion (see Figure 12-9). The classic presentation of a "lucid interval" after TBI is less common in children than adults.[25,31] Typical symptoms include headache, lethargy, vomiting, irritability, confusion, and decreased level of consciousness. Progressive deterioration can result in seizures, hypertension, respiratory instability, pupillary changes, posturing, and cardiovascular compromise. Indications for evacuation can be size of lesion (>40 mL) or a neurologically deteriorating patient.[31]



• **Figure 12-9** Axial computed tomography with contrast demonstrating epidural hematoma *(black arrows)* and classic lenticular or concave contour. Overlying scalp hematoma is noted *(white arrow)*.

Subdural

shaped lesions on the surface of the brain follow the convexities and tend to encompass more of the hemisphere (Figure 12-10). These lesions are often associated with mass effect and cortical edema. Operative intervention is indicated when neurologic decompensation occurs in the presence of subdural hemorrhage and parenchymal injury.[25]

Acute subdural hematomas have a worse prognosis when compared to epidural hematomas because of the associated brain damage. In infants, it is possible to tap the subdural space at the level of the fontanel and produce rapid decompression. Patients with a midline shift greater than 5 mm should have prompt evacuation of clot and decompression via craniotomy.[31]

Subacute subdural hematoma can present in a similar fashion to acute hematoma but with signs of elevated ICP (frontal bossing, enlarged heads, dilated scalp veins, sunsetting eyes, papilledema, and bulging fontanels). The CT scan often shows isodense or hypodense fluid collections at the cerebral convexities. MRI studies may be helpful in diagnosing ongoing bleeding.[33] As with acute subdural hematomas, operative evacuation is often necessary.

Chronic subdural hematomas can cause symptomatic elevation of the ICP and may require intervention to manage increasing cranial expansion. Presentation is similar to those of a subacute subdural hematoma. Management options may include serial percutaneous CSF or hematoma drainage, limited craniotomies to drain and irrigate the subdural space, and subdural/peritoneal shunts.[31]

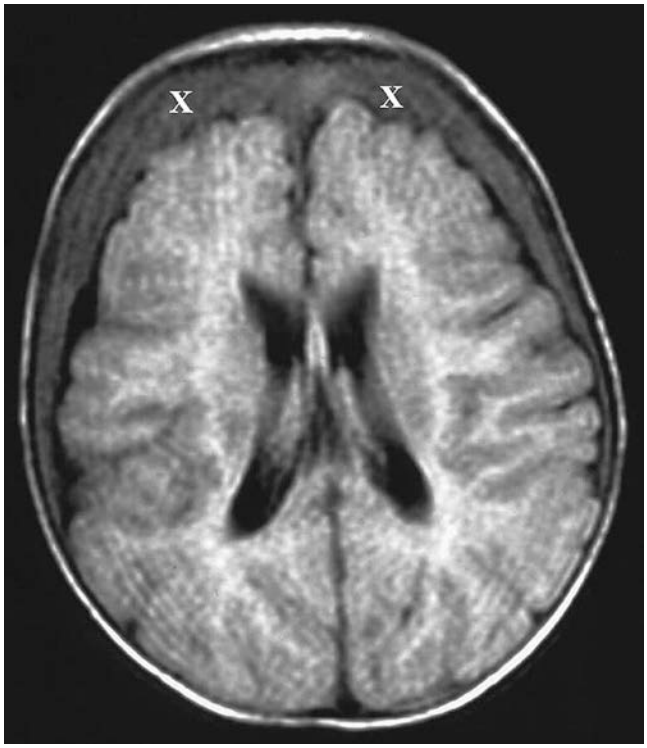


• **Figure 12-10** Axial computed tomography with contrast demonstrating subdural hematoma with irregularity that follows the contours of the cranial and cerebral surfaces *(arrows)* and encompasses more of the hemisphere.

Subarachnoid hemorrhages (SAH) are also common in children.[6] Subarachnoid bleeding in acutely traumatized children is common but rarely results in aneurysmal bleeding as seen in adults. This often occurs over the convexities of the brain affected by coup-contrecoup injuries, particularly over the frontotemporal poles. Traumatic SAH can also occur in the inter-hemispheric fissure and in the basilar cisterns and is secondary to disruption of the fine pia-arachnoid vessels. If associated with minor trauma, surgical intervention may not be warranted. However, evolving hydrocephalus may result during the chronic (resorptive) phase of subarachnoid hemorrhage, requiring ventricular shunting (Figure 12-11).

Skull fractures are commonly associated with head trauma in children (up to 21% reported).[9] CT is the diagnostic study of choice for skull fractures, which will allow simultaneous evaluation of the underlying parenchyma (Figure 12-12). The four major types of skull fractures are linear, depressed, diastatic, and those at the skull base.[34,35]

Linear skull fractures (simple "cracks") are the most common and should be followed closely for epidural hematoma. Depressed skull fractures indicate more forceful blunt trauma than linear fractures, and those that are greater than the bicortical thickness of the skull table and have dural tears require operative management.[35] Grossly displaced skull fractures are often associated with dural tears and parenchymal injury and therefore portend a



• **Figure 12-11** Resolved subarachnoid hemorrhage on magnetic resonance imaging in young child with residual hydrocephalus. (From Horswell BB, Istfan S: Child maltreatment, *Oral Maxillofac Surg Clin North Am* 24(3):511-517, 2012.)

worse prognosis. A majority of displaced skull fractures are open fractures. The distribution of fracture location is:

- 75% fronto-parietal
- 10% temporal
- 5% occipital
- 10% other or combined

Skull base fractures are uncommon in young children. Clinical signs of skull base fractures include raccoon eyes (periorbital ecchymosis) and Battle sign (mastoid ecchymosis) (Figure 12-13). Hemotympanum and oto-rhinorrhea are signs of basal skull fracture, and if this is noted, a cerebrospinal fluid (CSF) leak can be detected by the presence of β2-transferrin or CSF fluorescein dye study. Careful evaluation of cranial nerves I, III, VI, VII, and VIII, which traverse the skull base, should be undertaken. The low risk of meningitis in basilar skull fractures (2% to 9%) does not support the routine use of prophylactic antibiotics and may potentiate the development of resistant organisms.[36-38] On the other hand, children with a basilar skull fracture and a CSF leak should be considered for vaccination against *Streptococcus* pneumonia because of the risk of pneumococcal-associated meningitis.[39]

Secondary Brain Damage in TBI

The foundation of contemporary TBI management include thorough triage, resuscitation, emergent surgical evacuation of mass lesions, control of ICP, support of cerebral perfusion pressure (CPP), multimodal monitoring, and optimization of the neurovascular physiologic environment.[32-40] Secondary damage involves the progression of damage within the brain resulting from evolving edema, ischemia, and necrosis.[40,41] Hypotension and hypoxia can further exacerbate damage; therefore, elevated ICP or decreased CPP are to be avoided.

Keys to Avoiding Secondary Damage

- Establish baseline neurologic exam and repeat often (age-appropriate best verbal, motor, and pupils)
- Keep Pao_2 >80 mm Hg, Sao_2 >95%, $Paco_2$ 35-40 mm Hg
- Keep blood pressure in high-normal range
- Correct hypotension, hypoxia, hypoglycemia

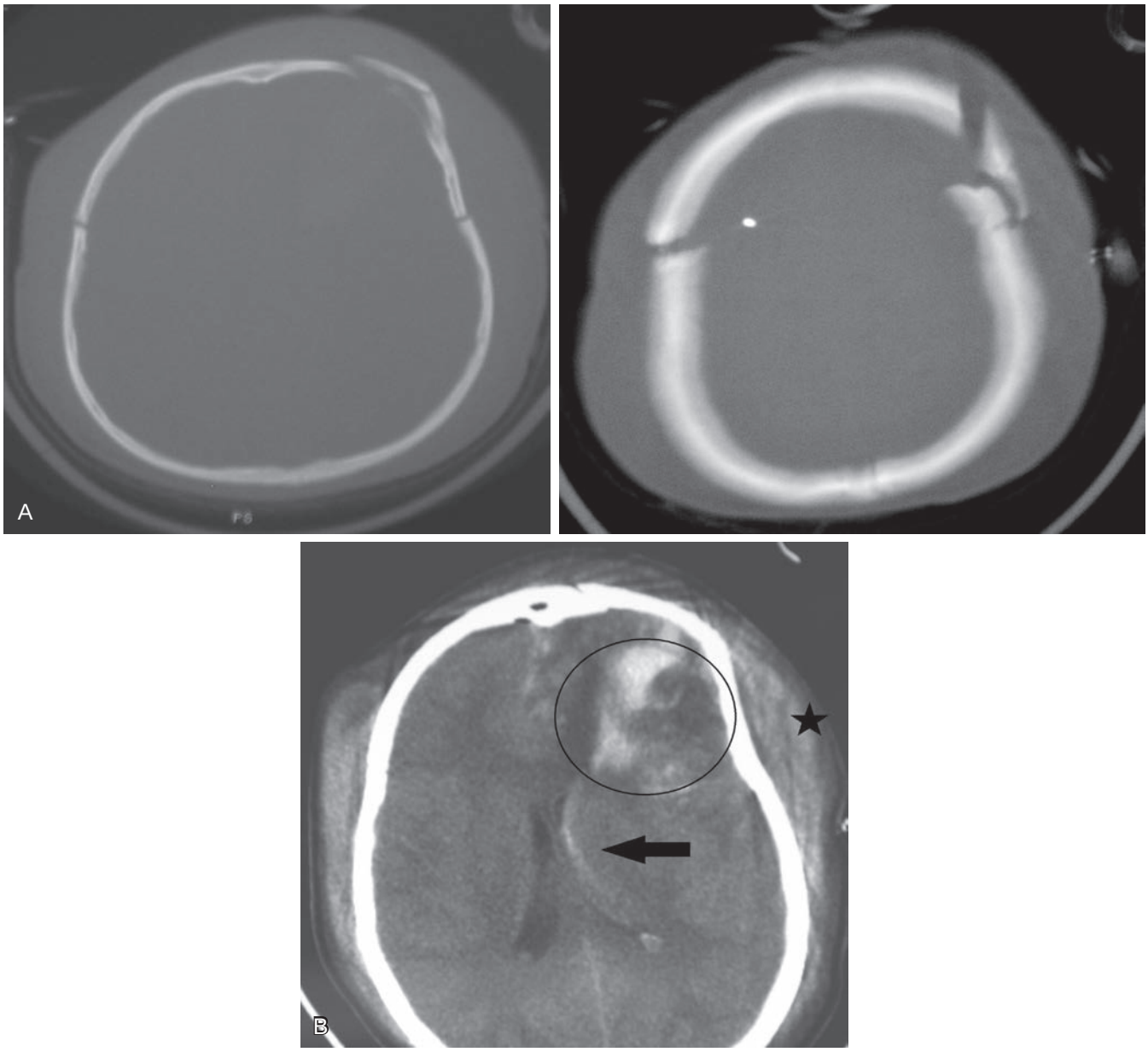
ICP Monitoring in TBI

ICP monitoring should be considered for any child with a GCS score less than 8.[40] Cerebral perfusion pressure is considered the pressure gradient that is ultimately the driving force required for supplying cerebral metabolic needs. CPP is easily measured from ICP with the mathematical difference between the mean arterial pressure and ICP. Cerebral blood flow (CBF) is defined as the blood traversing through the cerebral circulation. In normal adults, CBF is 50 to 55 mL/100 g of brain tissue/minute. In children, CBF is relatively higher, corresponding to their age. However, cerebral autoregulation is often disrupted after severe TBI, thereby making CBF difficult to interpret and use.[41] Treatments are directed toward decreasing ICP and optimizing CPP. Pediatric TBI guidelines involve maintaining CPP between 40 and 65 mm Hg. There are no studies to support maintenance of CPP above any target threshold in infants or children in TBI to improve mortality or morbidity. However, a threshold below 40 mm Hg perfusion pressure appears to be associated with increased mortality; therefore, most treatment guidelines recommend a minimum CPP of 40 mm Hg.[42] ICP elevations above 20 mm Hg are not well tolerated and are associated with poor outcomes.[43,44] Sustained increased ICP may result in decreased cerebral perfusion and lead to subsequent herniation. Therefore, patients with sustained ICPs greater than 20 mm Hg should have intraventricular devices placed that effectively allow drainage of CSF and direct decrease of ICP.[19]

Ventilation should maintain a $PaCO_2$ of 35 to 40 mm Hg, as hypercapnia may cause significant increases in cerebral blood volume and flow. Hyperventilation can temporarily assist in reduction of ICP by causing cerebral vasoconstriction and thereby reducing cerebral blood flow if herniation is imminent; however, prophylactic hyperventilation to achieve a $PaCO_2$ <30 mm Hg should be avoided as it results in reduction of CBF and consequent ischemia. The clinical signs of herniation include nonreactive, dilated pupils, and Cushing triad (abnormal respiration, hypertension, and bradycardia).[45]

Management of TBI

Mannitol usage has fallen out of favor due to several side effects, including the rebound effect of secondary cerebral ischemia, serum electrolyte imbalance, and hypovolemia.

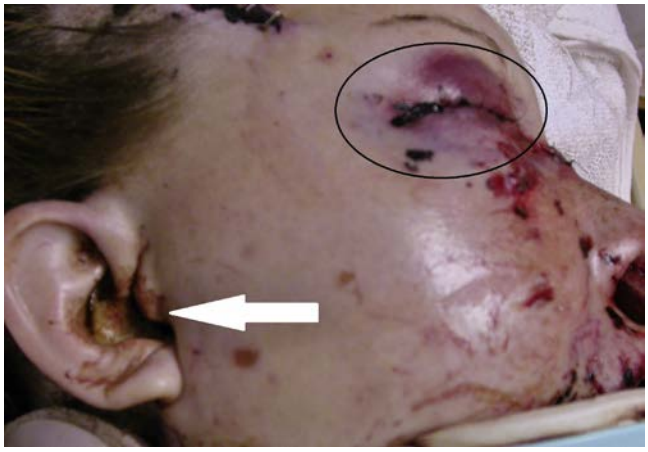


• **Figure 12-12** Computed tomographic *(CT)* images of pediatric skull fractures. **A,** Bone window CT demonstrating calvarial fractures. **B,** Brain window with contrast CT demonstrating scalp hematoma *(star)*, intraparenchymal hematoma *(circle)*, and edema with mass effect *(arrow)*.

Recent data suggest that 3% hypertonic saline should be used as the mainstay therapy to maintain serum sodium concentrations of 150 to 170 mEq/L and serum osmolarity of 360 mOsm/L, which is well tolerated in the pediatric patient with a head injury.[46,47] Hypertonic saline has also been reported to have several other potentially beneficial effects, including vasoregulatory, hemodynamic, neurochemical, and immunologic properties. Initial therapy should be 3 to 5 mL/kg or continuous infusion of 0.1 to 1.0 mL/kg/hr titrated to decreased ICP.[47]

Post-traumatic Seizures

When compared to the adult population, infants and small children are at an increased risk for post-traumatic seizures (PTS) due to increased excitability of the developing brain.[48] Post-traumatic seizures are the most common complication of TBI.[49] Non-accidental trauma is the strongest predictor for early post-traumatic seizures (EPTS), probably due to the repetitive nature of the injury over time.[50] Early post-traumatic seizures occur in 19% of children with TBI, usually manifest within 7 days of injury, and are typically self-limiting if the initial CT is normal.[46-48] Young age and non-accidental trauma are independent predictors for the development of seizures; therefore, prophylactic anticonvulsant therapy may be considered in the first week following severe TBI for those patients deemed at high risk for seizure activity (intra-parenchymal blood).[19] Treatment includes a loading dose of phenobarbital 15 to 20 mg/kg as a single dose with maintenance dose given 12 to 24 hours later at



• **Figure 12-13** Skull base fractures (peri-orbital ecchymosis and mastoid swelling, *(circle)* with resultant cerebrospinal fluid pooling at the conchal bowl *(arrow)*.

5 mg/kg/day divided every 12 hours and subsequently titrated for therapeutic levels at 15 to 40 mcg/mL. No firm data in the pediatric literature suggest that these medications improve long-term outcomes or reduce the incidence of late post-traumatic seizures.[50,51]

Current data indicates that treatment with corticosteroids does not confer improved functional outcome, decrease mortality, or reduce increased ICP in children with TBI.[52] Given the lack of evidence and the potential harm from these medications, corticosteroids are not routinely recommended in the management of pediatric TBI.

It is estimated that 21% to 42% of children with severe TBI will develop refractory intracranial hypertension despite aggressive medical management.[51] Decompressive craniectomy, high-dose barbiturate therapy, hyperventilation, lumbar drain placement, and the use of moderate hypothermia should be considered in these patients.[52] Finally, therapeutic hypothermia may be considered as a second-line therapy; however, the benefits seen in animal models remains unsubstantiated in large randomized clinical studies in humans. Data extrapolated from the adult literature indicate that hyperthermia adversely affects TBI outcomes, and it may be advisable to consider *passive rewarming of the mild to moderately hypothermic* child with isolated head injury.

Summary

The assessment of the injured child remains a dynamic process with ever-changing variables and treatment strategies that continue to be refined with ongoing research. The principles described in this chapter are a guide to assist the clinician in the evaluation and management of the child with life-threatening injuries. Particular attention is given to the recognition and management of TBI in children, as this is key to reducing mortality and morbidity in this susceptible population. Guidelines are established to help orchestrate a clear and quick management scheme in the midst of a commonly chaotic trauma setting in the hope that clinicians can quickly identify, treat, and prevent ongoing injury.

Wound Repair in Children after Injury

Principles of Tissue Repair in Injury

Wound healing traverses a complex and connected process from a site of injury to a stable scar. The detailed and interrelated mechanisms of inflammation, coagulation, chemotaxis, phagocytosis, cellular recruitment and differentiation, growth factors, mediators and cytokine production, vascular ingrowth, and ultimate connective tissue organization proceeds along a multiple-level trajectory of cascading events. The biologic detail and data accompanying those events is monumental and beyond the scope of this chapter. However, it is necessary that the surgeon involved with the care of the injured child and the corresponding wounds understand basic tissue healing mechanisms and how they may be altered by adverse forces or, alternatively, harnessed to achieve a good outcome.

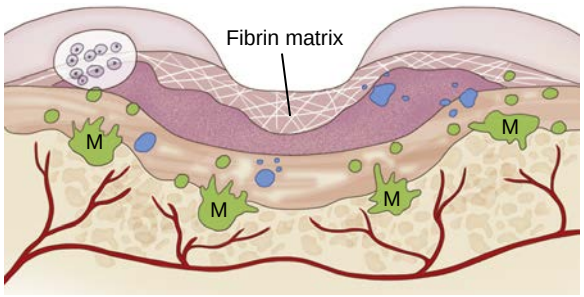
"Children are not small adults" is oft quoted regarding the care of children due to basic anatomic-physiologic differences and attendant strategies. This is particularly true for wound healing. Basic distinctions are observed and understood in wound healing for individuals as well as classes of patients, including children. Their stages, course, and trajectory in tissue repair are basically those of young healthy adults, but there are accelerated and exaggerated responses that should be recognized.

Although fetal wounds heal without scars because of a limited inflammatory response (amniotic bathing) and absence of transforming growth factor beta (TGF-β), postnatal tissue wounding takes on an accelerated and even more pronounced dynamic within days after birth.[53-55] This response accounts for the higher incidence of hypertrophic scarring in children after injury.[56,57] This can lead to a devastating effect on a child's well-being.[58]

Basic Soft Tissue Injury and Physiology

The complexity and degree of soft tissue disruption in children's injuries requires a basic understanding of connective tissue, epithelial, and osseous repair in children. Children heal at an accelerated and more pronounced rate than the adult patient. Generally speaking, children heal quickly but do so with more scarring, particularly in the dermis.[57-60]

Tissue repair begins seconds after injury with the coagulation cascade and formation of the platelet plug.[61-64] The coagulation cascade ends in the conversion of fibrinogen to fibrin and the formation of a gel (provisional) matrix that provides a primitive scaffold for subsequent events. The acute *inflammatory* response (hours to 2-3 days) soon follows with tissue leakage, cellular egress, and cytokine and factor release (Figure 12-14). Neutrophil and macrophage recruitment (monocyte precursors in circulation) accelerates and peaks at about 2 and 5 days, respectively, after injury; these cells contribute to the amplification of



Keratinocyte migration over the granulation bed from cytokine (TGF-B) signaling

• **Figure 12-14** Diagram of reepithelialization with keratinocyte migration *(circle)* with macrophage *(M)* release of factors in response to cytokine signaling in the matrix gel and wound bed.

cytokine elaboration and release into the fibrin clot. Further, macrophages begin the simultaneous process of microbial phagocytosis, foreign body degradation, and processing matrix component breakdown products. Evidence suggests that neutrophilic predominance fades after day 3, and any significant presence in the wound thereafter may suggest impaired healing. Macrophages dominate the wound at the latter phase of inflammation and into the next phase of proliferation and are necessary for a stable, healing wound. It is important that no or little disruption of the provisional matrix occur, thus invoking more inflammation and delays in healing, which contributes to more scar formation.

After the inflammatory response, the *proliferative* phase ensues, with formation of a weakly arranged granulation tissue bed in the site of injury. This phase of wound healing generally proceeds from 4 to 21 days after injury. This granulation bed is composed of fibroblasts, macrophages, and endothelial cells that have been chemotactically attracted to or differentiated into building-block cells. Fibroblasts are the workhorse cells for building a more stable matrix with the cytokine-induced degradation of the initial fibrin matrix and formation of a collagen matrix. Into this matrix, fibroblasts produce collagen, principally type III collagen (types I, II, and III collagen are termed *fibrillar collagen*). Type III collagen predominates initially because of the hypervascular response in early repair. Fibrillar collagen dominates the early scar and will correspondingly increase in amount if the scar is not managed with reduction of tension and application of subtle pressure (wound support dressings, i.e., Silastic or hypoallergenic skin tapes). The degree to which this cascade of events proceeds and matures is variable, but as mentioned earlier, the process is more pronounced and faster in children.

The last and longest phase of wound healing is the *remodeling* phase, which proceeds up to 1 year after injury. This phase is characterized by wound contraction and collagen remodeling. Obviously the mechanisms during the first 21 days of wound healing that propelled such cellular activity and proliferation must be turned off to avoid an immature and unstable wound. These mechanisms are largely still unknown but probably work through contact inhibition of epithelial cells, fibroblast regression through molecular signaling, vascular maturity, and other environmental components. During remodeling, myofibroblasts in the surrounding tissue contract at the wound margins and reconstituted tissue to form a more densely compacted matrix. Remodeling involves formation of a more organized extracellular matrix, completed angiogenesis, and more mature collagen fibers (type I production from fibroblasts and breakdown of type III collagen) with elastin arranged in a tight, more parallel, and covalently bonded matrix.

Reepithelialization of damaged dermis begins within hours of injury with migration and proliferation of surrounding epithelial cells.[63] Immature keratinocytes, more prevalent in younger dermis that has not been exposed to injurious agents (aging process), release matrix metalloproteases and plasmin that assist in basement membrane disassociation and subsequent cell migration. Immature and burgeoning keratinocytes at the wound margin proceed onto the granulation bed (see Figure 12-14). This migration is promoted by growth factors, principally TGF-β which has a dual effect of promoting migration while also inhibiting proliferation, thus encouraging *horizontal* movement rather than the *vertical* hierarchy which exists in mature epidermis.[63,65,66] Once contact is made with opposing keratinocytes over the underlying matrix bed, this migration and proliferation stop, preventing overexpression of factors, cellular overgrowth, and hypertrophic scar formation.[64,65]

Soft tissue wound repair is a complex process that results in a mature scar. As repair proceeds, the wound gains strength, with about 20% tensile strength of unwounded tissue at 21 days, and attaining about 70% to 80% strength at the end of remodeling.[62] Younger children attain final wound integrity more quickly and to a higher degree of tissue strength compared to that in adults.

Bone Healing after Fracture

Initial injury at the site of fracture invokes the same acute inflammatory response as in soft tissue. There is an immediate vascular constriction to slow bleeding in concert with platelet clumping to form a platelet plug. Dilation then follows to allow neutrophils and platelets to spill into the developing clot. Platelet-mediated cytokines are released after degranulation within the organizing fibrin clot, including TGF-β, platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF).[67] These mediators effect the extravasation of plasma proteins into the maturing clot, enhancing further cellular recruitment and elaboration of other cytokines—interleukin (of several subtypes), tumor necrosis factor alpha, and PDGF. Principal among these cytokines is TGF-β, which exerts a wide response in the acceleration of the cascade of inflammatory events via rapid chemotaxis of neutrophils and monocytes to the site of injury. This process is accompanied by simultaneous vascular budding and neo-angiogenesis within the granulation matrix and scaffold of early organization.[68] These events occur within hours after injury and progress over the next 2 to 3 days after injury. Bone morphogenetic protein (BMP) belongs to the TGF-β superfamily and includes several subclasses of BMPs

TABLE 12-5 Growth Factors in Fracture Repair

Factor	Source	Function
TGF-B	Platelets, bone matrix	Stimulates proliferation of undifferentiated mesenchymal cells
BMP	Osteoprogenitor cells, osteoblasts, bone matrix	Promotes differentiation of committed mesenchymal cells into chondrocytes and osteoblasts
FGF	Macrophages, chondrocytes, osteoblasts	Mitogen for mesenchymal cells, chondrocytes, and osteoblasts
IGF	Bone matrix, osteoblasts, chondrocytes	Promotes proliferation and differentiation of osteoprogenitor cells
PDGF	Platelets, osteoblasts	Mitogen for mesenchymal cells and osteoblasts; macrophage chemotaxis

(2,4,6,7) which invoke osteoinduction through stimulating mesenchymal cells (in turn having been stimulated to become committed to bone production through TGF-β influence on *undifferentiated primitive* mesenchymal cells) to transform into osteoblasts.[67,69] Insulin growth factor (IGF, types 1 and 2) is the most abundant factor and has both paracrine and endocrine functions. It stimulates endochondral proliferation at the growth plates without maturation and also plays a role in intramembranous osseous healing. IGF-2 is potent and has wide-ranging influence on several target tissue cell types.[68,69] Table 12-5 lists several of the primary growth factors involved in fracture osseous repair.

Fracture Healing Mechanisms

Fracture healing is dictated by the location of the fracture, the health of the callus formed around the fracture, and the strain placed across the callus.[70] Systemic and local tissue factors play respective roles as defined later in this section. *Primary bone healing* takes place when bone fragments are firmly or closely abutting. This is essentially intramembranous bone healing and takes place in a stable fracture environment with little to no callus formation. Rapid vascular budding from the margins takes place with reestablished blood supply within a few days of injury. Endosteal activity is increased, osteoblasts stimulated, and haversian canals are directly remodeled in primary fracture healing.[71]

Increased strain, fragment mobility, and bony margin gap play a role in determining osseous healing by *secondary* means. Periosteal and soft tissue responses are key, there is initial hematoma formation which becomes the initial matrix, and growth factors are released to stimulate cellular differentiation and endothelial budding. An interval phase of *soft callus* formation of differentiated chondrocytes holds the fracture, but this can be easily disrupted by excessive forces, including surgery.[72] If stability exists, then osteoblastic differentiation and bone formation is encouraged, resulting in a *hard callus* of woven or immature bone. These intermediate and latter stages of secondary bone healing are respectively shortened in youthful bone (3-4 weeks) compared to that in adults (6-8 weeks), given equal forces applied across the site of injury.[72,73] Remodeling is a process of several weeks to months, attained earlier in children and modulated by external forces applied to the fracture site.

Barriers to Healing

Generally speaking, children heal well, and in the setting of a healthy child with favorable tissue profile and low bioburden (this will be reviewed later), a wound should predictably heal with little issue. It is important, however, to recognize those conditions, then recruit appropriate systemic and exogenous adjuncts to turn the wound to an optimal healed state—minimal deformity and good function.

Systemic Factors

Most children are in good health, they do not have age-related damage to tissues, they are in prime cardiopulmonary condition and, for the most part, are nonsmokers and free of substance abuse. With that understood, the surgeon can expect wounds in a healthy child to heal fast and predictably.

There are some systemic factors that should be taken into consideration in a child with injuries.[74] Table 12-6 lists several disease states that can adversely affect wound healing. Children with any of these conditions may have altered or deficient responses to wound healing; therefore not only will the phases of tissue repair be prolonged, but a poorer wound more susceptible to breakdown or infection may be created. If poorly managed, deformity, chronicity, pain, and dysfunction may result with increased costs and burden of care.

Diabetes

It is well known that poorly controlled diabetes promotes increased demands on wounded tissue by poorly reducing the bio-burden of the wound. Bio-burden is that condition of a wound that has increased demands placed upon it for healing, principally due to the bacterial load in the wounded tissue, foreign body and microbial removal and the cellular response to accomplish it, microbial competition for oxygen and nutrients, and breakdown products that may further injure the resident cells and tissues, thus promoting an undesirable and prolonged inflammatory response and ultimately reducing wound integrity and strength. Diabetes further exacerbates the challenges to wound healing through insufficient vascular delivery of oxygen and

TABLE 12-6 Systemic Factors and Wound Healing

Diabetes	Poor tissue health; increased O_2 free radical damage, cellular dysfunction, leukocyte dysfunction in hyperglycemic state; increased microbial substrate
Immune altered states (including corticosteroids, NSAIDS)	Relative immune incompetence and poor resistance response; deficient chemotaxis; dysregulated cytokine, hormone, complement and factor production signaling
Connective tissue disorders (Ehlers-Danlos, Marfan, Werner)	Poor wound substrate production and matrix formation; altered fibroblast collagen production; weak scar
Malnutrition (vitamin deficiency, malabsorption)	Deficient collagen cross-linking; growth factor and collagen production deficiencies; altered chemotaxis, weakened cellular defense and poor inflammatory response
Hematologic (anemia, hemoglobinopathies, coagulopathies, factor deficiencies)	Poor oxygen delivery and off-loading; poor clot and provisional matrix formation; deficient cascade and cellular event sequences; hematoma formation and prone to wound breakdown
Obesity	Relative hypoperfusion in cutaneous and subcutaneous tissues; prone to hematoma, seroma formation; adipokines exert a general negative response on immune and inflammatory processes
Stress	Poor cell-mediated response; immune system dysregulation

After Percival SL, Hill KE, Williams DW et al: A review of the scientific evidence for biofilms in wounds. *Wound Repair Regen* 20(5):647-657, 2012.

nutrients. Leukocyte chemotaxis and the cellular ability to engulf and phagocytize microorganisms are weakened in the hyperglycemic state.

Immune Deficiency

Immune deficiency diseases and states are many and complex. Any altered ability of systemic host response to wounding, bacterial invasion, steps of provisional and mature matrix formulation (which the acute inflammatory and proliferative phases of wound healing are part of and build upon), and tissue collagen maturation will result in a poor wound state. Medications such as corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) suppress cellular wound response, fibroblast differentiation, and production of collagen, weaken collagen cross-linking, and reduce wound contraction and maturation.

Connective Tissue Disorders

Connective tissue disorders generally affect tissue proliferation and maturation, which will result in a poorly constructed wound with limited tensile strength. Principle diseases of connective tissue integrity are Ehlers-Danlos and Marfan syndromes. Thin, inelastic cutaneous tissue is more prone to injury, breakdown during healing, and prolonged healing. Malnutrition, principally protein and vitamin deficiencies, directly and adversely affect cellular metabolism through poor energy production, poor nutrient absorption, hypoalbuminemia (a decrease in the body's main serum-binding protein), and vascular fragility and compromise.

Hematologic Disorders

Hematologic disorders are varied in disease and expression. Anemic states have a direct consequence on wounded tissue if oxygen carrying capacity is diminished to the point that the high oxygen demands of injured tissue exceed supply. Wound healing stops, and the bio-burden necessarily increases. Usually mild anemia can be overcome with increased oxygen administration and iron administration if there is iron deficiency (this response is not immediate). Moderate to severe anemia or hemoglobinopathies, such as sickle cell anemia, will result in poor oxygen delivery to injured tissue. Usually, severe anemia will require a blood transfusion to overcome the deficiency state until the anemia is treated. Sickling of hemoglobin in sickle cell anemia requires immediate management with increased oxygen administration, warming the patient, hydration measures, and stopping stressors.

Coagulation disorders can also adversely affect wound healing. During the initial tissue response in injury, the coagulation cascade and platelet function must proceed normally to initiate and form a fibrin clot. It is within this primary matrix that the many events of inflammation and proliferation take place on the way to healing. Further, an expanding wound defect with poor clot formation or integrity will impede further healing processes, may contribute to increased bio-burden, and may inhibit endothelial formation in the granulation bed.

Obesity

Obesity is a problem in American youth; a significant portion of children presenting to the hospital with injury are obese (the Centers for Disease Control and Prevention estimates that about one third of all U.S. children are overweight or obese). Moderate obesity is defined as >40% above ideal body weight for age and sex, and moderate to severe obesity has a deleterious effect on tissue healing responses. Generally, poor healing in obesity relates to a corresponding vascular decrease in cutaneous and subcutaneous tissues with consequent diminished oxygen delivery to injured tissues. Adipokines are adipose cytokines that have modulating expression, chemical signaling, and impact on tissues through *pro-* and *anti-*inflammatory

mechanisms, as well as a key role in tissue insulin resistance. Evidence suggests that injured tissue has a prolonged inflammatory response due to the more predominant and forceful action of adipokine-mediated pro-inflammatory agents.

Local Factors

The health and integrity of the wound bed is significant for healing. Obviously, a breach in the soft tissue necessarily results in a change to the vascular network, may result in devitalized tissue, and introduces foreign body contaminants and bacteria into the wound. Each of these local barriers to healing will be reviewed.

Dermal Integrity

Intact skin and mucosa serve as the first host defense to disease and protects underlying tissues from exposure, dehydration, mechanical and biologic injury, and bacterial colonization. To the same degree of injurious breach of the dermis is a corresponding injury to underlying structures. Particularly exposed to contamination are the relatively avascular perifascial spaces, fat, and devitalized tissue. Gross contamination of these tissues necessitates thorough debridement and washout to promote the healing response. Tearing of the blood vessel network, particularly in the richly vascularized cutaneous tissues, results in relative tissue hypoxia in the wound bed and surrounding tissues. An abbreviated period of hypoxia follows every injury and serves to initiate the inflammatory response; however, prolonged tissue hypoxia will slow or halt the proliferative phase of healing.

Foreign Body

Accompanying the injurious insult may be the forceful introduction of particulate foreign bodies, contaminated liquids, or air. Further, nonviable bone fragments and soft tissue will also serve as a foreign body nidus that will increase the bio-burden of the wound and interfere with normal tissue healing by invoking a prolonged inflammatory response. Foreign bodies are quickly colonized by microorganisms, particularly gram-positive organisms such as staphylococci, which form a surface biofilm resistant to antimicrobial action. A 10^3 increase in minimal bactericidal levels has been determined necessary for most antibiotics in the face of a colonized foreign body contaminant.[73-75] Particulate matter such as road dirt, tar, and metallic substances can "stain" or tattoo the soft tissue, contributing to chronic inflammation, delayed healing, or an unsightly scar.

Infection

Any open wound has a bacterial load that may become problematic to healing. Microorganismal tissue loading can be characterized as[73,74]:

Contamination: bacterial presence without proliferation

Colonization: bacterial proliferation without signs or symptoms of infection

Critical colonization: progressive bacterial growth that is nearing the point of overwhelming tissue host defenses

Infection: Proliferation, invasion, and spread of bacteria beyond the wound margins with signs and symptoms of host response—swelling, erythema, pain, fever, purulence, leukocytosis, and tissue dysfunction (neural loss, joint immobility, thrombosis, etc.)

It is important to recognize that these various levels of bacterial loading in a wound will increase bio-burden and will tilt the wound toward delayed or ineffective healing.[76] Bacterial overgrowth (critical colonization or infection) results in production of free radicals injurious to healing tissue, cellular breakdown with release of proteases and enzymes, and the production of organismal toxins.[75] Management directives to include washout of contaminated or colonized wounds, or debridement (incision, drainage, and washout) of infected wounds, must be carried out to positively influence and promote healing. Even though "youthful health and vigor" are very important, the surgeon cannot entirely rely on them to supplant these management directives in the face of a contaminated problem wound with increased bio-burden.

Patterns of Injury in Children

Soft Tissue

Young children who sustain a force to the facial region distribute that force differently as compared to adults. The frontal-orbital region is a correspondingly larger and exposed area of children up to about 5 to 7 years of age before midface expansion takes place. Traumatic forces are more often delivered to this region and thus, traumatic brain injuries occur more commonly when the frontal-facial region is struck by blunt force.[15,24,76,77] Blows to the midface in younger children are to a smaller region of interrelated "soft" bones connected with wide sutures, buttressed by unerupted teeth, and set in the midst of absent or developing sinuses. There is a tendency to "bendiness" of the midface in children that will evenly distribute forces and result in more contusion and hematoma formation, and less fracture formation or displacement.[78-80] The very elastic soft tissue envelope of the facial skeleton gives way under blunt force, does not tear as easily as in adult soft tissues, but does result in respectively more significant hematoma formation and edema. The highly vascularized craniofacial tissues in children contribute to "exaggerated" swelling that can mimic or suggest more underlying injury than is actually present. These patterns of injury should not preclude the surgeon from keeping in mind that these forces will translate intracranially, as children are more apt to suffer TBI in the absence of fractures from upper facial blows than in the adult (due to the fragile interconnecting bridging veins and more loosely bound dural attachments).[15,16]

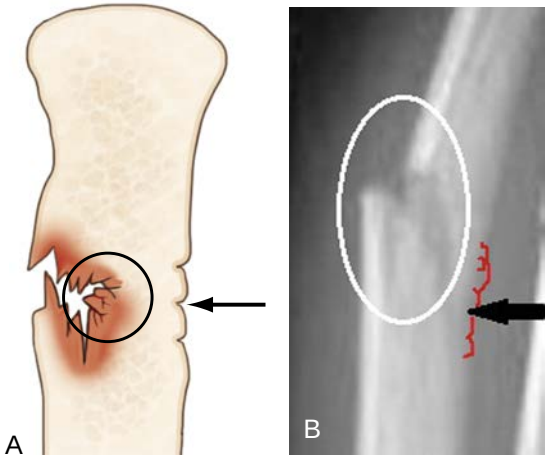
Traumatic forces directed to the lower face or neck in children can result in damage to the mandible and airway, respectively. Condylar fractures may not occur after a blow to the chin due to the elasticity of bone; however, intracapsular hematoma formation and microfracturing of the condylar surface may occur, which may have an effect on initial healing with increased fibrosis, scarring, and growth perturbations. Blows to the neck region may result in cartilaginous injury of the airway, and particular attention should be given to careful

assessment of the child early in management who has bruising and swelling around the neck.[20] Because of the higher location of the cricoid in children, this area can be damaged by blows to the submental and chin area. Actual tracheal or thyroid cartilage fracture is less common in young children compared to adolescents or adults; however, the small, easily collapsible airway in children combined with swelling will contribute to airway embarrassment very quickly and should be monitored.[18]

Skeletal

Fracture patterns in children are different than in adults due to thinner cortices, increased cortical elasticity, and relatively enlarged cancellous portion.[81] Bone in children has a lower modulus of elasticity, lower bending strength, and lower mineral content. The low bending strength induces more strain in pediatric bone than for the same stress on adult bone, which allows for greater energy absorption before ultimate failure and fracture. Several fracture mechanisms are recognized in orthopedics[81-83]:

- *Plastic deformation:* Blunt force applied to a bone results in microscopic weakening of the convex surface without translation to the concave surface. The surface morphology and contour may be changed, but a fracture does not take place. Mild deformations may be likened to a deep "bone bruise." Trabecular edema and intrabony architecture disruption of the cancellous portion may occur. Injury has occurred, but its effect may not be detected until growth has been adversely affected in later years. The mandibular condyle is especially susceptible to this mechanism of "non-fracture" injury. A more forceful or direct injury to the chin may result in a "*buckle-type fracture*," which is classically seen in long bones after compression forces are applied along the axis. There is compression fracture of the condylar surface and minor bulging of the condylar neck where trabecular compression has taken place. Active physiotherapy after a very short period (3-5 days) of immobilization is necessary for optimal healing in these fractures.



• **Figure 12-15** Diagram **(A)** and radiograph **(B)** of greenstick fractures, common in children. Force *(arrow)* is applied to the concave surface, which results in compression with buckling, but the convex *(*opposite, *circle)* surface tension is overcome and fractures.

- *Greenstick fracture:* A force is applied to a bone surface (concave) and the tensile resistance of the opposite or convex surface is overcome and fractures, but the concave surface remains intact though deformed or bent through compression (Figure 12-15). The thick, supple periosteum in children assists in keeping the pliable bones from completely fracturing and being displaced. Greenstick fractures are seen primarily in the mandible, but also nasal bones, zygomatic arch, and the thin calvaria of young children. Mechanical (applied) or resting (implied) immobilization for a period of 7 to 10 days followed by active physiotherapy is recommended, as tolerated and according to comfort levels of the child.
- *Complete fracture:* As the term implies, the force is excessive and results in complete bicortical bony separation, with or without fragment displacement. Complete fractures are generally detected on plain radiographs, though in children, some nondisplaced fractures may not become detectable until after a period of several days when initial fracture healing is underway.[83,84] Older children and adults suffer complete fractures more often than younger children due to increasing maturity and mineralization (brittleness) of bone and the significant forces they may be exposed to in accidents or assaults. Complete fractures require stable immobilization or fixation mechanics applied to the fracture to achieve satisfactory healing and avoid deformity and dysfunction.

Finally, loading and skull fracture characteristics, as noted in cranial trauma in infants and young children, suggest that skulls with patent sutures are subject to increased blunt force–induced TBI. This is due to higher strain in the calvarial surface and less absorptive capability of energy forces at the sutures.[84] This means that greater impact force is necessary to result in skull fracture, something to consider when examining an infant with a "low-fall" reported injury.

Summary

Wound healing in children is an accelerated and sometimes exaggerated response to the inflammatory mediators involved in injury and repair mechanisms. This often works to the advantage of young children—quick healing, faster recovery to function, and few long-term residual problems as compared to wound healing in older children or adults. Although these mechanisms of repair are advantageous and desirable, such responses to injury may result in overelaboration of collagen development, resulting in hypertrophic scars in complex soft tissue wounds. Excellent and early repair and wound support adjuvants are important in attaining a final scar and tissue state that is cosmetic, functional, and without long-term residual compromise of holistic health and psychological overtones. Healthy children will generally recover well from their injuries, provided expert surgical management and appropriate support resources are employed early on and throughout the healing period, and perhaps beyond.

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13

Pediatric Craniomaxillofacial Trauma and Management

BRUCE B. HORSWELL, LEWIS C. JONES

Introduction

Facial injuries and fractures continue to increase in the United States despite advances in car seats, vehicle safety, and other accident prevention measures. A survey of pediatric emergency departments conducted by the National Trauma Registry from 2001 to 2005 showed that 4.6% of the nearly 300,000 pediatric trauma patients had facial fractures.[1] This does not include the many fractures (such as nasal bones) that do not present for formal evaluation or management. The Centers for Disease Control and Prevention (CDC) lists "unintentional injury" (abuse) as the leading cause of death for all pediatric patients more than 1 year of age for each of the past 10 years.[2] Despite efforts at prevention, trends continue to increase for injuries such as traumatic brain injury (TBI)—although TBI-related deaths have remained stable over the past decade (2001-2010), there has been an overall increase in the rates of TBI emergency department visits.[3] In the United States in a single year (2011), more than 650 children under the age of 12 years died and 148,000 were injured due to falls alone.[4] The cost of nonfatal injuries to the craniofacial region for children in 2012 alone was estimated by the CDC to be around $1.7 billion.[4]

Epidemiology and Trends

A recent study of trends in emergency department visits for pediatric facial fractures demonstrated that 75% of these patients were male and 72% were 15 to 21 years of age. The most common fractures were nasal and mandibular, which is consistent with other trauma database surveys.[1,5] Patterns of causes of facial fractures vary by gender and age. Facial fractures in girls are most often related to falls and motor vehicle collisions (MVCs), whereas in boys fractures are due more to firearms, recreation-related injuries, and assault. Children living in households with low annual income are more exposed to injury from firearms, violence, and MVCs.[5]

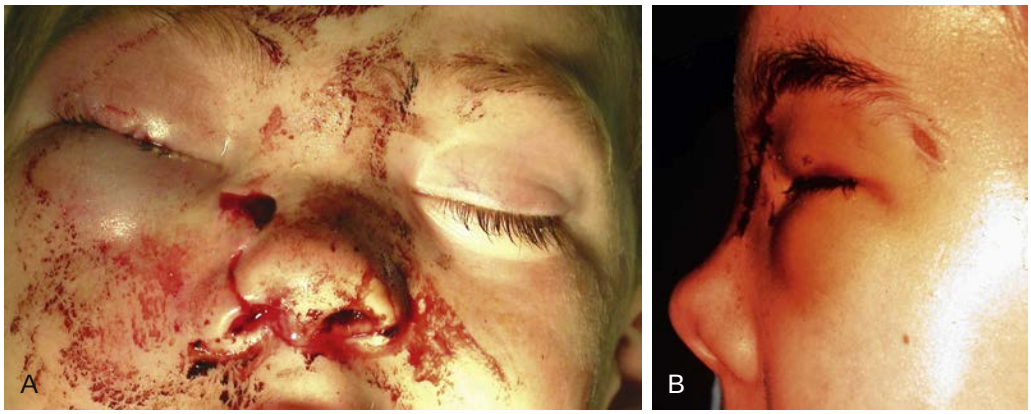
Injury in children follows a bimodal distribution with has slowly increased, most likely due to children being left in improper care or engaging in risk-taking behavior.

Injuries associated with facial fractures are often serious because of the proximity of special organs, neurovascular structures, and the airway. It is prudent for the practitioner responsible for managing these injuries to be aware of these associations and perform a comprehensive workup before proceeding with management of the injuries. The surgeon needs to understand the development of the facial skeleton and its functional complexities during growth.

Assessment

History

The history of the accident includes the time, place, mechanism, others involved, and whether the event was witnessed; these aspects should be carefully elicited and recorded. Vaccination history needs to be documented and updated as necessary. If an animal was involved in the injury, such as a bite wound, the identification and location of the animal and need for possible quarantine must be determined. Rural injuries, particularly in livestock or poultry operations, are more prone to exposure to species-dependent pathogens, which will direct antibiotic regimens accordingly. Finally, the possibility of abuse needs to be ruled out. Mechanism of injury and the history must be reviewed, corroborated, reconciled, and reported if there is any suspicion of abuse. Oral and maxillofacial surgeons are in a key position to see children with facial injuries; therefore, they are held accountable to properly investigate and report any injury judged to be possibly initiated by abuse.



• **Figure 13-1** **A,** Significant naso-frontal swelling and pseudo-hypertelorism in a 3-year-old without fracture. **B,** Blunting of naso-frontal angle and loss of nasal projection suggests midface fracture with retro-impaction.

Physical Evaluation

Evaluation always begins with the Advanced Trauma Life Support (ATLS) protocol, which starts with an orderly and simultaneous approach to airway/breathing/circulation/deficits. With a secure airway and stable circulatory system, the mental status of the patient should be checked and rechecked appropriately for age and development (refer to Tables 12-1 through 12-3 in Chapter 12, Assessment and Management of the Injured Child). Charts with pictures that the child can name will allow for gross visual acuity verification. Extraocular movements can be verified by keeping the head still while an "attention holder," such as a colorful light or object, is moved in various directions to document ocular mobility and gaze. Repeat of these initial evaluations is necessary to closely ascertain neurologic status and detect any changes from the baseline that may indicate progression of injury.

Soft tissue injuries, including lacerations (particularly of the scalp), ecchymosis, abrasions, or avulsions may require attention to prevent ongoing blood loss. Injuries to the periorbital area should raise concerns for ocular trauma and may require evaluation by an ophthalmologist to rule out ocular damage. The nasolacrimal system should be evaluated, which may require general anesthesia for a comprehensive exam. In the uncooperative child, a complete exam will also include full evaluation of the nose to ensure no septal trauma and otoscopic examination of the ear canal and tympanic membrane. As with any exam, a consistent, repeatable, and systematic approach is the best way to identify injuries so they can be appropriately addressed.

Once the soft tissue exam is completed, methodical palpation beginning at the scalp and moving forward and down over the forehead and to the orbital rims and then inferior along the zygoma, maxilla, and mandible, including the preauricular region of the condyle, can help to identify fractures. Nasal saddle deformity and swelling over the nasofrontal region raise concern for naso-orbito-ethmoid (NOE) fractures. Nasal drainage is a concern for cerebrospinal fluid (CSF) leak as a result of dural tears and frontal sinus fractures. Loss of nasal projection and a blunted nasofrontal angle may indicate midface fracture with retrograde impaction; on the other hand, severe swelling of the nasal bridge can mimic hypertelorism (Figure 13-1), though there are no naso-orbital fractures. A "bowstring test" can help check stability of the medial canthal element; however, this can be difficult to assess in the awake, injured child. Symmetry of malar projection and flattening should be noted. Further, a down-slanting orbit (dystopia) may accompany significantly displaced zygomatic-orbital fractures. Jaw function is evaluated by checking for dental segment mobility, change in occlusion, deviation or pain with function, and bony irregularities. Guarding, pre-auricular swelling, tenderness, and deviation away from the injured side should alert the clinician to possible hemarthrosis, whereas deviation toward the side of injury usually indicates fracture displacement with foreshortening of the condylar-ramal segment. Dental status should be recorded as well as primary, mixed, or permanent dentition.

Radiographic Evaluation

Imaging is obtained to confirm suspicions generated on physical exam. Plain films in some instances are quite useful, such as a panoramic image for evaluation of dentition and mandible fractures, or submental vertex views that allow evaluation of the zygomatic arches. Computed tomography (CT) allows for a more detailed evaluation of the structures imaged, but does raise concern for cumulative doses for repetitive CT imaging in young children. New technology such as cone-beam CT helps to minimize the exposure while maximizing the data obtained from the exam. Finally, ultrasound can be used for soft tissue screening, such as hemarthroses, deep hematomas, and possible intracranial injury in the young child with open sutures. Ultimately, the clinician needs to determine the necessary imaging based on the physical exam.

Growth and Development

Airway and Sinuses

The airway and its associated sinuses develop throughout childhood and into adolescence. Changes that occur anatomically within the airway from infancy to adulthood

include the superior (or cephalad) positioning of the larynx in the infant (refer to Figure 12-3 in Chapter 12). An infant's larynx is at the level of C3-4 (cervical spine), which descends to C 4-5 in the adult. This cephalad positioning of the larynx affects visualization because of the proximity of an axis angled away from the trachea, then broadens during growth and flattens over time, as well as changing its axis to be parallel to the trachea. Finally, the narrowest point of the airway is at the glottis in the adult, but at the cricoid cartilage in an infant (subglottic).[6] These changes become relevant in the injured child who may require intubation or a surgical airway.

The paranasal sinuses develop throughout childhood and into adolescence. Studies based on CT scans demonstrate that the sinuses develop in the following order: ethmoid, maxillary, sphenoid, then frontal sinus.[7,8] They continue to develop into adolescence, with the ethmoid sinus completing its growth by the age of 12 years and the frontal sinus continuing to develop into late adolescence.[9] Injuries to the sinuses raise concern for post-injury obstruction. Obstruction of the duct or ostium can lead to obstruction, stasis, infections, chronic discomfort, and late mucocele development.

Injuries to the lower airway (oro- and hypopharynx) can manifest as dysphonia, dysphagia, and severe pain after injuries to the tongue, hyoid, or laryngeal cartilage. Speech is the result of a complex coordination of muscles and requires the harmonious relationship of lips, dentition, gnathic skeleton, tongue, velar mechanism, vocal cords, and airflow. Injury to any of these structures can result in decreased quality and production of speech.

Subglottic stenosis is one of the more problematic complications of prolonged intubation. In one prospective study of 120 children, there was an 11% incidence of subglottic stenosis in children intubated over 24 hours.[10]

Craniofacial Skeleton

The growth of the craniofacial skeleton is a complex dynamic of interrelated events that may be adversely affected by injury. The frontoparietal calvarium, nasomaxillary complex, zygomatic-orbital region, and mandibular corpus are formed principally through intramembranous ossification, while the non-calvarial parts of the occipital, sphenoid, and temporal bones and the mandibular condyle form through endochondral ossification. As these bones grow and develop, they mineralize, lose elasticity, and become less resistant to applied forces and fracture. An additional concern with pediatric fractures is the potential for disruption of normal growth vectors and "centers." The mandibular condyle (with its progressive endochondral growth and remodeling) and the nasal vault and septum (responsible for midface projection) may not respond to normal developmental influences of the expanding airway, oropharynx, and functional soft tissue envelope if severely injured.[11,12] The younger the child, the more deleterious injury is to growth vectors and mechanisms.

Increased periosteal activity in children can speed recovery through increased bone formation. This is often seen as a positive physiologic mechanism, but in intracapsular condylar fractures or injuries with hemarthrosis, inopportune bone formation can lead to ankylosis, immobility, and deformation. Further, prolonged maxillomandibular immobility in growing children can result in fibrous or pseudo-ankylosis.

Fracture Management

As with any fracture, the goals of treatment include restoration of form and function. The special considerations in children are those of future growth of the patient. Treatment (or improper treatment) may result in growth disturbance and gnathic compromise. Fixation devices may migrate during growth and later become problematic. The surgeon must decide on using open versus closed techniques, the type of fixation, grafts and adjuncts to healing, and timing of additional interventions. Therefore, it is important to understand the options available in order to address pediatric fractures appropriately and ensure restoration of form and function while minimizing growth disturbance.

Frontal Bone and Sinus Fractures

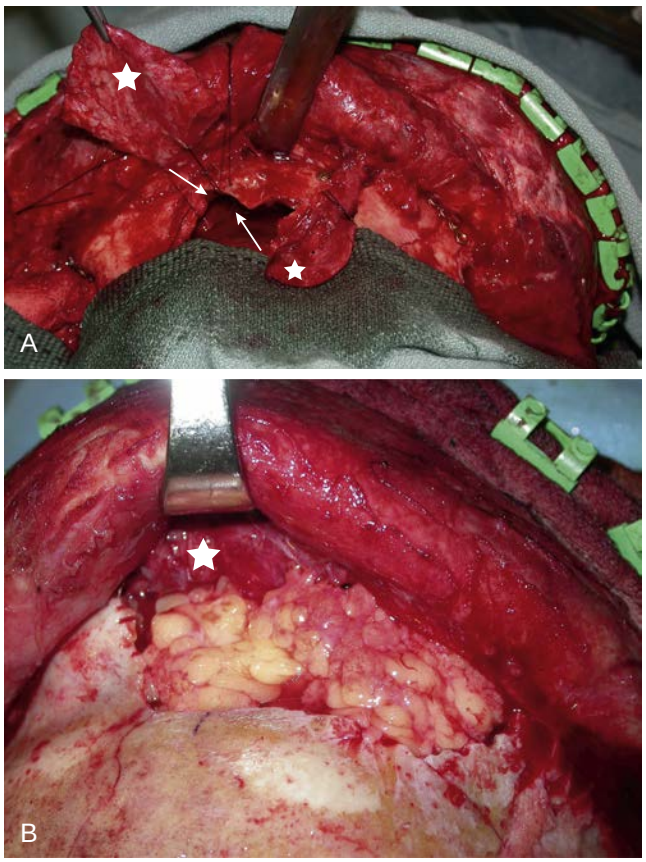
The incidence of frontal sinus fractures correlates with the development of the frontal sinus. The frontal sinus begins as an outgrowth of the nasal region that becomes radiographically evident at 4 to 5 years of age, achieves adult configuration by adolescence, and reaches full volume by the age of 20.[13] Concomitant intracranial injuries are more likely in children with frontal sinus fractures than in the adult, most likely because of the high forces required for fracture of the frontal bone.[14]

Frontal sinus fractures require repair when there is significant displacement of the frontal table that would result in cosmetic defects, retro-displacement of the posterior table, persistent CSF leak, or obstruction of the nasofrontal duct/outflow tract. Injuries without significant displacement of the anterior and/or posterior tables should be managed conservatively. This is accomplished with antibiotics (if there is a history of chronic sinusitis), decongestants as needed, head elevation, and sinus precautions. Long-term follow-up is necessary in order to detect early mucocele development. A follow-up screening CT of the paranasal sinuses at 4 to 6 months is recommended.

In cases requiring operative intervention, the repair should start with an approach that will result in a cosmetic scar—usually a coronal incision with wave incision design, or access gained through existing lacerations, though these may limit appropriate access. The fractured portions are removed and mucosa completely removed. The decision of how to treat the sinus (cranialization vs.

obliteration) should be determined by the state of the posterior table. Comminution of the posterior table, loss of dural integrity, and obvious CSF leak direct the surgeon to cranialization as the preferred treatment. Dural repair, grafting, and confirmation of cranial integrity are possible through complete removal of comminuted posterior table segments. If the posterior table is intact or with nondisplaced fractures and no CSF leak, obliteration of the sinus may be the treatment of choice. The outflow tract can be obliterated with fat, fascia, or pericranium. The author's preference is to use a pedicled pericranial flap (Figure 13-2, *A*) with fixation by tissue fibrin glue and obliteration with calvarial shavings or abdominal fat (see Figure 13-2, *B*). The outer table is then reconstructed with the use of resorbable mesh/plates/screws and harvested bone grafts if indicated. Small posterior drains and a firm dressing should be placed to prevent hematoma formation.

signs or symptoms of fever, progressive erythema or edema in the region, new-onset or worsening headache, or a change in neurologic status should prompt CT radiographic evaluation. Small and intermittent CSF leaks usually spontaneously resolve within several days.[13,15]

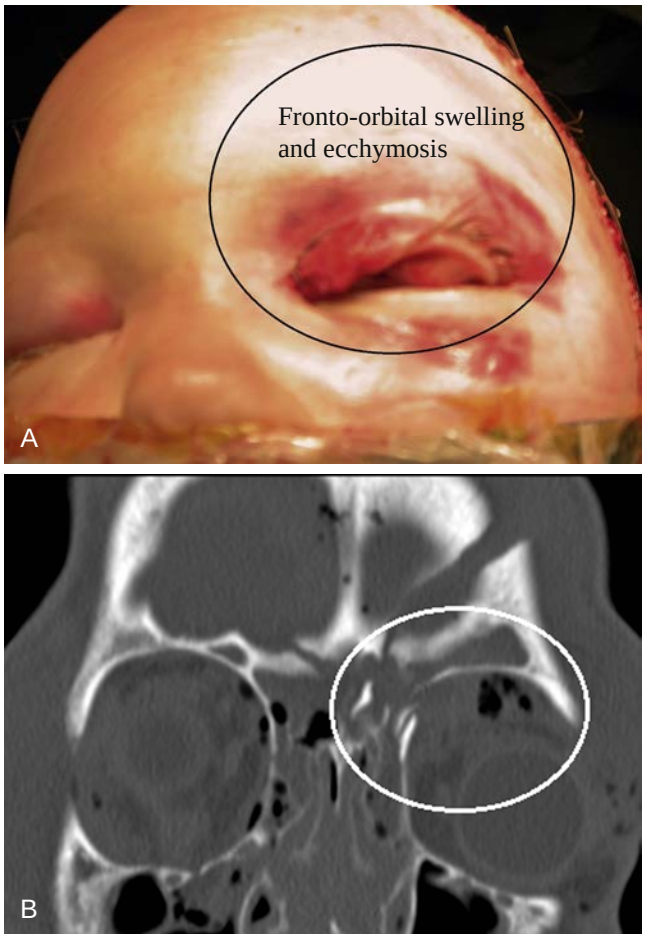


• **Figure 13-2** **A,** Pericranial flaps *(stars)* transferred into frontal recess over naso-frontal ducts *(arrows)*. **B,** Obliteration of frontal sinus with fat. *Star* indicates pericranial flap in place.

Finally, recent techniques using CT-guided technology and endoscopically assisted reduction of frontal sinus fractures have been described and, in cases with mild to moderate displacement of the frontal table, may allow reduction of fractures without significant scarring from access incisions.[15,16] Preservation of sinus integrity and physiology through appropriate surveillance and endoscopic management is now the preferred option in most frontal sinus fractures in children.

Orbital Fractures

Age plays a large role in the fracture pattern of the orbit when trauma is sustained to this region. A recent study of 312 pediatric patients over a 9-year period (4 months to 16 years of age) revealed results consistent with the anatomy and development of this region. Children less than 8 years of age were more likely to suffer orbital roof fractures (Figure 13-3), while those older than 8 years were more likely to suffer fractures of the orbital floor.[17] This correlates well with development of the orbit, which matures around the age of 7 years, as well as development of the maxillary sinus, which increases in volume and results in a larger surface area of the thin orbital floor and subsequent fracture.



• **Figure 13-3** **A,** Five-year-old boy with significant orbital trauma from an ATV rollover. **B,** Frontal and orbital roof fractures *(circle)* in child.

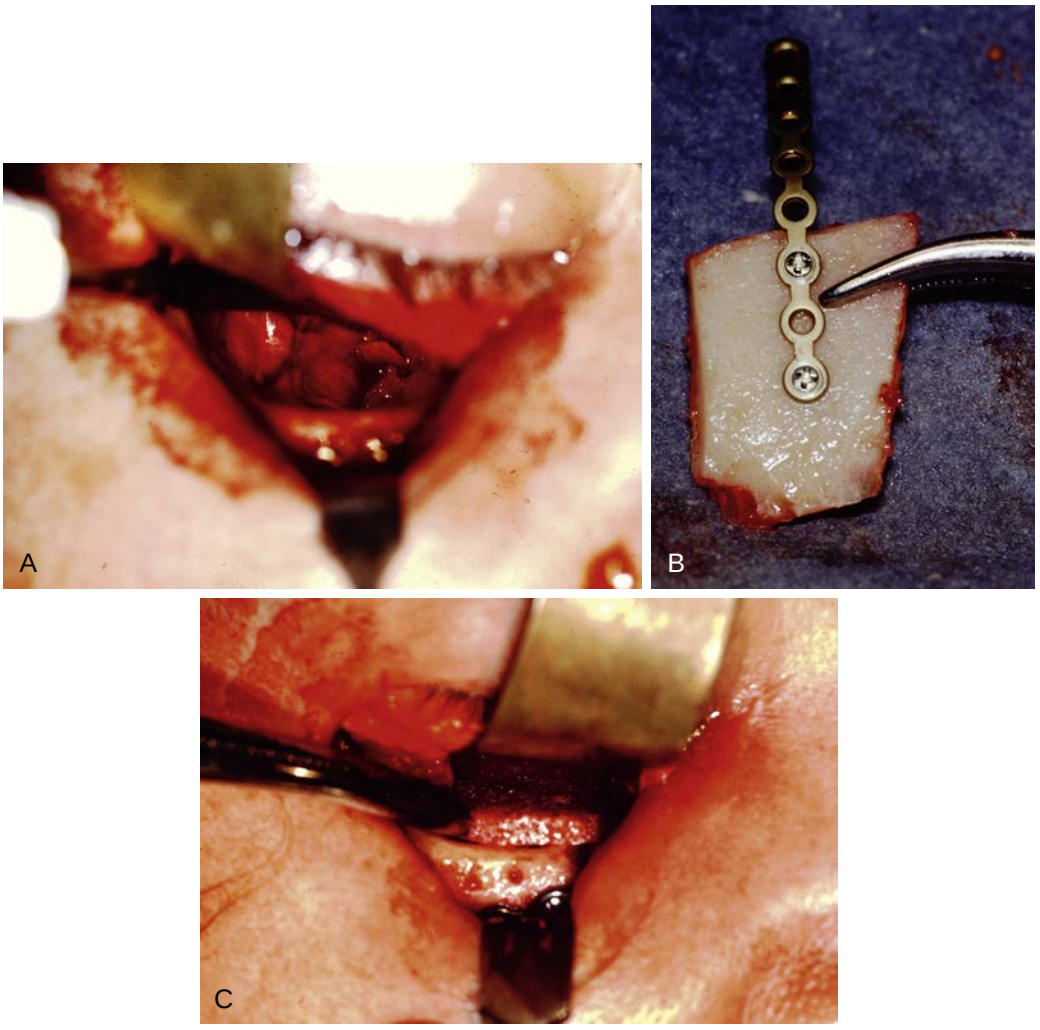
Timing of repair of significant orbital floor fractures in children is crucial, as there are improved functional outcomes when these fractures are repaired early (within 48 hours).[17-20] Trapdoor fractures are more common in children due to the elasticity of the thin orbital bone; thus, the associated rectus musculature and periorbital fat become entrapped despite a lack of radiographic evidence of a bony defect (Figure 13-4).[19] A thorough ophthalmologic exam will reveal restriction of ocular movement with diplopia, often accompanied by nausea and vomiting.[19,20] The "white-eyed" blowout fracture with its lack of associated subconjunctival hemorrhage or chemosis is considered an urgent ophthalmologic condition that requires early surgical intervention before ischemia and necrosis of the entrapped tissue ensues.[21]



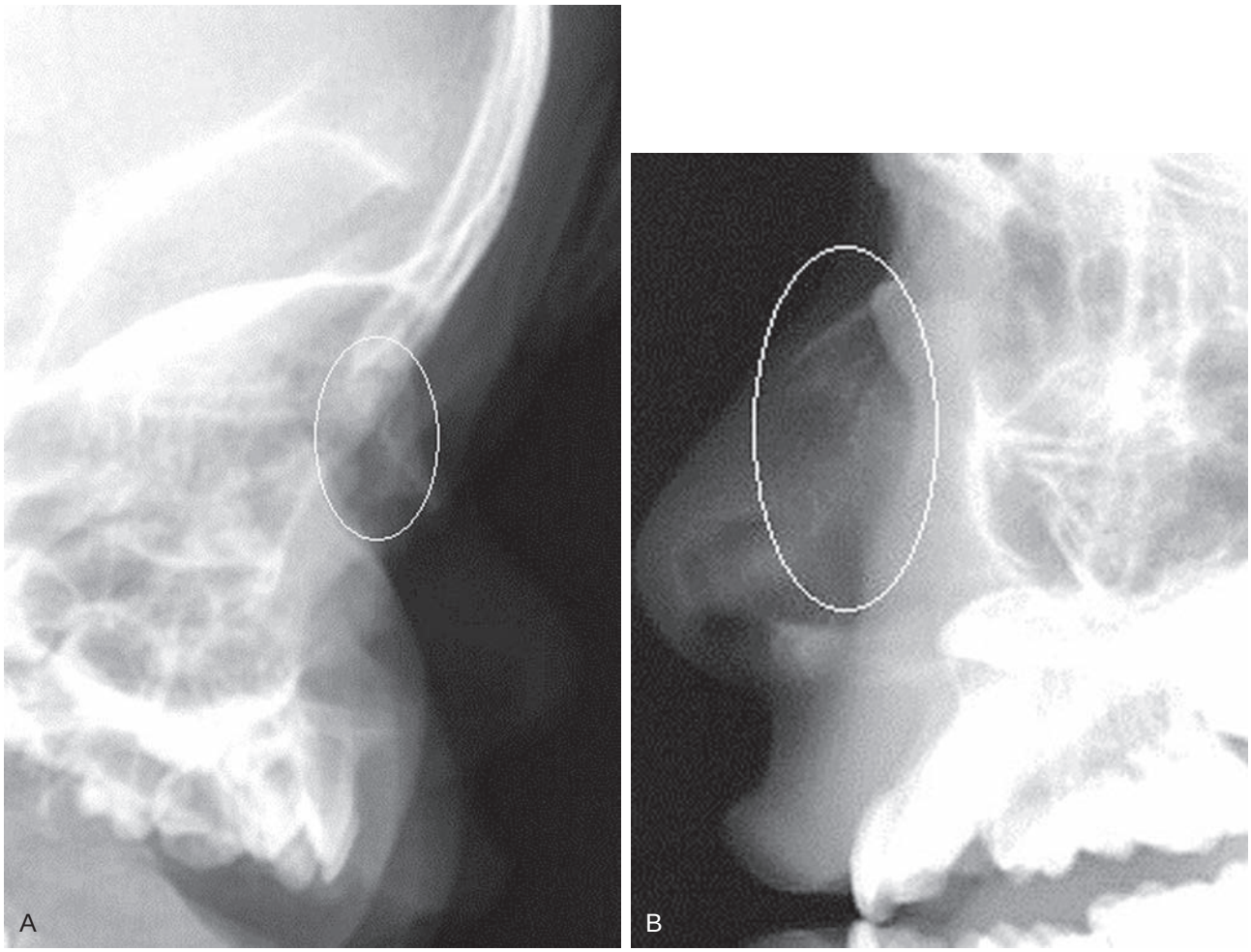
• **Figure 13-4** Blowout fracture of left orbit with soft tissue entrapment. Elevation of the eyes reveals the entrapped left periorbita that prevents elevation.

Fracture repair requires volume restoration of the orbit, periorbital content restoration, and forced-duction test to confirm a lack of entrapment. Autogenous tissue (costal cartilage/bone or calvarium) can be used in order to establish orbital restoration and integrity (Figure 13-5).

Intraoperative and acute complications of pediatric orbital floor fractures include oculocardiac reflex with profound bradycardia, persistent nausea, visual changes, and enophthalmos/exophthalmos. Delayed presentation of gaze restriction due to a pronounced inflammatory reaction to resorbable orbital mesh has been reported.[22,23]



• **Figure 13-5** **A,** Operative photo of blowout fracture of the orbital floor. **B,** Calvarial bone graft adapted to fixation plate for orbital floor repair. **C,** Bone graft in orbital floor defect.



• **Figure 13-6** Plain radiograph image of a 1-year-old **(A)** and 10-year-old **(B).** Notice the wide naso-maxillary suture in the infant compared to the older child, which, in the setting of injury, may suggest a fracture.

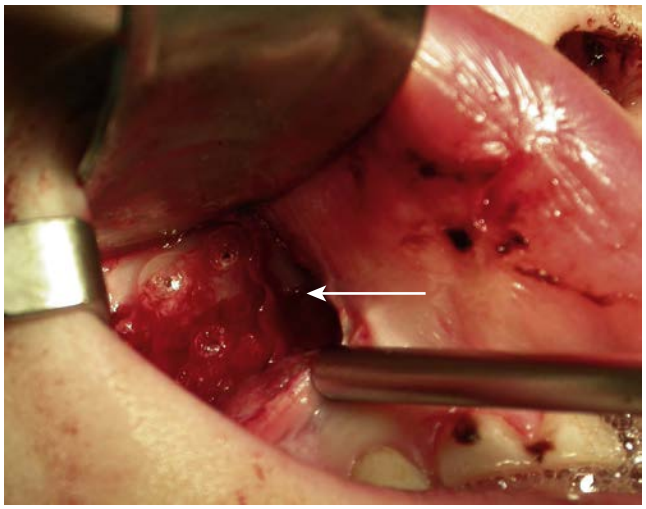
Nasal Fractures

Nasal-septal fractures are among the most common injuries in children, yet are often underreported.[24-26] A recent retrospective study of more than 350 nasal bone fractures revealed that the most common causes were falls, sports incidents, interpersonal violence, and motor vehicle crashes.[27] Nasal injuries in the pediatric population differ in that the cartilaginous region and the immature bone are more pliable than in adults.[26] Deformation and greenstick fractures are more common as a result, which may be clinically evident initially after injury. The deformity resolves to some extent over the immediate post-injury period, though bony deformation may persist. A good indicator for possible surgical intervention is nasal airflow obstruction that does not resolve. Plain radiographs will detect grossly displaced fractures but not greenstick or minimally displaced fractures. Wide fronto-naso-maxillary sutures in young children are often misinterpreted as a "fracture" by some radiologists or emergency personnel and must be interpreted in light of the clinical presentation (Figure 13-6).[2]

Palpation of this region for step deformities or asymmetry is difficult if the child is uncooperative. Waiting for swelling to resolve, usually 3 to 5 days, to detect any residual deformity and careful assessment of nasal airflow are helpful to determine need for surgery. If clinical exam is not possible, then CT evaluation is recommended.

Treatment is best performed with closed reduction and a minimalist approach to avoid any future growth disturbances. Reduction should be performed within 7 days (or when swelling has resolved) of fracture as children will heal quickly and increased force may be necessary to obtain mobilization and reduction in order to overcome any deformation.[28]

When performing closed reduction, the surgeon should measure externally before placing the instrument intranasally to reduce the fracture. This will minimize the risk of placing the instrument unnecessarily deep in the nasal cavity with consequent nasofrontal or ethmoid air cell penetration. After reduction, careful evaluation for bleeding should be done; if there is prolonged oozing, temporary tamponade can be obtained with an astringent on a soft gauze strip. Once hemostasis has been confirmed, a conformable anatomic splint should be placed over the dorsum and secured to aid in protection. Postoperative complications include



• **Figure 13-7** Operative photo of a resorbable plate at the zygomatic buttress *(arrow)*.

epistaxis, septal hematoma, obstruction, sinusitis, and need for reoperation due to inadequate reduction. Activities with the potential for contact, such as sports or recess, should be avoided for the first 6 weeks following a reduction unless full-face protection is provided.

Midface Fractures

Fractures of the zygoma and maxilla are uncommon in children compared to adults. An immature and more pliable facial skeleton with less prominent midface, small paranasal sinuses, and unerupted teeth (which act as intrabony "buttresses") affords some resistance to fracture forces, particularly in young children.[26,29] These fractures are often the result of sports injuries, motor vehicle collisions, and interpersonal violence.

Evaluation should include a full ophthalmologic exam. Loss of malar projection and symmetry, mandibular dysfunction due to zygomatic arch fracture, sensory changes, and orbital volume changes should be noted.

Patients with mixed or primary dentition may make it difficult to place conventional arch bars on the more bulbous primary teeth. In order to obtain intraoperative maxillomandibular fixation (MMF), a Risdon wire can be bonded monocortical screws (Figure 13-7).

Mandibular Fractures

Mandible fractures are among the most frequent facial bone fractures encountered, second to nasal fractures.[24,26,29-31] Mechanisms of injury include falls in younger children and vehicular crashes and sports injuries in adolescents. In young children the most common fracture of the mandible is the condyle, which then decreases in incidence with age.[32] Reports have suggested that up to 20% of condylar fractures are bilateral.[33-35] Fractures of the angle and body regions increase with age and with development of third molars.[36-38]

Treatment protocols should be categorized according to anatomic location of the fracture and developmental age. Young children have a great capacity for healing and remodeling; therefore, conservative management is preferred with simple MMF, whereas adolescents are treated similarly to adults.

Condylar Fractures

Intracapsular fractures are a concern for the development of ankylosis. Non-operative therapy with active physiotherapy is instituted as early as cooperation and comfort allow.[39] Evacuation of hemarthroses is not routinely performed in young children. Long-term follow-up with periodic radiographs to document condylar development and symmetry is prudent.

Treatment of condylar fractures is usually accomplished with a short period (5-7 days) of MMF in young children and longer periods (2 weeks) in pre-adolescents. Early mobilization and measured, prescribed physiotherapy encourage resolution of hematoma and edema and prevents muscular envelope contractures. Elastic or wire MMF may be used during the immobilization period and entirely depends on cooperation and airway status. A large prospective study with 61 patients under the age of 12 years showed no statistical difference in functional outcome between wire and elastic MMF.[40] As it is more easily tolerated and safer, elastic MMF for guided function should be implemented unless severe or complex comminution dictates strict rigid immobility.

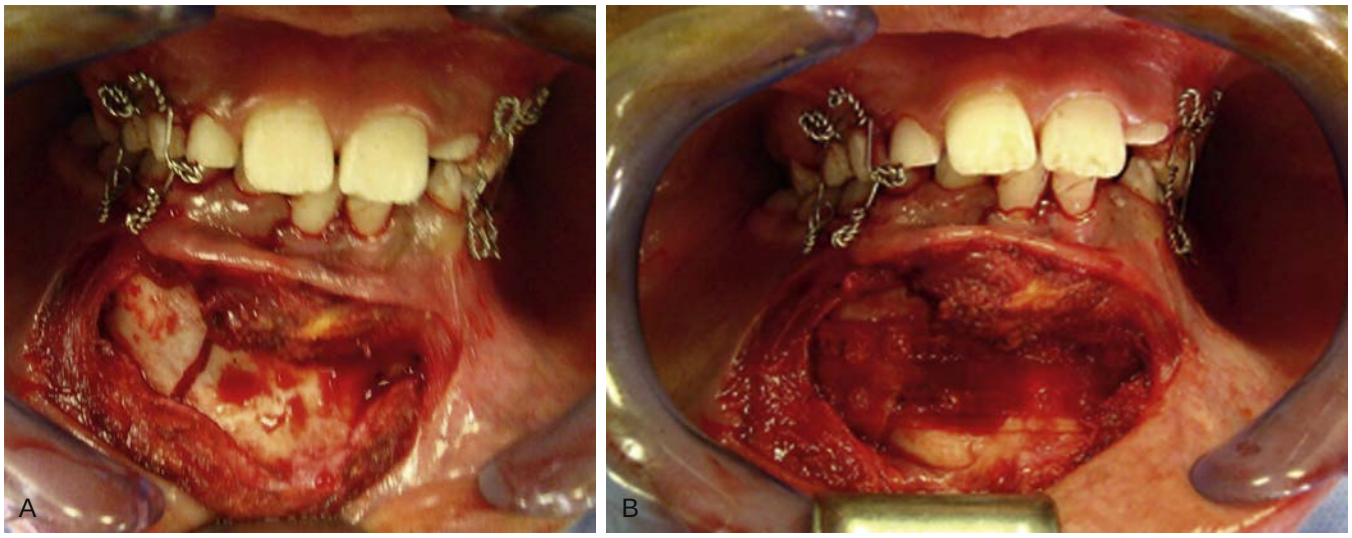
Body and Symphyseal Fractures

Treatment of mandibular fractures with developing dentition in place is more complex for symphyseal, body, and angle fractures. The first step is establishing proper occlusal relationships with MMF. This can be challenging due to the short clinical crowns of primary and erupting teeth. Bonded Risdon wires provide dental fixation devices for establishing the occlusion. A single titanium or resorbable plate (double or strut plates) with monocortical screw fixation generally provides all the fragmentary stability required for primary osseous healing (Figure 13-8).[31,41,42] If the fracture appears to require additional stability, a short 1- to 2-week period of MMF will allow for adequate fracture healing prior to mobilization of the mandible.

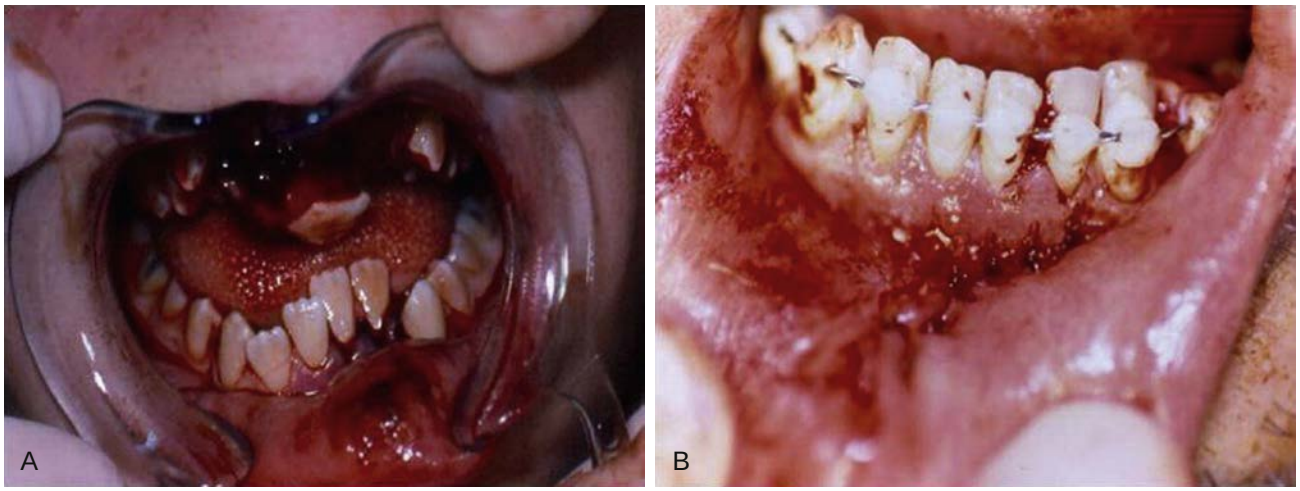
Dentoalveolar Injuries

It is important to be familiar with dentoalveolar injuries, as they are common in children. Approximately one third of all cases are associated with adjacent facial soft tissue injuries.[43,44] Management of these injuries will depend on the associated injuries, numbers and class of teeth traumatized (primary vs. permanent), and condition of the supporting alveolar bone and muco-gingiva.[45]

The simplest of dentoalveolar injuries is that of the avulsed primary tooth. Primary teeth are not replanted,



• **Figure 13-8** **A,** Ivy loop fixation prior to plate placement of parasymphysis fracture of the mandible. **B,** Single "ladder" type resorbable plate with monocortical screw fixation. (Source: Morris C, Kushner GM, Tiwana PS: Facial skeletal trauma in the growing patient, *Oral Maxillofac Surg Clin North Am* 24(3):351-364, 2012.)



• **Figure 13-9** **A,** Dentoalveolar fractures with displaced teeth. **B,** Composite splint bonded in place. (Source: Morris C, Kushner GM, Tiwana PS: Facial skeletal trauma in the growing patient, *Oral Maxillofac Surg Clin North Am* 24(3):351-364, 2012.)

but space needs to be maintained for spatial eruption patterns to be preserved; therefore, referral to a pediatric dentist is recommended. The avulsed permanent tooth with an open apex and less than 1 hour ex situ should be replanted and splinted for 2 to 4 weeks while monitoring for revascularization versus necrosis, infection, or loss of attachment. A helpful website developed by the International Association of Dental Traumatology out-

njuries and is available at

ments can be maintained with bonded wires (Figure 13-9), acrylic splints, or, if the bony segment is large enough, small fixation plates. Again, a conservative approach to these injuries in the young or mixed-dentition child is warranted.

Prevention of orofacial injuries in children is important. Mouthguards should be encouraged for any sport with the potential for contact-induced injuries to the oro-dental region. The mouthguard rule in collegiate sports was noted to decrease dental trauma from 280 events in 1970 to 55 in 1973 when the rule was first instituted.[46] Pediatric patients should be questioned as a matter of routine during well-child visits regarding the use of mouthguards and protective equipment in sports and recreation.

Soft Tissue Injuries and Management

The advent of sport vehicles, fast-paced recreational activities, risk-taking behavior in adolescents, and so forth have all translated into children more at risk for injury, particularly of the

facial region. Consequently, soft tissue injuries are common, particularly in the younger population. In order to address such injuries well, a careful examination process is warranted.

Inspection of facial soft tissue injuries in children should be performed in a controlled environment with parent or caregiver present and with adequate lighting and removal of extraneous noise or activities. Setting the stage for evaluation begins with a thorough review process with the caregiver and/or witness, done in a gentle but direct tone. This can be challenging in light of a severe soft tissue injury. Constant visual evaluation of the child, without the laying on of hands, allows for confirmation of patient stability, facial animation, and mental status changes.

Physical examination should note tissue margins, deficits and avulsions, possibility of retained foreign bodies, and damage to important underlying structures including salivary ducts, nerves, vessels, and/or muscle. The extent of the injury and age of the child will dictate the appropriate setting for treatment. Verification of vaccination status, especially tetanus currency, is recorded. A history of resistant or recurrent staphylococcal infections should prompt adequacy of previous treatment, by whom, and a nasal swab obtained to rule out staph colonization.

Superficial Wounds

Any wound, regardless of the depth or extent, requires thorough cleansing before closure. All debris must be removed, and tissue margins should be uniform and clean without foreign body discoloration. Superficial wounds with no missing tissue can usually be closed in a single layer. Often these wounds can be coapted with cyanoacrylate (tissue adhesive) if no tension exists at the wound margins. A prospective study by Singer and colleagues demonstrated similar cosmetic outcome with cyanoacrylate or standard closure with nonresorbable suture.[47] Placing adhesive near the eyes or lips in a restless child is to be discouraged. Several studies have also proven acceptable cosmetic outcome with the use of resorbable suture material.[48,49] Resorbable materials are preferable to extensive suture removal in a young child who may not tolerate suture removal in the ambulatory setting.

Deep Wounds

Deeper wounds require inspection for involvement of muscles, nerve, lacrimal system integrity, and salivary gland or ductal tissue injury (Figure 13-10, *A*). Most eyelid and lacrimal injuries will require sedation or general anesthesia for a proper evaluation in the young child. Facial nerve injury may be difficult to ascertain with extensive damage, swelling, and an uncooperative child. Animation may be recorded for later comparison during healing.

Judicious use of deeper, buried sutures to reduce tension and subcutaneous pull-out permanent sutures left for 2 to 3 weeks will significantly reduce tension, provide support to the healing wound, and reduce the number of cutaneous sutures required (see Figure 13-10, *B*). Liberal use of wound support tapes for 2 to 3 weeks postoperatively and then Silastic sheets (see Figure 13-10, *C*) for several weeks will reduce scarring.

Nerve Injuries

Generally, young children recover predictably from a nerve injury because of healthy neural tissues that exhibit pronounced axonal regeneration after contusion or transection. Sensory nerves that are injured in young children will predictably heal with return of normal dermatome sensory distribution. Adolescents with larger transected sensory nerves should be ideally repaired or given the option of repair, as one would with adult patients.

Injury to the facial nerve that occurs distal to a vertical line dropped from the lateral canthus is likely to undergo neural arborization and does not benefit from micro-neurosurgical reanastomosis. However, larger branches of the facial nerve proximal to this line do benefit from primary micro-neurosurgical repair.[50] Reapproximation of epineural tissue at the time of the initial repair is preferable and leads to the best possible outcomes. Reapproximation should be accomplished under magnification with 8-0 or 9-0 permanent suture.[51]

Glandular and Ductal Injuries

Lacerations of the salivary gland and ductal structures are managed differently depending on location. Intraparenchymal injury of the gland requires only closure of the capsule, a pressure dressing over the gland, and possibly a small dependent drain to prevent salivary accumulation.[52] Ducts (Wharton or Stenson) that are extraparenchymal and amenable to identification of proximal and distal stumps should be repaired with primary anastomosis over a stent that will be left in place for 2 to 4 weeks. Animal models have shown that reanastomosis should be performed with nonresorbable suture to minimize inflammation that accompanies degradation of suture material.[53] If the duct cannot be repaired, diversion of the proximal stump intraorally or tying off the proximal end and invoking an inflammatory sialadenitis with eventual ductal fibrosis and glandular involution can be performed.[54]

Complications of salivary gland repair include sialoceles that can usually be managed with repeated aspirations, antibiotics, and antisialogogues.[55] Established and recalcitrant parotid sialoceles, though uncommon in children, can also be managed with intraoral diversion for creation of a controlled intraoral fistula.[56]

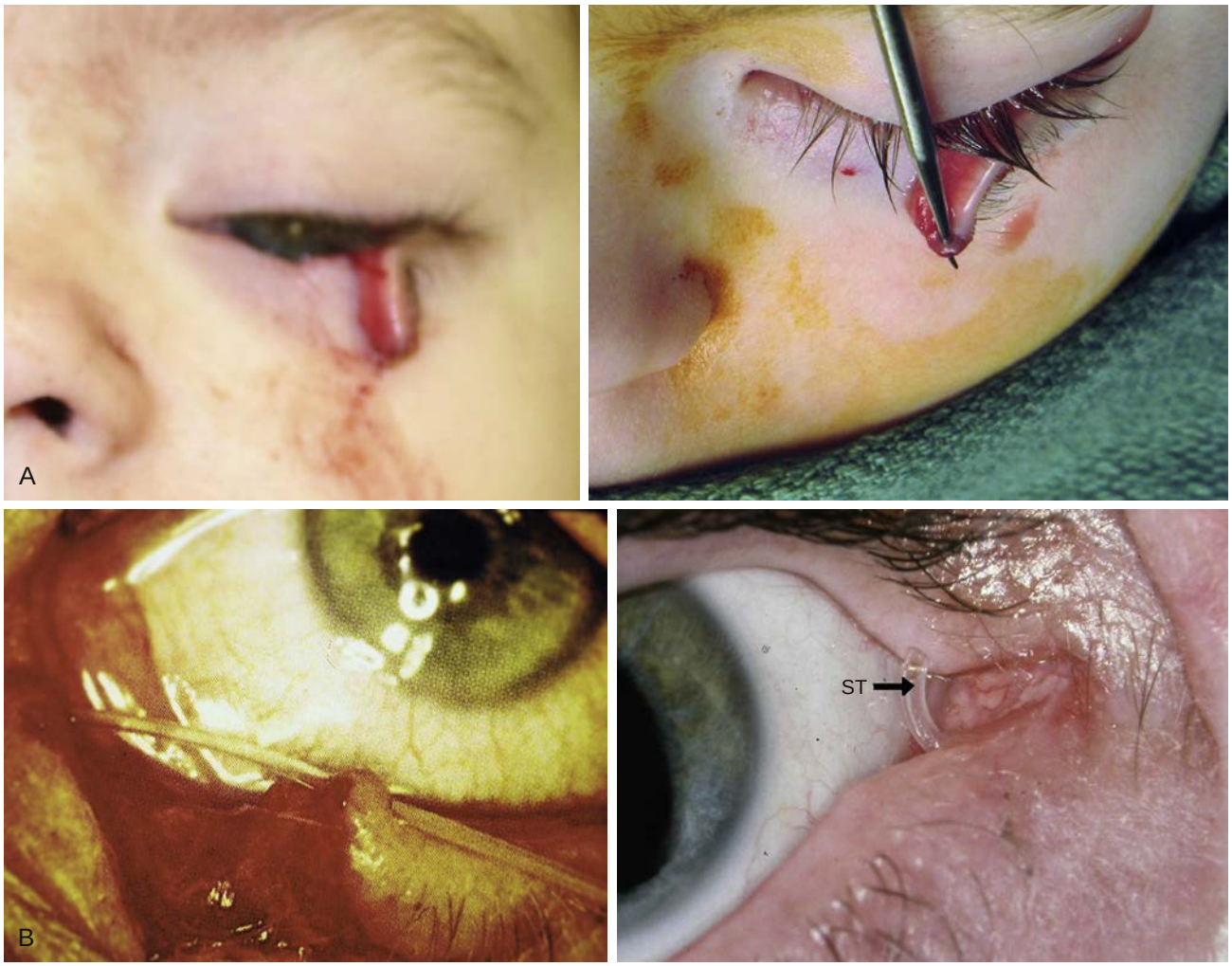
Lacrimal Injuries

Disruption of the nasolacrimal canalicular system requires attention within 48 hours of injury to avoid very rapid scarring and ductal stenosis. The laceration traversing the canaliculus is identified with a Bowman probe or dilator (Figure 13-11, *A*) and irrigation attempted to confirm transection. Designed



• **Figure 13-10** Wound care to diminish hypertrophic scar formation. **A,** Dog bites to the face in a child at risk for hypertrophic scarring. **B,** Subcutaneous pull-out suture to maintain non-tension in the dermis during healing. **C,** Silastic sheets to maintain subtle pressure on the maturing scar to diminish hypertrophic scar formation.

Silastic tubes can then be placed at the time of the initial repair and left in place for several weeks (see Figure 13-11, *B*). Anchoring the distal tube ends intranasally with suture high in the nasal vestibule is key to prevent dislodgement. Antibiotic/anti-inflammatory ophthalmic agents are used for 1 to 2 weeks, and thereafter a simple wetting agent can be used to maintain hygiene and patency. The tubes are easily removed after several weeks of healing.[57] Associated eyelid wounds are then closed in the usual fashion, taking care to restore the anatomic lamellae of the eyelid. Complex eyelid and lacrimal wounds require loupe magnification or an operating microscope for adequate surgical management.



• **Figure 13-11** **A,** Lacrimal injury from torn lower eyelid. Avulsed lower eyelid at the medial canthal region involving the canaliculus with dilator probe in place. **B,** Lacrimal duct repair with prepared silicone tubes *(ST)* placed through upper and lower canaliculi, passed into the lacrimal sac and nasolacrimal duct.

Avulsive Injuries

Local Flaps

Loss of tissue in children always presents a challenge to the reconstructive surgeon because of the limited tissue depot in children as compared to the redundancy that exists in older patients. Depending on the location and defect size, local tissue rearrangement with rotational, interpolation or advancement flaps can be used for small to moderately sized defects.[58,59] Areas from which pedicled random pattern flaps can be raised to cover defects include the post-auricular, cervical, and lateral cheek with lateral canthotomy. Axial-pattern flaps include the glabellar (supratrochlear), submental (deep lingual), buccal myomucosal (facial), nasolabial (superior labial and angular), and lower lips/Abbé (inferior labial). Careful and conservative design for skin flaps in the facial region in children is paramount and should not be undertaken until the procedure has been thoroughly planned and reviewed with the parent and patient, if an older child. Placing new incisions to gain transposed tissue for defect fill on the young face should be limited and predictable. This concern has led to tissue recruitment through expansion.

Tissue Expansion

Tissue expansion allows for the use of similar-appearing skin to cover the defect, although disadvantages include the time involved in the staged operation and multiple office visits for serial saline injections.[60]

Tissue recruitment in children is generally limited to the scalp, forehead, and neck regions, as these areas lend to the nearby depot of similar tissue that can be expanded and transposed into the target site (Figure 13-12). Care must be exercised to place the access incision distant from the expander and target recipient site in order to avoid dehiscence and exposure of the reservoir. Exposure does not necessarily condemn the device, though its utility for further expansion is complete. For comfort and ease for access in children, the expander ports can be left externally to avoid

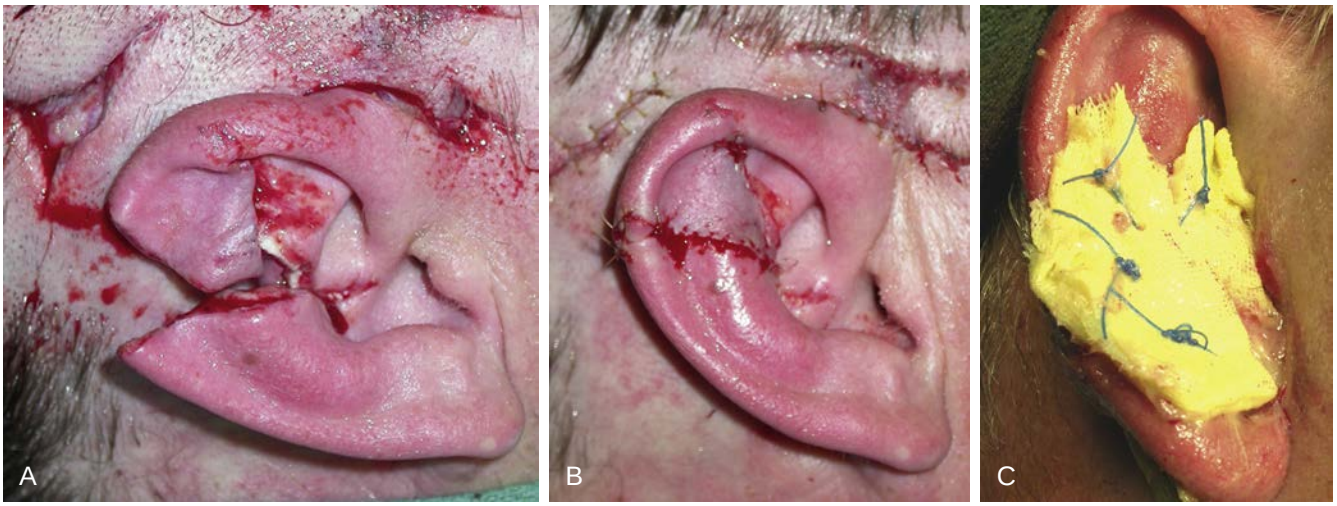


• **Figure 13-12** Tissue expansion. (Hogg NJV: Primary and secondary management of pediatric soft tissue injuries. *Oral Maxillofacial Surg Clin N Am* 24(3):374, 2012.)

percutaneous injections; there is no significant increase in infection rates with external ports. [61]

The biology of expanded tissues has been well studied, confirming that there is increased microvascularity to the expanded skin. This has a positive effect on tissue survival over that of acutely transposed tissue in a random-pattern flap. There is also an accompanying thickening of the overlying epidermis and simultaneous thinning of the dermis during the 2 to 3 weeks after expansion. Underlying muscle thins and atrophies but does rebound, whereas adipose tissue remains atrophied. Intraoperative on-table expansion can be used, especially in children, because of the better viscoelastic properties of youthful dermis. However, this does not recruit "new" tissue, but rather represents a stretching of the tissue as a "creep" mechanism.[62]

Expansion is performed on-table until overlying skin blanches; this resolves after several minutes. If not, then several milliliters of saline are removed until skin vascularity returns. Serial expansion then takes place every 2 weeks with 10 to 15 mL of saline injected in each expander or as comfort allows. Children usually tolerate expansion well if pre-injection ibuprofen or acetaminophen is administered 30 minutes before expansion. After the desired amount of tissue expansion has been attained (slightly overestimated amount of tissue), expander removal and flap rotation and inset is performed.



• **Figure 13-13** **A,** Complex ear laceration with torn cartilage. **B,** Repair of laceration. **C,** Bolster dressing to conform to ear anatomy and support tissues.

Special Regions

Lacerations of certain regions of the face require particular attention in repair due to the delicate aesthetic and specialized nature of the tissues. These regions include the ear, nose, eyelids, and lips. Knowledge and understanding of the related tissues and care given to proper anatomic restoration and tissue support will optimize healing. Cosmesis and function are paramount in these delicate regions and demand the surgeon's best effort to obtain physical, social, psychological, and emotional well-being after injury in the child.

Ear

Lacerations of the ear should be closed in a meticulous layered fashion to reapproximate the cartilaginous structures. Oversuturing the cartilage should be avoided, if possible, as the cartilage is soft, thin, and easily torn, especially in the young child. A tapered, non-cutting needle with either semipermanent or permanent suture (less inflammatory potential) is recommended.

Significant composite defects of the ear are approached in a staged fashion. Local soft tissue flaps and harvested cartilage from the opposite ear or rib are used for framework once the recipient site has been prepared and there are no signs of infection.

Complex, avulsive, or shredded ear wounds require support. Therefore, a lightly affixed bolster should be applied (Figure 13-13). The petrolatum-impregnated gauze dressings work well to conform to the ear contours, help discourage hematoma formation, and support neovascularization when the tissues are stabilized and protected. The outer helical skin is left exposed to verify vascularity and a large, fluff dressing placed for 3 to 5 days for protection while the child is sleeping or at play.

Lip

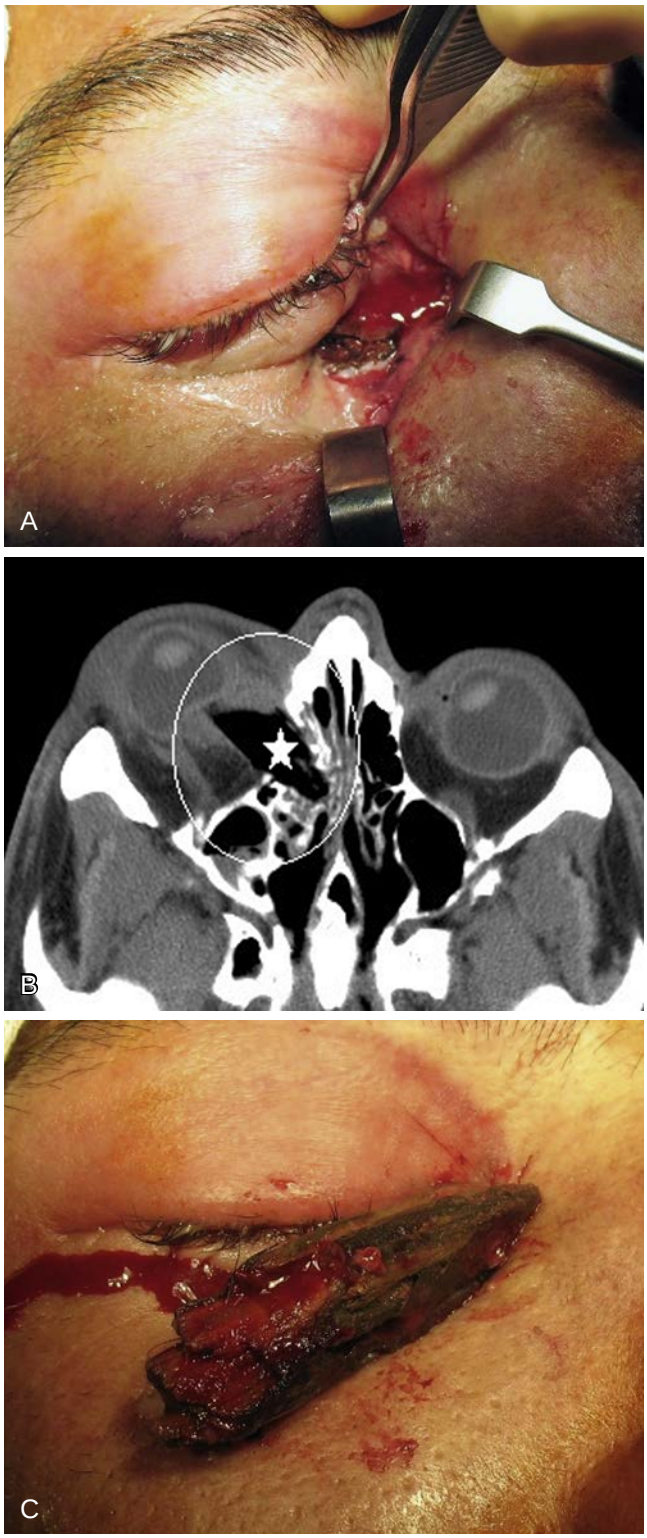
Children are apt to injure the lips from falls, sports contact, vehicular crashes, dog bites, assault, and play. Trauma to the lip region requires precise reapproximation of the orbicularis oris to restore function and avoid a postoperative furrow where a dehiscence of the muscle could develop if not properly repaired. This kind of defect is often seen in the cleft lip condition when there is imprecise muscle reconstruction. An optimal cosmetic result requires careful reapproximation of the vermilion border/white roll (indistinct at times in the lower lips of children); thus loupe magnification is usually necessary. If a significant portion of the lip and vermilion is missing, such as in a dog bite injury, then techniques such as an Abbé flap (lower lip pedicled flap to upper lip defect) should be considered for lip reconstruction. As the Abbé flap is based on the inferior labial artery, immediate reconstruction can take place in a contaminated bite wound. Division of the pedicle is done 2 to 3 weeks later.

It is also important in lip reconstruction to take measures to avoid loss of vestibular height, where possible, as once scar contracture has taken place, future tissue rearrangement and vestibuloplasty is much more challenging. Local buccal mucosal advancement flaps during the initial repair can often help to maintain vestibular height and depth.

Eyelids

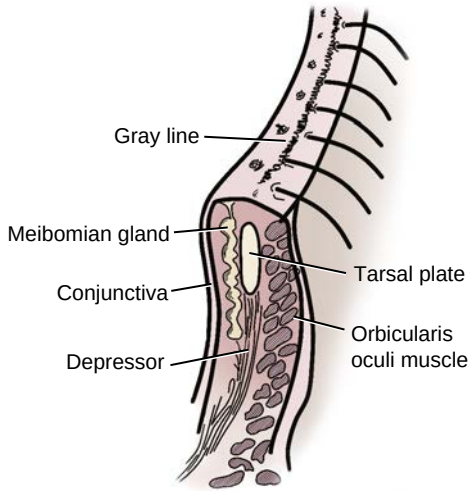
Penetrating or complex orbital injuries should undergo CT evaluation before exploration and repair (Figure 13-14). The mechanism of injury may dictate the kind of injury encountered. Complex wounds to the eyelids can result in lid contracture, ectropion, entropion, trichiasis, blepharitis, exposure keratoconjunctivitis, and vision changes. Meticulous repair, usually in the operating room with a microscope, is required for extensive eyelid reconstruction. Preservation of all tissues is a goal, even if they are devitalized. Viable tissue should be maintained, carefully restored, and supported in order to maintain lid length, fornix depth, and healthy palpebral function. Devitalized or ischemic skin can be prepared and used as a free graft.

The lamellae of the upper (three compartments) and lower eyelids (two compartments) are restored or supported to the

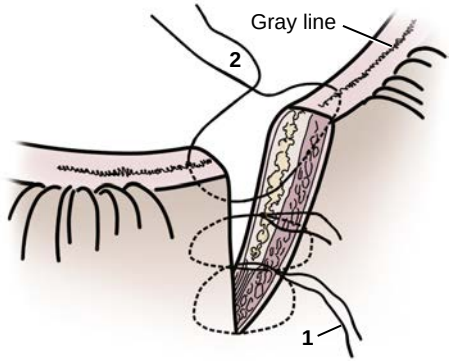


• **Figure 13-14** **A,** Penetrating orbital injury after being thrown from bike and striking tree. **B,** Axial CT demonstrating void *(encircled star)* on medial aspect. *Note* the deformation to globe from mass effect. **C,** Retrieval of foreign body from medial aspect of orbit.

optimum that can be achieved at the initial repair (Figures 13-15 and 13-16). Allowing healing to proceed in the midst of tissue loss or inadequate restoration invites lid contracture, which can be difficult to overcome later. Temporary tarsorrhaphy sutures should be placed at initial repair to suspend



• **Figure 13-15** Diagram of basic eyelid anatomy and corresponding tissue compartments (lamellae). (With permission from Hogg NJV: Primary and secondary management of pediatric soft tissue injuries. *Oral Maxillofac Surg Clin N Am*, 24(3):368, 2012.)

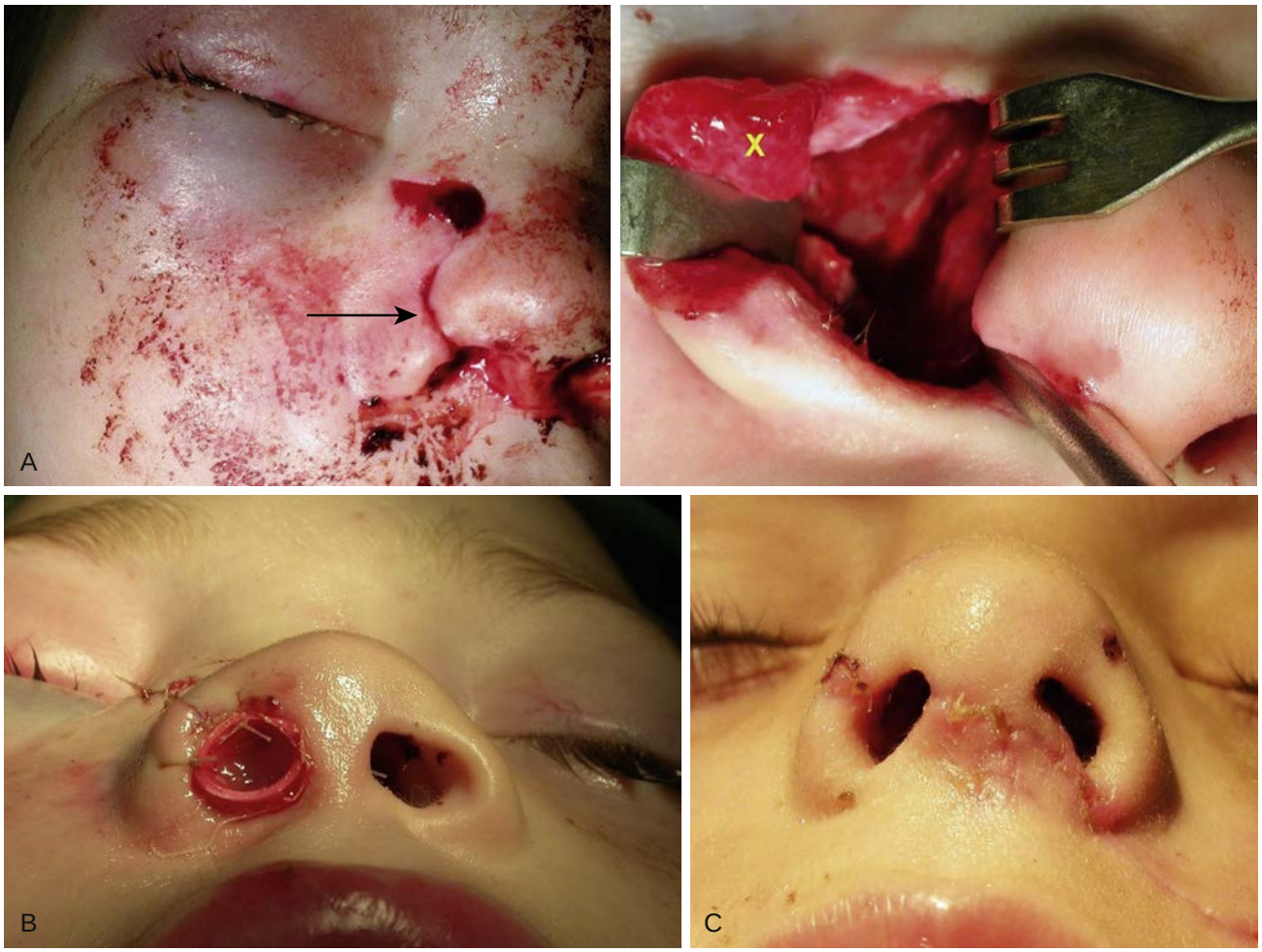


• **Figure 13-16** Diagrammatic repair of the lower eyelid. 1, Skin suture with tails left long. 2, Suture through gray line with tails left long and secured with skin tapes onto lower eyelid skin. (With permission from Hogg NJV: Primary and secondary management of pediatric soft tissue injuries. *Oral Maxillofac Surg Clin N Am*, 24(3):368, 2012.)

and support any eyelid that has a complex wound with tissue loss or has undergone grafting procedures (cartilage, mucosa, skin). Even young children seem to tolerate these stabilization sutures. Parents should be instructed on wound care, eye irrigation, and vigilance for postoperative infection. Temporary changes to the tear film, lid edema, and lacrimal stasis are to be explained and monitored. (Note: Lacrimal injuries are covered in the section "Deep Wounds.") Upper eyelid trauma with avulsive injury to the levator mechanism requires specialist repair, and referral is recommended.

Nose

Trauma to the nose, as with the ear, requires attention to various layers—vestibular skin and mucosa, cartilaginous elements, and overlying skin. The septal cartilage should be inspected to ensure that no septal hematoma exists that would require drainage and packing. Septal deviation, if significant, can be treated with closed reduction and placement of splints. Septal injury in children may result in growth disturbances;



• **Figure 13-17** **A,** Complex nasal wound with circumferential laceration *(arrow)* and cartilage disruption *(X)*. **B,** Repair of full-thickness nasal wound with stent in place. **C,** Similar case of full-thickness nasal wound after stent removal at 2 weeks.

therefore a supportive nasal septal stent should be placed for 2 weeks if there are fractures, torn mucosa, or hematoma.

Layered closure begins intranasally with the mucosa and vestibular skin. Careful *alignment of the alar rim first* will help to sort through the intranasal soft tissue elements. Torn mucosa or vestibular skin can invaginate into the wound; thus, careful lifting and alignment and judicious (resorbable) suture placement will ensure that lining tissue is reestablished. A few inter-cartilaginous sutures to support the upper and lower lateral elements, if avulsed from their cephalad anchoring points, and intra-cartilaginous alignment of torn cartilage is carried out. An intranasal stent to discourage circumferential scarring and stenosis is placed for 2 to 3 weeks (Figure 13-17). Skin repair with small permanent or resorbable sutures completes the repair, and a supportive external dressing or splint is placed for protection purposes.

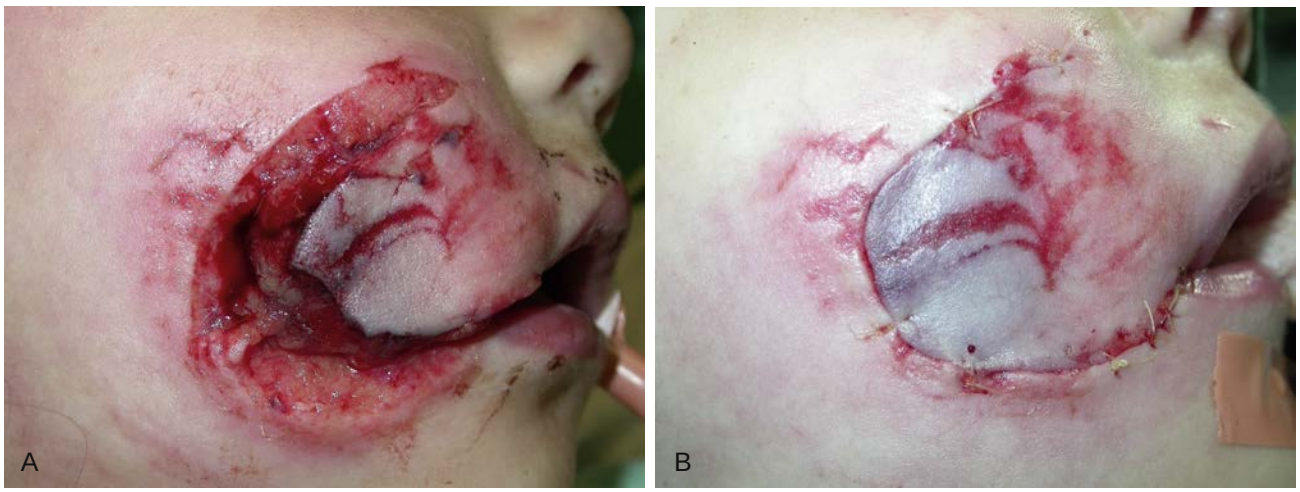
Bite Wounds

Children suffer over half of the animal (primarily dog) bites in the United States, and half of those bites will be to the head and neck region. Previously published data by the CDC demonstrated that the percentage of injuries to the head and neck region decreased with age with 65% in patients 0 to 4 years, 42% for ages 5 to 9 years, 20% for ages 10 to 14 years, and only 9% for patients over the age of 15 years.[62] Bite wounds to the head and neck are a compilation of crush, puncture, laceration, and avulsion tissue damage (Figure 13-18). Animal bite wounds contain the same oral pathogens as in humans in addition to *Pasteurella* spp and *Capnocytophaga* spp. Excellent vascularity of the head and neck decreases the risk of infection, though puncture wounds are more susceptible to infection.[63] Bites to the head by attack-dog breeds in children less than 3 years of age should prompt CT imaging to rule out skull penetration.

Verification of immunization status of the child is necessary, and if there is any doubt, then tetanus toxoid booster should be administered. Quarantine of the animal should be instituted through local law enforcement or the Humane Society. Treatment begins with thorough saline irrigation and debridement of any necrotic tissue and, if possible, attainment of primary closure.[64] Normal saline or a 1% povidone–iodine solution can be used as the



• **Figure 13-18** Avulsive bite wound with penetration to midface skeleton by a pit bull **(A)**. The nasomaxillary complex has been torn away from its base **(B)**.



• **Figure 13-19** **A,** Avulsive dog bite to cheek in toddler. **B,** Repair of cheek wound from dog bite after selective debridement and washout.

irrigant with either a syringe catheter for puncture wounds or gentle lavage with bulb syringe for open wounds.[65-67] High-pressure irrigation (>20 psi) is not necessary and can be damaging to the more delicate injured tissues in children.

The debridement and removal of ragged or macerated margins with a sharp tissue scissors or blade will allow for an even, well-aligned closure (Figure 13-19). Deep tissue approximation is key to avoid hematoma and dead space infection. Dependent drainage with small drains can be placed to augment dead space obliteration.

Children should be placed on combination penicillin or extended cephalosporin antibiotics and then followed closely to ensure that there are no signs of infection. Parents or caregivers should be informed that an intense inflammatory response will follow at 2 to 3 days after a bite injury, but infection is typified by pain, discharge, fever, and elevated white count.

Summary

The child with significant injuries is always an emotionally charged and challenging event for the treating surgeon. Severe injuries must be quickly assessed, the child stabilized, wounded tissue maintained and supported, appropriate immunization and antibiotic status initiated, and plans made for comprehensive management of fractures and soft tissue wounds. During this initial assessment period, consistent serial evaluation of the child is undertaken in order to confirm neurologic and physiologic stability and rapid detection of any progressive bleeding, intracranial lesions, or compromised airway.

Careful attention to soft tissue health; meticulous handling of torn tissues; restoration of anatomic layers and margins; repair of injured ducts, nerves, and specialized tissues; and support to the reconstructed area will greatly optimize healing potential in the pediatric patient and reduce ultimate scarring and dysfunction. Long-term wound support and Silastic sheeting will improve scar cosmesis.

Children with facial fractures heal quickly because of increased osseous activity of the periosteum and endosteum, improved vascularity, and overall general systemic health.

lized from MMF within 7 to 10 days and begin active physiotherapy.

The pediatric trauma patient presents a specific set of challenges to the oral and maxillofacial surgeon. These challenges can be due to behavioral issues, growth and development factors and concerns, anatomic (skeletal) immaturity, unerupted teeth, family and compliance issues, and the future holistic well-being of an injured child. Every effort should be given to early and comprehensive surgical care of children with craniofacial injuries in order to obtain a satisfying and lasting cosmetic result.

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14

Management of Avulsive Facial Injuries

LIKITH V. REDDY, WADE BARKER

Avulsive facial injuries are a complex problem for even the most experienced surgeon. They can present with extensive loss of both hard and soft tissues. Gunshot wounds, including those that are self-inflicted, are the most common etiology of avulsive facial injuries. Other causes include motor vehicle collisions, industrial accidents, and animal bites. The goal of this chapter is to aid the treating surgeon and to familiarize the surgeon in training with the management goals, sequence, and surgical options available to reconstruct these patients. Goals of reconstruction include restoring function as well as improving facial projection, contours, and esthetics. The surgeon faced with the task of reconstructing patients with large avulsive tissue loss of the face needs to have an understanding of wound management, particularly wounds resulting from high energy transfer. It is imperative that the surgeon have a candid discussion with the patient and family before beginning reconstruction to establish reasonable expectations for the outcome and the number of procedures necessary. One of the less commonly understood and appreciated aspects of the care of these patients is the psychological component and the psychosocial implications of these devastating injuries. The limitations of the surgical intervention must be understood by the patient and family as well as by the surgical team. This important point should be brought to light during the early phases of treatment so that realistic goals and expectations can be set.

Wound Assessment

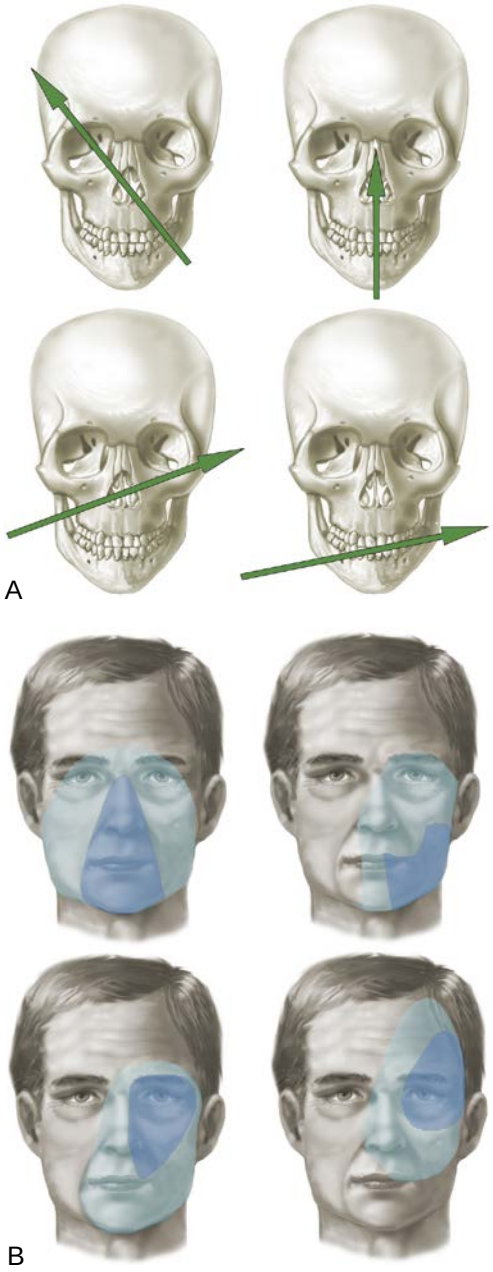
The predominant reason for large avulsive facial tissue defects at most Level I trauma centers is gunshot injuries. Clark and colleagues are credited with the most frequently used classification pattern for gunshot injuries to the facial skeleton.[1] They defined the following four patterns: the frontal cranium, the orbit, the lower midface, and the mandible. The resulting tissue damage from these patterns forms the zones of injuries. The zones are the central face, the lateral mandible, the lateral midface and orbit, and the lateral cranium and orbit (Figure 14-1). An understanding of ballistics is important because it helps the surgeon assess and understand the wound beyond what is clinically apparent. Gunshot wounds can be described as low or high energy based on the energy transfer characteristics between the missile and the tissue it encounters. High energy gun shot wounds and shotgun (pellet) wounds are the most likely to cause avulsive injuries of the face (Figure 14-2). Initially, the bullet crushes sufficient tissue to make an entrance wound through which the missile penetrates the underlying tissue, creating the zone known as the permanent cavity. Depending on the speed at which the bullet is traveling and the bullet's caliber, the walls of the permanent cavity may briefly radiate outward to form a temporary cavity.[2] The temporary cavity is a zone of radial tissue stretching secondary to expansile pressure changes in which tissue vascularity may be compromised. Because of this, secondary tissue necrosis may develop and the eventual wound may be larger than initially apparent.

Management

Initial Encounter

Airway

The initial assessment of patients with severe facial injuries should always center on assessing and securing the airway. Patients who have suffered significant facial avulsive tissue loss will often present with copious bleeding, and often debris in the airway. At the time of initial presentation in the trauma bay, these patients will often have a secured airway that was obtained in the field. In instances in which this has not occurred because of the complexity of the case, bleeding, and/or obscuration of the airway secondary to debris, the airway must be secured. The potential for cervical spine injuries must always be considered, and the neck should not be manipulated while securing the airway. If the conventional oral airway is not possible, a surgical airway should be obtained. The first and only airway that should be attempted in this situation is the cricothyroidotomy. This airway is simple and easy to obtain while requiring minimal dissection and limiting the potential for bleeding as with a tracheotomy. The cricothyroidotomy can later be converted to a tracheotomy in the operating room.



• **Figure 14-1 A,** Trajectory patterns of gunshot wound to the face. **B,** Corresponding zones of injuries. (Modified from Clark N, Birely B, Manson P et al: High-energy ballistic and avulsive facial injuries: classification, patterns, and an algorithm for primary reconstruction. *Plast Reconstr Surg* 98:583, 1996.)

Clinical Examination

Once the airway is secured, attention is diverted to the management of bleeding and other life- or limb-threatening conditions. Once the primary survey is completed, the maxillofacial specialist can then systematically and methodically assess the extent of the injuries, evaluating all of the injured structures as well as any missing tissues. Particular care is taken to assess nerve injuries and injuries to special structures such as the globe, salivary duct, and lacrimal duct (Figure 14-3). The assessment of the extent of hard tissue injury and loss is evaluated first clinically and then by diagnostic imaging.

Imaging

The vast majority of patients presenting to the emergency department with facial injuries will receive a computed tomography (CT) scan. The technological improvements in CT scanning now enable the clinician to immediately obtain very complex three-dimensional renderings of the facial skeleton that will aid in planning the surgical intervention.

Integration of three-dimensional scanning with CT angiography allows visualization of the regional vasculature, which can be assessed for injury or for potential sites of anastomosis in microvascular repair of the missing structures (Figure 14-4).

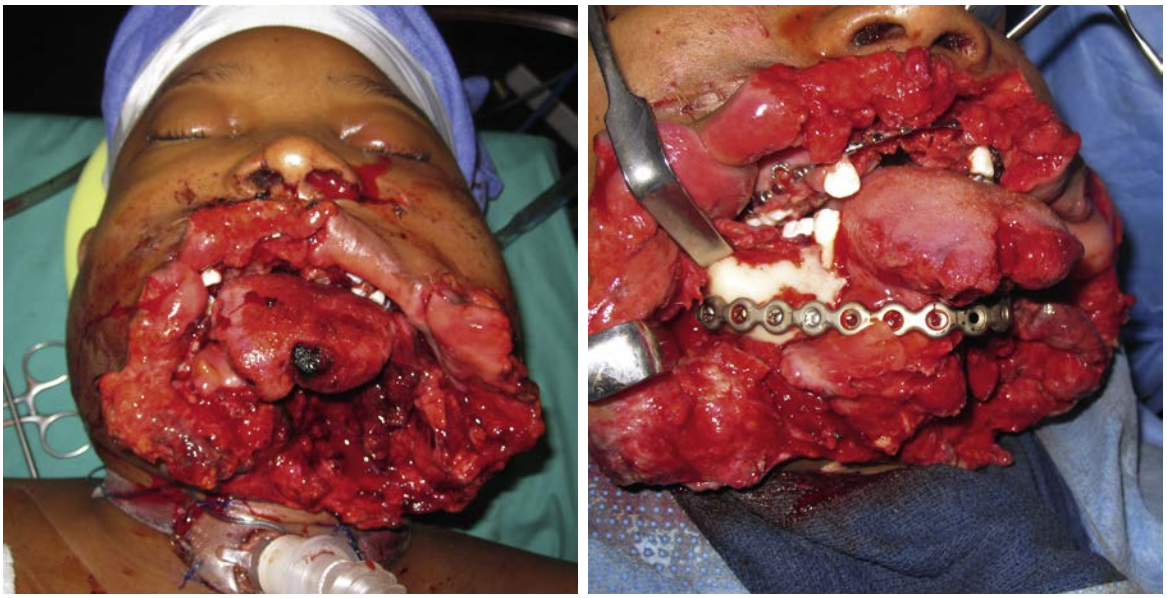
Surgical Management

Debridement

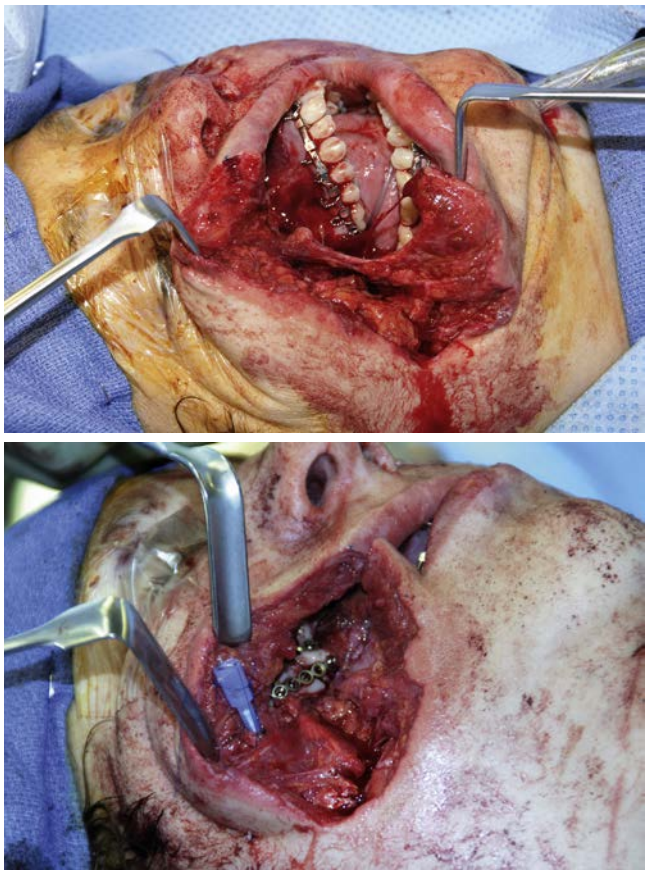
The conventional wisdom in management of gunshot wounds (GSWs) and other severe facial injuries with extensive tissue maceration is minimal surgical debridement. After the initial encounter and airway management and hemorrhage control, a very conservative surgical debridement is carried out. This initial debridement is performed on only obviously unsalvageable tissues, and care is taken to preserve as much viable soft tissue volume as possible. At the conclusion of the first debridement, establishment of occlusal relationships with arch bars may be done. The wound edges can be tacked to minimize desiccation of the exposed bone fragments where the tissue is not lost. The patient might need to be taken to the operating room for further limited debridement until the wound is declared adequately debrided. The additional goals during the phase of debridement includes creating a definitive airway as tracheostomy, closing of intracranial injuries, repair of ruptured globe injuries, and establishment and stabilization of occlusal relationships in remaining tooth-bearing segments. Aggressive debridement, particularly of skin margins and the tissues of the nose, palate, lips, and medial canthal areas, can complicate the choice of flap reconstruction or how a particular flap is inset. During the initial therapy, it is important to assess the extent of missing tissue, both hard and soft, and the surgical options available to reconstruct the defect. This includes the planning and need for potential local, regional, and/or distant flaps. This awareness will prevent the unwanted sacrifice of blood vessels that supply potential flaps or possible recipient vessels for later microvascular anastomosis. The end point for the debridement is the establishment of a healthy tissue bed for the eventual final reconstruction (Figure 14-5).

Reconstructive Concept

Historically, severe facial trauma often resulted in cosmetic and functional defects; however, advances in the science of reconstructive surgery and in the management of trauma patients have improved the morbidity associated with facial traumatic injuries. Current management reflects the evolution of both bony and soft tissue reconstruction principles and techniques. The functional units that are in the anterior



• **Figure 14-2** High energy transfer injury due to gun shot. (Missing tissues include lower lip, partial upper lip, cheek, anterior floor of the mouth and mandible wound demonstrating the missing tissues.)



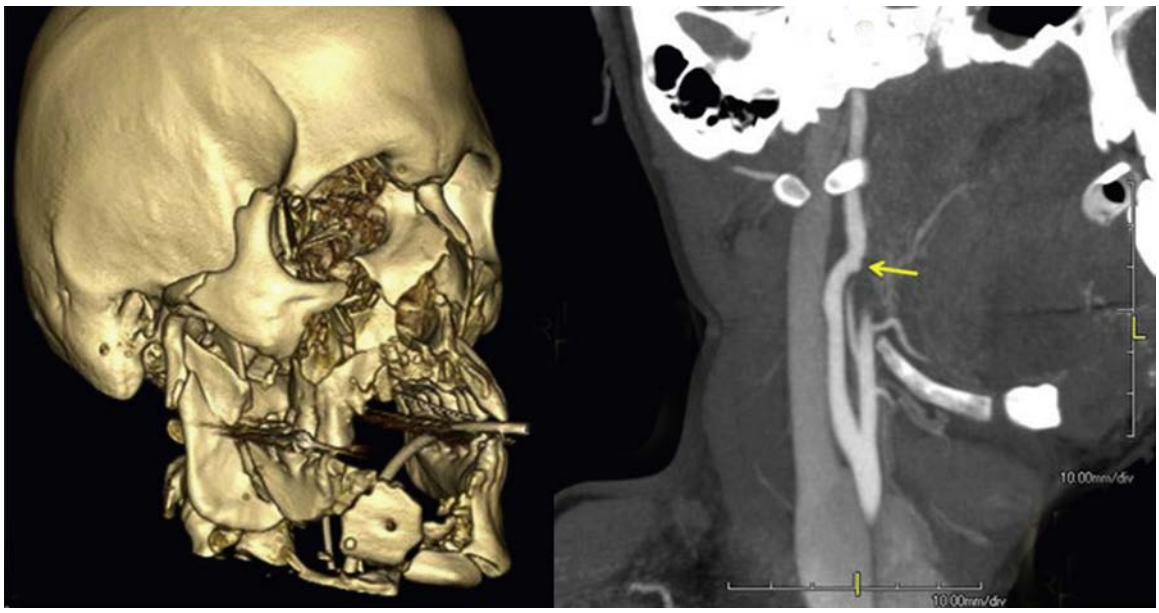
• **Figure 14-3** Injury due to a metallic projectile demonstrating Stensen duct injury and repair with cannulation, with skeletal repair.

face are the eyes, nose, and oral cavity. It is important preoperatively to evaluate the type of defect present and the anatomic location: a complete understanding of the function and esthetic relationship between normal face units. Often large avulsive wounds have adjacent facial bone fractures. The management of these wounds may best be approached in staged goals. The goals include restoration of the facial skeleton framework, definitive soft tissue reconstruction prosthetic rehabilitation in conjunction with flap selection, especially for the reconstruction of maxillary and mandibular defects.

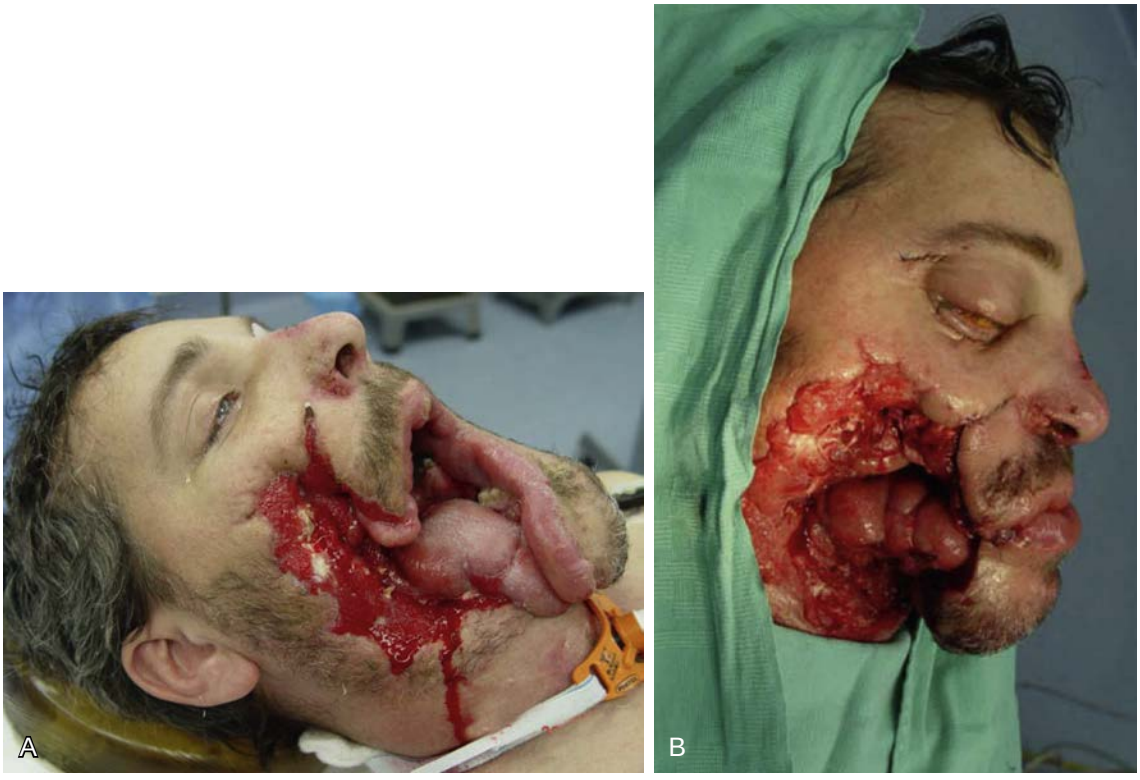
A staged approach to the reconstruction of the severe facial trauma patient allows a systematic and ordered approach to avoid overlooking important steps in the treatment. The surgical management of these patients can be broken into reconstructive and rehabilitative phases (Box 14-1).

The current reconstructive phase should be performed as soon as reasonably possible after the injury to maintain soft tissue volume and minimize scar contracture. The principles of free bone grafts for midface when adequate nasal or oral lining tissue is present, and (5) selection of a free tissue transfer flap that minimizes the need for adjunctive reconstructive procedures. The best available soft tissue closure that does not cause significant distortion of the soft tissues is employed. It must be kept in mind that the surgeon will be returning soon during the definitive reconstruction; therefore, any rotation or advancement flaps performed to obtain skin closure should be done with an eye toward that procedure. The size of the oral stoma should not be compromised to facilitate closure. Access to the oral cavity for the placement of dental implants and prosthetic work must be maintained.

The bone of the periorbital area, forehead, and nasal dorsum bear minimal tension and are easier to contour



• **Figure 14-4** Computed tomographic angiography demonstrating the location of vascular patency and location of vascular injury.



• **Figure 14-5** **A,** End point of debridement. **B,** Surgical debridement by 2 weeks show some early wound contracture.

with free bone grafts. Free bone grafts, especially cranial bone grafts, demonstrate excellent survival despite exposure to the sinonasal tract. If a small area of cranial bone graft is exposed within the sinonasal compartment, it usually gets covered with granulation tissue and mucosa with rigorous hygiene. The relatively thick cortical bone from this site facilitates rigid fixation, which is crucial to graft survival.

The reconstructive goals in the maxillary arch are to create a neo-alveolar ridge of stable bone that is suitable for prosthesis and close the palatal defect. This reconstruction should also provide replacement or support of facial soft

• BOX 14-1 Management of Avulsive Wounds

Both phases can be staged based on surgeon preferences, patient status, need for medical models, surgical guides, etc.

Reconstructive Phase

1. Debridement of foreign material and obviously nonviable tissue
2. Establishment of occlusal relationships
3 Extended access and exposure of fractures

5. Definitive free-bone graft reconstruction in areas with adequate soft tissue coverage
6. Reassess the missing tissue element. Selection of appropriate local and regional tissue flaps
7. Reconstruction of missing tissue elements with vascularized free-tissue transfer flap that includes underlying bone concurrently with the overlying soft tissue
8. Satisfactory soft tissue coverage of all underlying bone,

nasal and NOE regions

Rehabilitative Phase

1. Dental and facial prosthetic rehabilitation
2. Major flap debulking and contouring as required
3. Aesthetic and functional refinement
4. Adjunctive cosmetic measures

NOE, Nasoorbitoethmoid.

tissues. The reconstructed maxillary arch is frequently flatter than the native maxillary alveolar arch; hence the denture will not be stable and will require dentition or osseointegrated implants for retention.

The use of vascularized bone to replace large segmental areas of the mandible is currently preferred and is often essential if the injury has destroyed or avulsed significant floor-of-mouth and chin soft tissue. Vascularized bone provides a rapid, dependable reconstruction, may be inset with its own vascularized soft tissue coverage, and survives the contaminated environment of the floor of the mouth. The exceptions to vascularized bone reconstruction of the mandible are cases in which there is an adequate remaining soft tissue overlying the mandible. Patients with only isolated oromandibular wounds can return to good function and adequate cosmesis. In patients with large central soft tissue defects involving maxilla, mandible, and nose, the reconstructive outcomes are far from satisfactory.

The selection of free tissue transfer is only limited by the patient's overall injuries, surgical limitations, and the imagination of the surgeon. The following options are some of the flaps most commonly used by the author and do not represent all the options available for head and neck reconstruction (Figure 14-6).

Local/Regional

Local flap options are often limited in cases of large soft tissue loss. One of the areas where this may not be the case is in the reconstruction of lip defects. Often, one of the lips is involved and the other is spared. This sparing allows for the use of the uninvolved lip as a donor site for the reconstruction of the affected lip. The other site is the forehead. The paramedian forehead flap may be used in the reconstruction of nasal defects, which can range from small defects to as large as total nasal coverage. Mucosal injuries are often allowed to heal by secondary intention. However, in cases in which significant bulk is missing, a good option is the use of the facial artery musculomucosal flap.

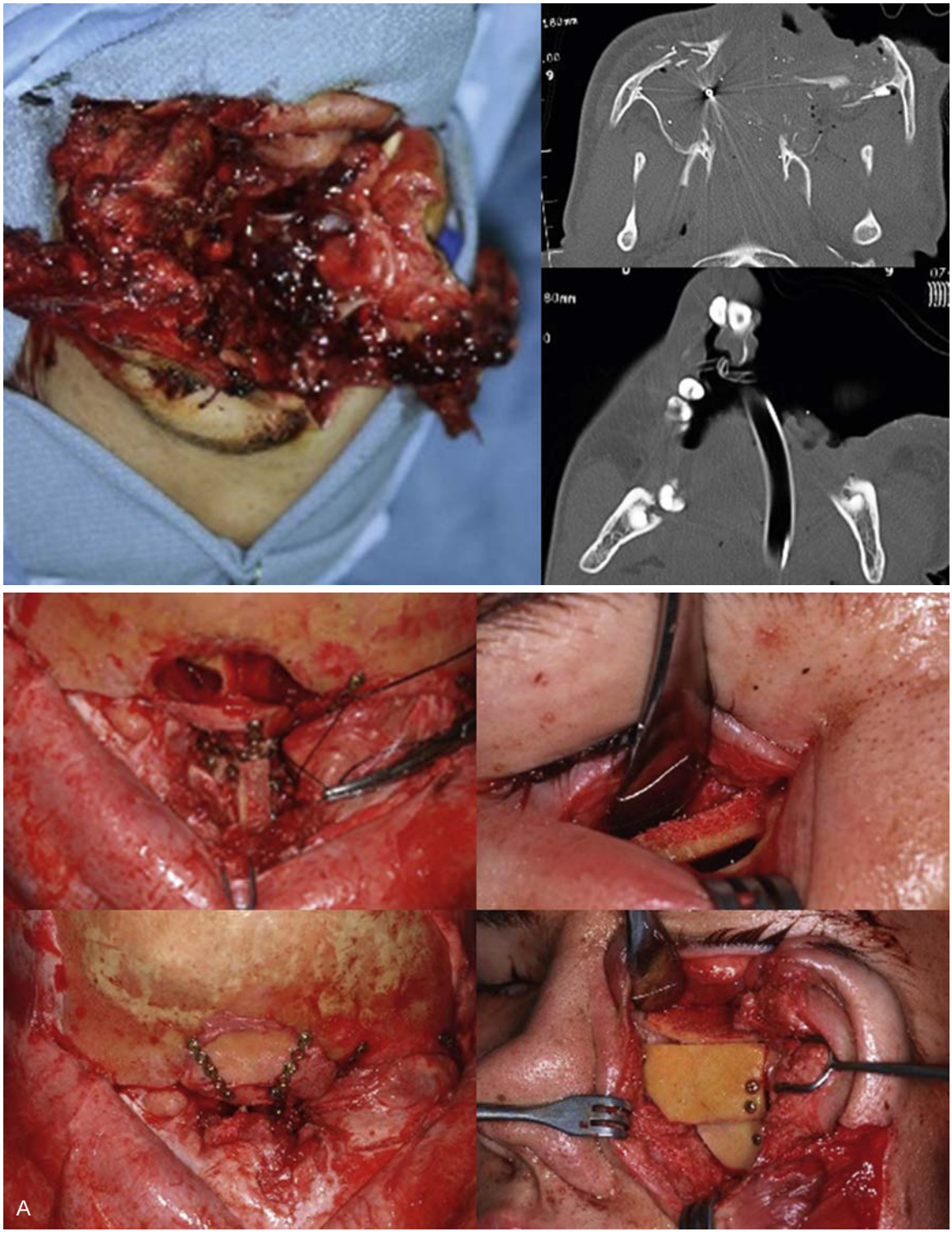
Abbe Flap

The Abbe flap has been in the armamentarium of maxillofacial surgeons for more than a century. It was first described by Abbe in 1898.[3] The flap is based on the superior and inferior labial arteries, which are branches of the facial artery. The utility of this flap cannot be overemphasized given its ability to replace like tissue with like tissue.[4] To improve the final aesthetic outcome, the defect may need to be extended to include the entire aesthetic subunit of the lip as described by Burget. When the defect is greater than half of a subunit, the full subunit should be excised. Extension of the wound is at times difficult to accomplish by the beginning surgeon because of fear of wasting tissues. This excision will allow for a better reconstruction by placing the incisions in a less conspicuous site. Once the defect is outlined, the width of the flap is decreased by approximately half, while maintaining a 1:1 ratio of the height of the flap. The ideal rotation of the flap is checked, and then the incision is begun on the contralateral side, away from the feeding labial artery. The incision is carried out to the full thickness up to about 1 cm of the remaining attachment of the artery and flap. At this point, careful dissection is undertaken to free as much of the muscle as possible to allow for proper arc of rotation, while still protecting the vascular pedicle. The skin is incised up to the vermilion without endangering the vascular pedicle, since it runs on the inner aspect of the lip.[5]

With the flap fully mobilized, the surgeon then begins the insetting by closing the mucosa, followed by muscular closure, and last skin closure. If this order of closure is not followed, the surgeon will be prevented or severely hindered from closing the mucosa once the muscular and skin closure is completed. The flap is allowed to develop collateral circulation for approximately 3 weeks or more before its release (Figure 14-7).

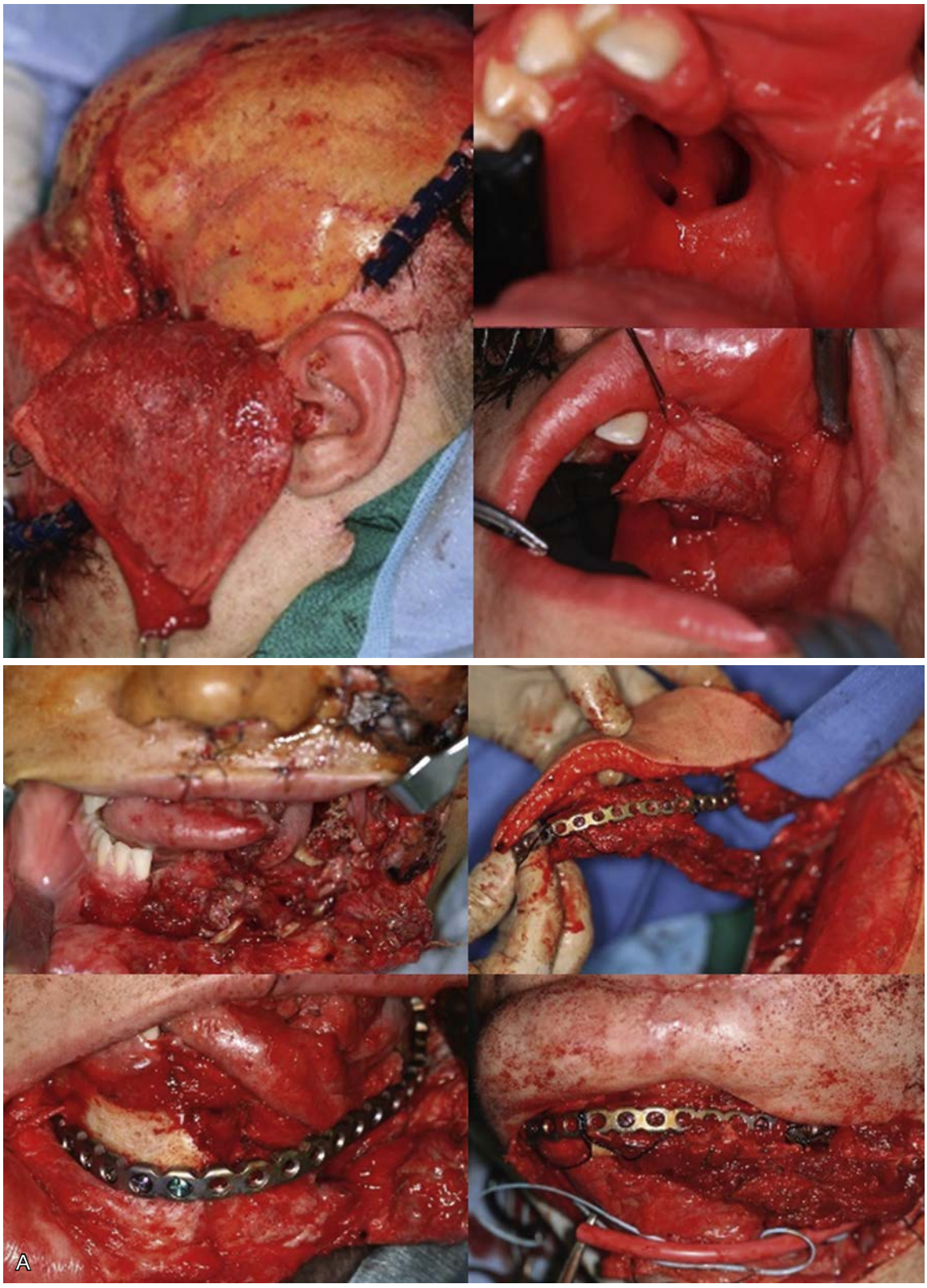
Facial Artery Musculomucosal Flap

The facial artery musculomucosal (FAMM) flap was first described by Pribaz and colleagues in 1992.[6] The flap is based on the facial artery and is an intraoral mucosal flap that can be used for a multitude of defects. The flap can be superiorly or inferiorly based and can rotate to reconstruct lip, cheek, floor of mouth, or palatal defects. The harvesting of the flap is first approached by using a portable Doppler probe intraorally to outline the path of the facial artery. Once the path is marked from the depth of the mandibular buccal vestibule to the maxillary vestibule, the width of the flap is marked. The intended defect size is limited to only 3 cm at its largest to



• **Figure 14-6** **A,** Surgical steps from bone graft—cranial bone grafts to nasal dorsum and midface, palate closure with temporalis flap, mandible reconstruction with osseocutaneous vascularized flap.

Continued



• **Figure 14-6, cont'd.**



• **Figure 14-6,** **B,** Rehabilitative phase demonstrating dental implants, prosthesis, debulking of the transferred tissue, and removal of the distant skin flap with adjacent tissue advancement after skin expansion.

Continued



• **Figure 14-6, cont'd.**

minimize scarring and postoperative trismus. The harvesting is done in a straightforward path by incising the marked flap past the buccinator muscle. The vessel is identified, ligated, and divided. Dissection is continued in the direction of the pedicle. Once the harvesting is completed, the donor site is closed in layers, and the flap is mobilized to the site to be reconstructed and is then inset (Figure 14-8).

Paramedian Forehead Flap

The paramedian forehead flap is one of the mainstay flaps for nasal reconstruction. This flap is most often used in the reconstruction of oncologic defects, but it can also be used for traumatic defects. The blood supply to the paramedian forehead flap is the supratrochlear artery. The design for this flap is most often based on a predetermined template. The author prefers to use the aluminum packaging of sutures as the material to outline the template for the defect. The template is transferred to the forehead region and the flap outline is marked. The elevation of the flap is in a subcutaneous plane until about 2 cm above the brow region. At this region the dissection is deepened to the periosteal plane and the flap dissection is completed. Rotation of the flap is checked to eliminate compression and kinking of the vascular pedicle (see Figure 14-3). The flap is then inset and, similar to other pedicled flaps, is allowed to develop collateral blood supply for about 3 weeks. It is then detached and the inset completed (Figure 14-9).

Cervicofacial Flap

The cervicofacial flap is a random flap that can be used to cover cheek defects and/or to bring like tissues to replace the skin component of previously transferred free flaps. The flap is marked from the area of the defect extending posterior and superior to the lateral canthal region. The incision is made to a level above the plane of the canthus and extended to the preauricular region, as with a rhytidectomy incision. The continuation of the incision in the neck is dependent on the extent of the defect to be closed. The incision can be extended to the chest region. The flap is then elevated in a subcutaneous plane and rotated to close the defect (Figure 14-10).

Temporoparietal Fascia Flap

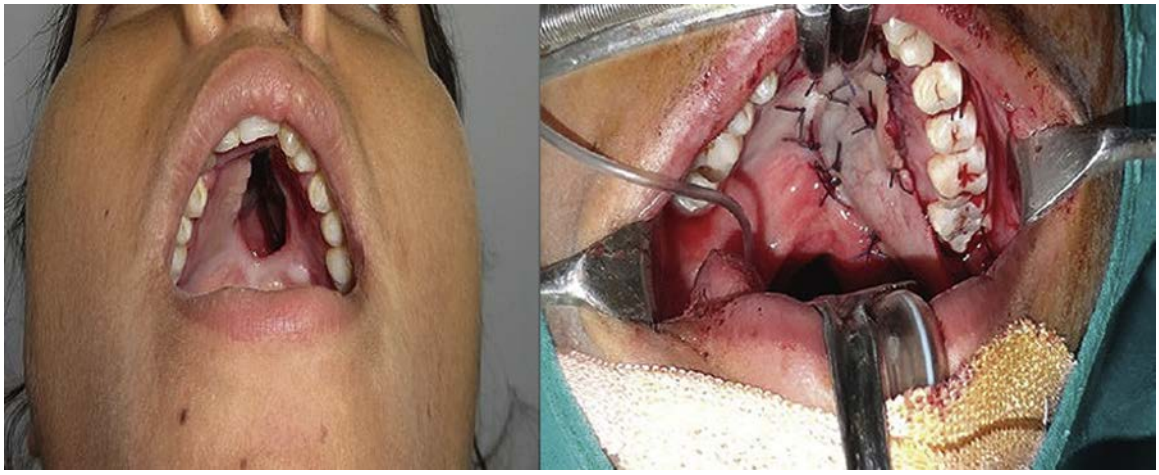
The temporoparietal fascia flap is a thin, pliable flap that may be used for the reconstruction of several facial defects. This flap may also be harvested as an osteofascial flap.[7] Its utility is based on its ease of harvest and reach. It may be used to reconstruct defects of the midface, maxilla, buccal mucosa, floor of mouth, and mandible. Harvesting of the flap is first carried out by using Doppler to determine the path of the superficial temporal vessels. Once this is marked, a small strip of hair is shaved along the temporal region in the manner of a bi-temporal flap design. A thin flap is then elevated just below the level of the hair follicles. Care is taken to not injure the vasculature of the flap, which is found directly under the raised scalp flap. Once the desired length and width of the flap are exposed, the temporoparietal fascia is elevated off of the temporalis fascia and transferred to the desired location. When this flap is used for intraoral reconstruction, a skin graft is rarely needed because the flap will mucosalize (Figure 14-11). However, when used to provide coverage for facial defects, a skin graft may be used to improve the final cosmetic appearance.

Submental Island Flap

A recent addition to the armamentarium of the head and neck reconstructive surgeon is the submental artery flap. The first description of this flap was by Martin and colleagues in 1993.[10] The flap had little recognition and use in head and neck reconstructive surgery until Vural and Suen[11] described its usefulness for the reconstruction of various defects within the head and neck. The advantages of the submental island flap are its pliability and its excellent color match for facial reconstruction. As the name implies, the submental island flap is an axial flap based on the submental artery and its vena comitans. The design of the flap is somewhat limited by the amount of submental skin that can be harvested while still allowing primary closure of the defect. The width of the flap is determined by doing a pinch test and marking the area. The skin paddle is drawn and a subplatysmal flap is elevated around it. The skin is sutured to the underlying fascia to prevent shearing.



• **Figure 14-7** Abbe flap reconstruction for upper lip avulsion.



• **Figure 14-8** Facial artery musculomucosal (FAMM) flap for reconstruction of palatal defect.

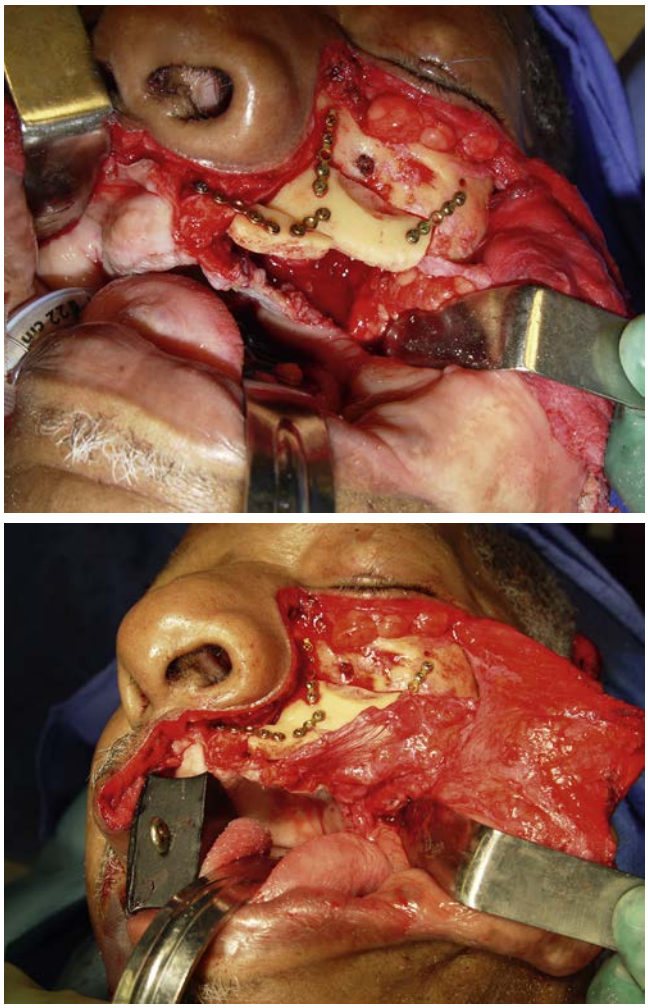


• **Figure 14-9** Reconstruction of inadequately reconstructed and scarred nose due to previous motor vehicle collision. The reconstruction is demonstrated by paramedian forehead flap for nasal dorsum and the ala, previous scarred tissue used for columella and inner lining, and cartilage framework reconstructed with rib cartilage.



• **Figure 14-10** Cervicofacial rotational flap for avulsive skin defect.

Elevation of the flap is begun at the contralateral aspect of the pedicle. The anterior belly of the digastric is identified, and the elevation is carried superficial to its fascia. Once the perforating branches of the contralateral submental artery are encountered, they are ligated and divided. The ipsilateral anterior digastric is disinserted from the anterior mandible, and a portion of the muscle is raised with the flap. Dissection is then continued along the submental artery toward its detachment from the facial artery. All of the minor branches are ligated and divided. The elevation is completed after the



• **Figure 14-11** Temporoparietal fascia flap for correction of sinus lining, cheek, and palate region.

desired length of the vascular pedicle is dissected, allowing for a tension-free arc of rotation of the flap to cover the defect. This flap can be used to cover cheek defects and all intraoral defects, including defects in the maxilla.[12] The submental island flap may also be harvested as a reverse flow flap, in which case the perfusion will be dependent on the angular artery.[13] When used as a reverse flow flap, this flap may reach as high as the orbit, and thus can be used to cover orbital and periorbital defects.[14]

Microvascular Free Flaps

The use of free tissue transfer allows for the reconstruction of large avulsive tissue defects with one operation. Free tissue transfer has made it possible to transfer well-vascularized bone and soft tissue flaps into a hostile environment with excellent survival of the flap tissues or free bone grafts invested by the vascularized flap.[15] Many free flap options exist for the reconstruction of these defects. The choice of which flap to use should depend on the needs of the defect and the ability to contour and adapt the chosen flap to the defect site. Some of the disadvantages of these flaps are the second donor site, color mismatch, and long operative time. The following are some examples of commonly used free tissue flaps.

Radial Forearm Flap

The radial forearm flap was first described by Song and colleagues in 1982.[16] This flap revolutionized the field of microvascular surgery and in particular the use of this technique for head and neck reconstruction. The radial forearm free flap (RFFF) is now routinely used in most major medical centers for the reconstruction of head and neck soft tissue defects. The use of this flap has also been described as an osteocutaneous flap[17] for limited bony reconstruction of the head and neck, particularly of the midface. However, because of the possibility of a radius fracture, using this flap as an osteocutaneous flap is rarely considered. The RFFF is based on the radial artery, and its venous drainage is provided by the paired vena comitans or the cephalic vein (Figure 14-12). Preoperative assessment for the use of the RFFF is based on Allen's test, which is the assessment of the collateral circulation between the radial artery and the ulnar artery on the palmar arches.

The flap is elevated while taking care to maintain the paratenon covering the tendons to ensure adequate acceptance of the skin graft that is used to cover the donor site.

Fibula Free Flap

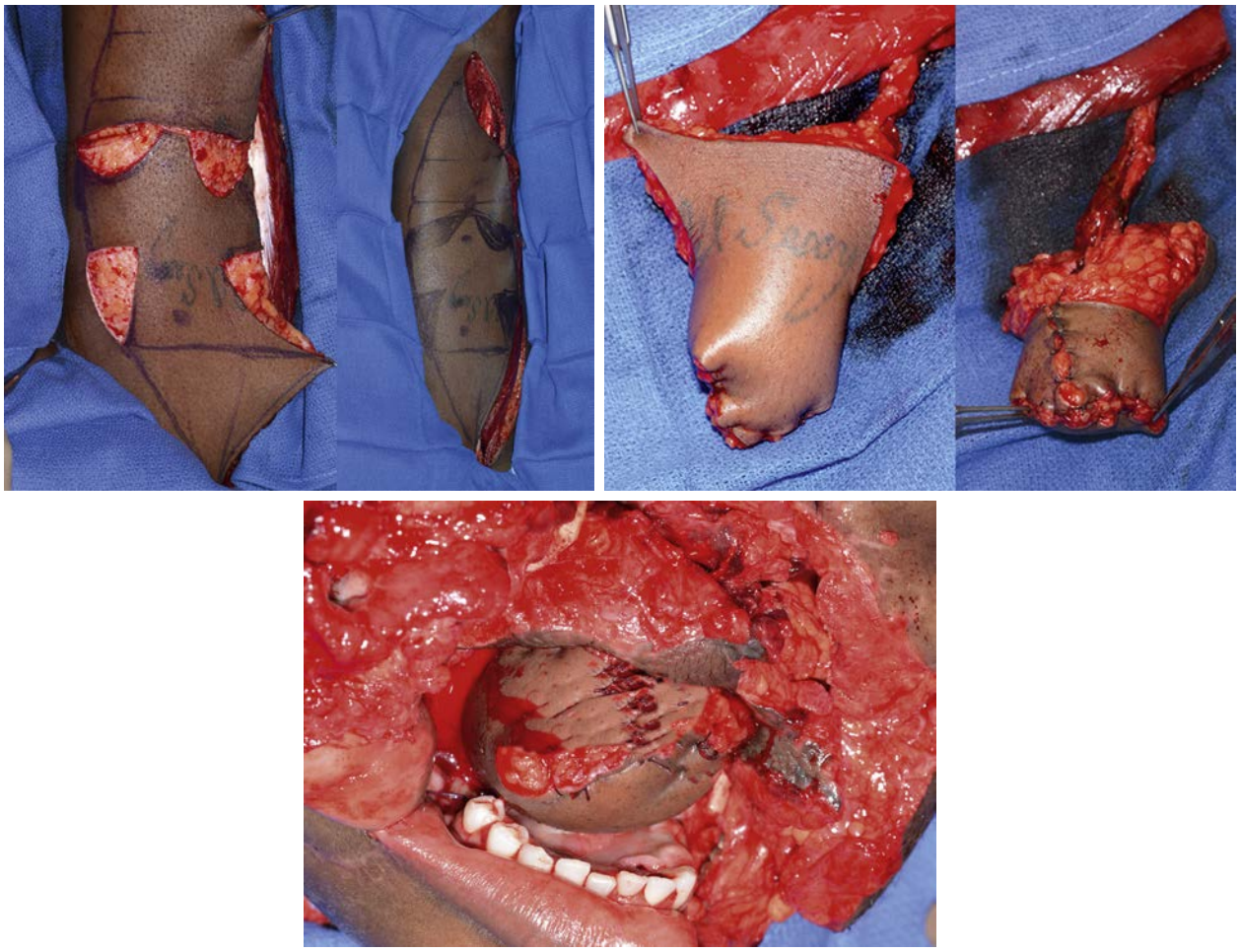
Since its description by Hidalgo[18] in 1989, the fibula free flap has truly become the "workhorse" flap for bony reconstruction in the head and neck, and in particular mandibular reconstruction. The fibula is a non-weight-bearing bone supplied by the peroneal artery. The peroneal artery sends perforators to the overlying skin. The length of the fibula is ideally suited for nearly all mandibular reconstruction, ranging from small to near-total reconstruction based on a single flap. The width and height of the flap are also well suited for mandibular and maxillary reconstruction because the flap will accept dental implants in a very predictable fashion, allowing not only for aesthetic reconstruction but also for functional reconstruction.

Anterolateral Thigh Free Flap

The use of the anterolateral thigh (ALT) flap in head and neck reconstruction continues to gain popularity in this country and has already become the preferred flap for small and large soft tissue defects in Asia. The ALT flap is one of the most commonly used perforator flaps for head and neck reconstruction. Wei and colleagues defined perforator flaps as those in which the source artery is deep and the branch that carries blood directly to fasciocutaneous tissue in its course to reach the skin passes through the overhanging muscular tissue without exclusively following the intermuscular septum.[19] The flap is based on the perforator branches from the descending branches of the lateral circumflex femoral artery and its vena comitans (Figure 14-13). In general, two to three perforators can be found to raise the flap. However, a single perforator can sustain an area of tissue as large as 22 cm^2.



• **Figure 14-12** Radial forearm flap for total upper lip and anterior premaxilla reconstruction.



• **Figure 14-13** Anterolateral thigh flap for tongue reconstruction for self-inflicted gunshot wound.

• BOX 14-2 Reconstructive Flap Options for Site-Specific Defects

Lip
- Abbe flap (cross lip)
- Facial artery musculomucosal (FAMM)
- Radial forearm free flap (RFFF) with palmaris longus tendon
- Anterolateral thigh (ALT)

Nasal Tip
- Nasal flap
- Paramedian forehead
- Bilobed

Total Nasal Defects
- Paramedian forehead
- Prefabricated flap (RFFF)

Eyebrow
- Subcutaneous island pedicle flap
- Free scalp graft
- Pedicle superficial temporal artery scalp flap

Ear
- Reanastomosis of avulsed ear if adequate vessels remain
- Temporoparietal fascia flap coverage of rib

Cheek (Through-and-Through)
- Double island pectoralis major myocutaneous flap
- RFFF
- ALT
- Combination of free tissue and local
- Combination of one flap and skin graft of the exposed surface

Cheek
- Cervicofacial
- Submental island flap
- RFFF
- ALT

Scalp
- Rotation flaps
- Orticochea (banana peel) flap
- ALT
- RFFF
- Latissimus free flap

Maxillary Bone
- Bone graft with mesh retention
- RFFF osseocutaneous
- Fibula
- Deep circumflex iliac artery (DCIA)
- Scapula

Mandible
- Bone graft (anterior vs. posterior iliac crest)
- Fibula
- DCIA
- RFFF (osteocutaneous)

Deep Circumflex Iliac Artery Flap

The deep circumflex iliac artery (DCIA) flap is another popular option for free tissue transfer to restore the soft tissue and bony contours of the mandible. The DCIA is an ideal flap to restore the width and vertical dimension of the man-

serve as soft tissue coverage for the graft intraorally. A skin paddle can also be taken with this flap. Disadvantages of this are the relatively short 4- to 5-cm vascular pedicle available, higher potential donor site morbidity, and sometimes bulk.[20] A vein graft may be taken if a longer pedicle is required.

Site-Specific Reconstruction

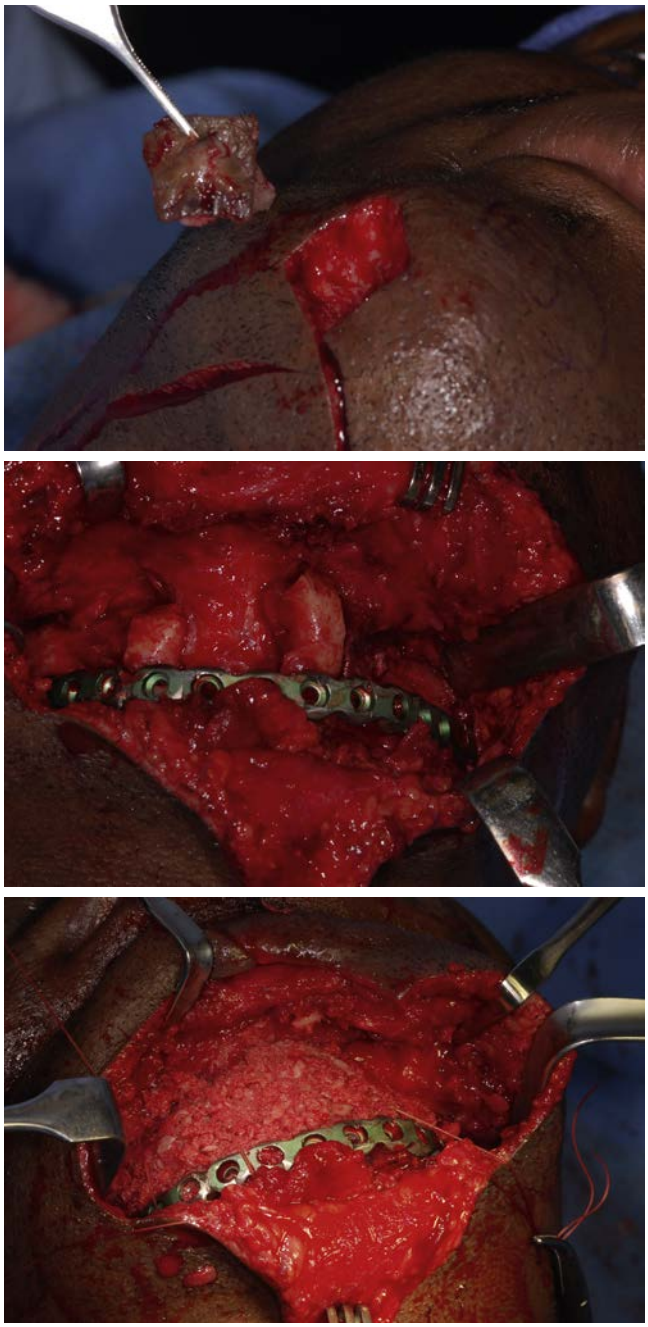
Because of the constraints of this chapter, a detailed description of a site-specific reconstructive algorithm is not possible. Refer to Box 14-2 for an overview of the author's preferred flap options for defects involving a variety of facial areas. The following is a description of reconstructive options for commonly injured sites.

Lower Face/Mandible

The reconstruction of mandibular defects can be a challenging problem because of the need to meet not only functional but also aesthetic requirements. The assessment of the type of reconstruction needed depends on the assessment of the integrity not only of the soft tissues in the neck but also, more critically, of intraoral soft tissues. The surgeon must determine the need for hard and soft tissue required to reconstruct the defect. Bone-only reconstruction is undertaken when there is adequate intraoral soft tissue and skin coverage in the neck. In this circumstance, the reconstructive option is dependent on the amount of missing bone. In most instances, if the size defect is less than 8 cm in length with good soft tissue bed and coverage, a nonvascularized graft may be used secondarily (Figure 14-14). The site of harvest for the graft is dependent on the surgeon's preference. The most commonly used site for such a defect size is the anterior iliac crest, given that the average amount of bone that can be harvested from this site is about 50 mL. If the defect is greater than 5 cm, the author prefers to use the fibula as an osseous-only flap. The fibula can be inset either with 2.0 mandibular plates or with a 2.4 mandibular reconstruction bar.

In situations in which the defect includes not only the bone but also the soft tissue, an osseocutaneous or osseomusculocutaneous fibula flap may be harvested to reconstruct the defect (Figure 14-15).

Other options to reconstruct these defects would include the use of scapular flap or the deep circumflex iliac artery (DCIA) flap. When only soft tissue is desired,



• **Figure 14-14** Reconstruction of mandible defect with iliac crest bone graft.

with the idea of performing delayed bony reconstruction, the surgeon may use the submental artery flap, the ALT flap, the RFFF, or any other soft tissue flap available that would cover the defect without prohibiting later reconstruction or unnecessarily causing problems to the patient.

Midface Defects

Avulsive defects of the midface may pose significant challenges to the surgeon and may cause significant psychological problems for the patient.

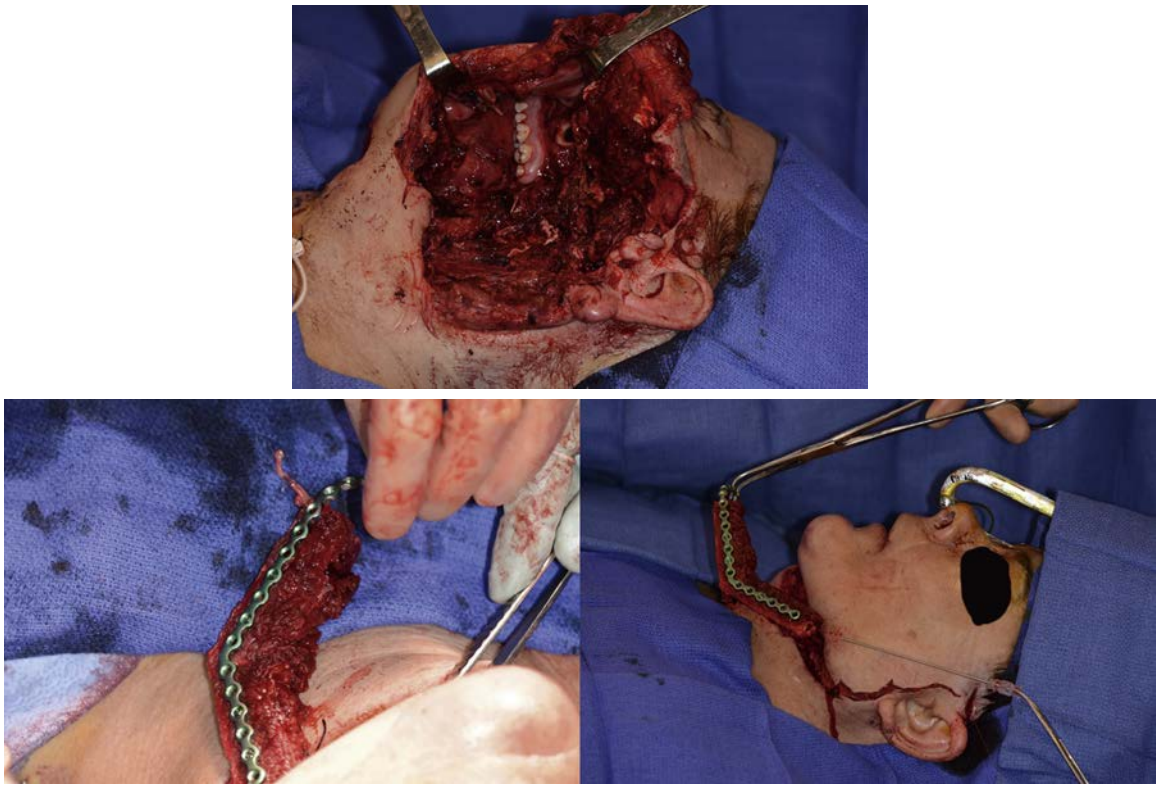
Nasal Defects

As a result of the central location of the nose within the facial structure, defects of this anatomic unit are very difficult to reconstruct and camouflage well. Nasal defects range from small soft tissue defects, which can be reconstructed with a skin graft, to total rhinectomy defects, which would necessitate extensive reconstruction with local flaps as well as cornerstone of nasal reconstruction depends on reestablishing the nasal lining and adequate nasal support (both bony and cartilaginous) and providing nasal skin coverage. The skin coverage of the nose should be based on the subunit principle as described by Burget and Menick.[22] Adjacent tissues are commonly used for the reconstruction of nasal lining. Examples of adjacent flaps used for the nasal lining are the nasolabial flaps in a turned-in fashion or a turned-in paranasal flap. In cases in which the septum is intact, the contralateral septal mucosa may be elevated and brought in through a small slit in the dorsal aspect of the cartilage, passed to the other side, and used as a lining. The cranial bone is often used as the ideal donor site for a bone graft to provide bridge support to the nasal dorsum. One of the advantages of this donor site is its accessibility when combined with a paramedian forehead flap. Reconstruction of defects of the skin is dependent on the size of the defect and the integrity of adjacent tissues. Various options are available for small ablative defects, ranging from the use of bilobed flaps, V-Y dorsonasal flaps, or skin island flaps to nasolabial flaps. Larger defects, including up to total loss of nasal skin, may be covered with the use of the paramedian forehead flap. If this is not available, then free tissue transfer may also be an option.[23,24] Free tissue transfer may range from a radial forearm flap to a prefabricated forearm or anterolateral thigh flap. In these cases, the entire nasal structure is fabricated at the donor site, and after completion of the staged prefabrication, the flap is harvested and transferred to the defect site.[25]

The complete reconstruction of extensive nasal defects is a staged process that may require up to four surgeries, with the last procedures being the thinning of the flap and final cosmetic touch-ups. The last surgeries often can be carried out using local anesthesia or light sedation.

Lip Defects

Like nasal injuries, lip defects can range from small to total. The approach used by the author when dealing with lip defects is dependent on the site (i.e., upper lip or lower lip). Defects of the upper lip that are less than 25% of the total upper lip length may be closed primarily without the need for reconstruction. Defects of the lower lip that are less than one-third total lip length may also be closed primarily without significant distortion of the lip and resultant microstomia. The flap for lip reconstruction most commonly used by the author is the Abbe flap. This flap may be used to reconstruct



• **Figure 14-15** Fibula osseomusculocutaneous flap for mandible reconstruction.

either the lower or the upper lip. When defects of the lip are primarily centered on the mucosa or the vermilion, the FAMM flap may be used to reestablish thickness while providing the desired mucosal coverage.[26] A host of other local flaps have been described for reconstructing lip defects, but their description is beyond the scope of this chapter.

In cases of near-total or total lip loss, the option preferred by the author is microvascular tissue transfer. The most commonly employed free flap for total lip reconstruction is the radial forearm free flap with the palmaris longus tendon.[27,28] The ALT flap may also be used to reconstruct total lip and chin defects.[29] In cases in which total lip reconstruction is needed, the surgeon must anticipate sagging and thus use fascia or tendon to resuspend the lip and establish the commissure. Like the reconstruction of total nasal defects, the reconstruction of total lip defects is a multistage reconstruction, requiring replacement of the missing tissue followed by replacement of the lip vermilion and re-creation of the philtral ridges.

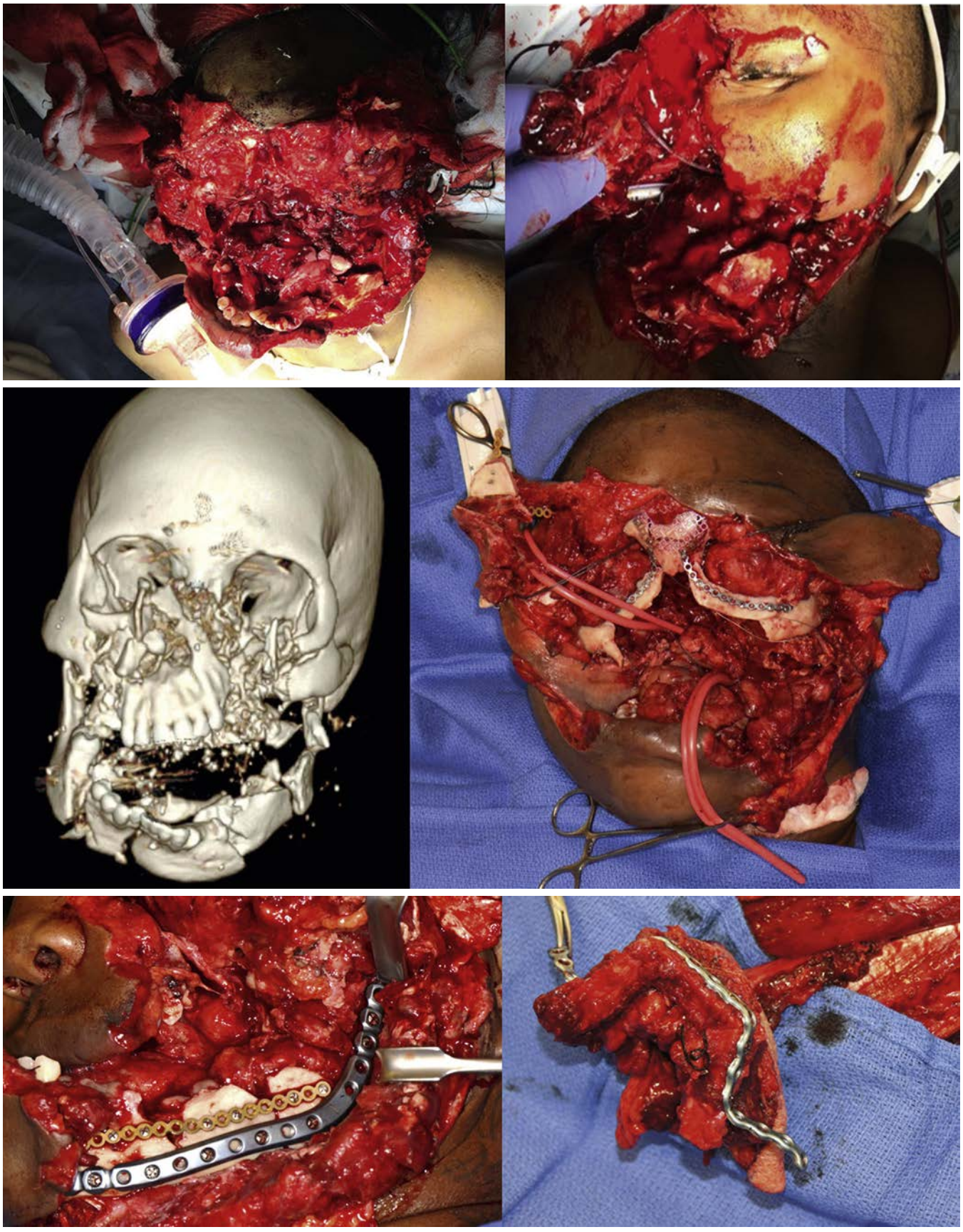
Cheek Defects

Injuries of the midface region have the potential to damage not only the soft tissue and the underlying bone but also the facial nerve and the parotid duct. When dealing with avulsive defects in the cheek, potential injuries to these structures must be assessed and, whenever possible, should be addressed. In the majority of cases, the defect is centered around missing skin and subcutaneous tissues. Significant loss of soft tissue of the cheek needs to be assessed for the amount of thickness needed. When the thickness is superficial but greater than what would be satisfactorily reconstructed with a skin graft, the cervicofacial flap may be employed. In cases in which the defect is through-and-through, several options would be available. A regional flap such as the pectoralis major flap may be used either as a double paddle or as a single paddle with skin grafting of the exposed muscle. The main drawback of these defects is that they are static reconstructions and the patient will have the sequela of loss of the facial nerve.

Large bony reconstruction of the midface may be provided by the use of the scapula free flap or the fibula flap. The fibula free flap is optimal for reconstruction for large bone and soft tissue defects of the midface region. The fibula flap is contoured to re-create the missing structure while the soft tissue component is used to bulk the missing soft tissue (Figure 14-16).

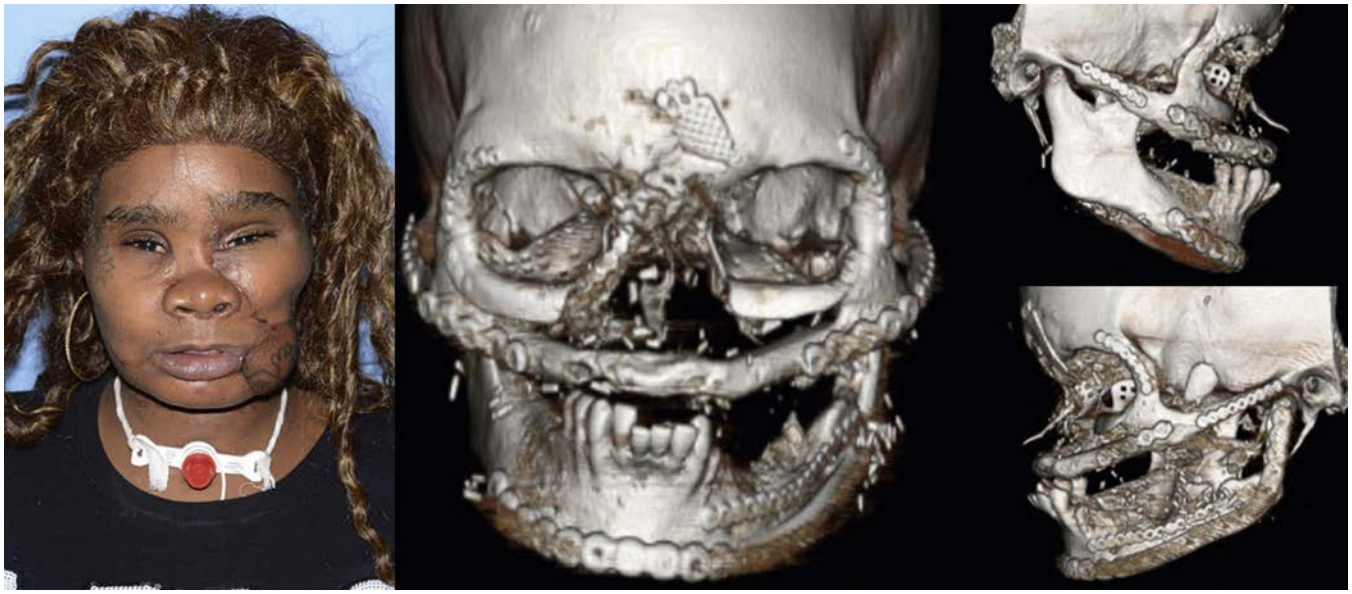
Scalp Defects

Scalp defects are often encountered in association with severe motor vehicular accidents, especially when the patient is ejected from the vehicle. These defects are often highly contaminated with road debris, and the extent of missing tissue is often difficult to assess in the trauma bay. These patients need to be brought to the operating room to have thorough irrigation of the site and assessment of the amount of missing tissue. The surgical options available



• **Figure 14-16** Reconstruction of nasal dorsum and orbits with cranial bone grafts, and the maxilla with osseomusculocutaneous flap.

Continued



• **Figure 14-16, cont'd.**

range from a simple skin graft if the pericranium is intact to more complex options. Small defects can be closed with advancement of a pinwheel releasing flap. Moderate-sized defects may require a greater degree of rotation from the flaps (Figure 14-17). Once the flaps are elevated, the advancement is aided by scoring the pericranium. Large defects may be reconstructed with either the Orticochea three-flap technique or free tissue transfer. The free tissues commonly used in scalp reconstruction for large to total scalp defects are the ALT flap[30] and the latissimus dorsi flap.[31]

Aesthetic and Prosthetic Rehabilitation

Once the main surgical procedures have been completed, the final steps in reconstructing avulsive defects are debulking and serial excision surgeries. The goal of these procedures is to complete the reconstruction and allow the patient to return to daily activities. These procedures typically include prosthodontic reconstruction and facial aesthetic procedures (Figure 14-18). A team approach to the care of these patients cannot be overemphasized. The reconstruction of bony defects with free tissue transfer or with nonvascularized bone allows for the eventual placement of dental or other facial implants, while soft tissue reconstruction provides the platform for soft tissue prostheses such as eyes, ears, and noses (see Figure 14-16). The maxillofacial prosthodontist is charged with the task of making the prosthesis that bridges the limitations of surgical reconstruction.

Last, aesthetic surgical techniques, ranging from dermabrasion to scar revision, help to camouflage the scars and the transition between native tissues and transferred tissues. A thoughtful and systematic approach to the care of patients with large avulsive facial injuries positions the surgeon and the patient on the best possible path to the optimal outcome.

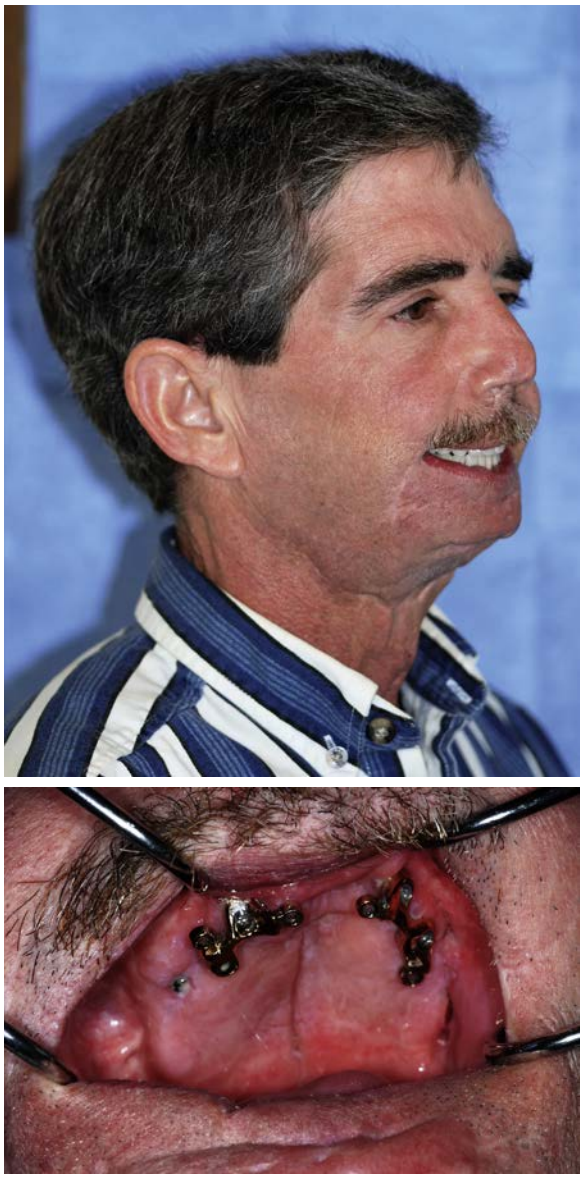
Complications

problems with vision, mastication, oral stoma competence, speech, and swallowing. Early institution of antibiotics, debridement of nonviable tissues and foreign matter from the wound, and stabilization of fractures will reduce the risk of serious infection. Gunshot wounds lead to progressive extensive soft tissue damage that can increase the risk of vessel thrombosis, particularly venous, if free tissue transfer reconstruction is performed too early. Return to the operating room after reconstruction for wound irrigation in suspect cases reduces the risk of free flap compromise and potential loss. All definitive bone grafts should be surrounded with vascularized tissue and rigidly fixated. Mucosal and flap closures in the floor of the mouth must be watertight. If infection does occur in the neck, prompt drainage and diversion away from the vascular pedicle should be undertaken. If the vascular pedicle is exposed to the infection, it should be covered with a regional myofascial flap. Nonvascularized bone reconstruction of the mandible

nasal projection and shape, traumatic telecanthus, apparent asymmetry of the position of the eyes, and unsatisfactory facial contour due to underlying bone or overlying soft tissue irregularity.



• **Figure 14-17** Closure of scalp defects with scalp rotation flaps.



• **Figure 14-18** Prosthetic rehabilitation of reconstructive defects require dental implants due to flat alveolar ridges with no lip, alveolar transition.

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15

Treatment of Maxillofacial Gunshot Wound Injuries

EDWARD J. MILLER JR., STEVEN H. CHO

Gunshot wounds (GSWs) to the maxillofacial region continue to be a major public health concern in the United States. A thorough understanding of the scope of the problem and its specific relation to the surgeon treating these patients is essential. In the United States, the number of deaths per year due to injury by firearms is approximately 10.4 per 100,000. Causes of death due to firearm mortality include accidental discharge of firearm, suicide, assault by firearm, and firearm discharge of undetermined intent. Deaths from injury by firearms exclude deaths due to explosives and other causes indirectly related to firearms.[1]

Firearm-related injuries have declined 69% over the past two decades in the United States. The majority of these GSW injuries are nonfatal but do require hospitalization.[2,3] According to Kalesan and colleagues, there were 478,400 fatal and nonfatal firearms incidents in the United States in 2011, and 97.4% of these incidents were nonfatal. Overall, 75% of those injured required medical attention, and 80% of those requiring medical attention were hospitalized.[3] On average, there are 32 gun-related fatalities every day in the United States, and 140 are treated for a gun assault in an emergency room.[4] Of those injured, approximately 6% of GSWs involve the face, and male patients make up more than 80% of the population of GSW victims.[5]

Classification of Bullets and Firearms

Caliber is a term used by ammunition and firearm manufacturers in the United States to indicate the diameter of a bullet in hundredths of an inch or millimeters. A bullet that is 22 hundredths of an inch (.22) in diameter is called a 22-caliber or 9-mm bullet.[6] In general, the wounding power or lethal power of a projectile is proportional to the caliber. Any caliber of handgun or rifle can produce a lethal injury.[7] A cartridge is a single unit of ammunition consisting of the cartridge case, primer, and propellant with or without one or more projectiles. The cartridge designation typically includes a numerical value to indicate the approximate diameter of the bullet and will often include the manufacturer's name.[8]

Components of Ballistic Missiles

A round is one complete unit of ammunition. This includes the bullet, the cartridge case, the powder, and the primer.[9] The projectile or the bullet is the missile that is expelled and strikes the target. The accelerant, such as gunpowder or cordite that allows for expulsion of the projectile from the weapon, is the propellant. The primer is the device for igniting the propellant and sending the projectile on its flight. The container that packages the bullet, propellant, and primer as a single unit is the casing.[10]

Types of Firearms

There are three types of firearms: handguns, rifles, and shotguns.

The handgun is the smallest and the least powerful of all firearms. There are three common types of handguns: single-shot pistols, revolvers, and semiautomatic pistols. The single-shot pistol holds only a single round of ammunition and must be reloaded after each shot. Revolvers have a number of firing chambers in a revolving cylinder where each chamber in the cylinder is loaded with a single cartridge or charge. The semiautomatic can fire multiple shots, as many as 15 to 19 rounds. It uses the recoil generated by the fired cartridge to eject the empty cartridge case, load the next cartridge, and cock the hammer. Handgun injuries generally have a tendency to push away or stretch soft tissues including vessels or nerves, as opposed to creating avulsive wounds.[10]

A long gun is any firearm that is larger than a handgun with a barrel between 10 and 30 inches. The design of the long gun is intended for the user to hold and fire it using both hands. The long gun is generally held against the hip or the shoulder.

A rifle is named for the spiral fluting (rifling) carved into the inner surface of its barrel. This creates a self-stabilizing

spin to the single bullets it fires. Rifles, with long barrels and higher velocities, are very powerful and very accurate at long distances. They have the potential to destroy a large amount of tissue, as they are high-velocity, high–kinetic energy (KE) projectiles with the tendency to yaw, tumble, and fragment.[6,11]

Rifles, at distance, are similar to handguns because of low energy transfer. At close range, however, there is increased potential injury due to velocity and high energy transfer. Rifles have the capacity for high-speed automatic fire with a very small impact area. There is usually an exit wound, which may be stellate and larger than the entry wound. The existence of avulsive soft/hard tissue wounds and significant fragmentation of bone can be characteristic findings of rifle wounds.[10]

Shotguns are predominantly smoothbore firearms designed to fire a number of shots. Generally, the higher the shot number, the smaller the size of the pellets. The pellet sizes can range between 2 mm (#9 birdshot) used for small targets such as fowl and 8.4 mm (#00 double-aught buckshot) intended for larger game such as deer. A shotgun shell may contain one large projectile (called a slug) used for more powerful targets such as bear.[6,12]

Shotguns are similar in external appearance to rifles, but

that it would take to equal 1 pound when placed in a gun barrel of given diameter. This indicates the weight of the pellets fired by the weapon. A 12-gauge shotgun shoots pellets that weigh ½₂th of a pound each.[7]

Shotguns have a large impact area with considerably less range and accuracy. When a shotgun shell is fired, it breaks apart and the outer layers fall away, allowing pellets to separate radially, spread in a cluster, and become less aerodynamic as they pass through air. Pellets lose KE and velocity as they travel to the target; however, the larger impact area can compensate for reduced accuracy, overcoming the need for precision because the pellets spread during flight.[6]

Shotguns may cause minor to massive damage, depending on the range from the target and the size of the pellets fired. Shotgun wounds are unique because of the way the shotgun shells are constructed and the importance of range from gun to victim. Close-range wounds may involve massive tissue destruction and are equivalent to high-velocity GSWs. The pellets penetrate tissue and transfer kinetic energy to the victim, unlike other types of GSWs. Moreover, the pellets rarely exit the body. This means that all of the kinetic energy is transferred to the target tissue.[13]

Furthermore, there is a higher degree of contamination and presence of propelled gas and shock waves in shotgun injuries at close range. When the muzzle of the weapon is in contact with the target, the effect of gas that is discharged under pressure into the wound can be an additional source of tissue displacement, injury, and thermal burning.[8,10]

Two types of shotgun wound classification systems are described in the literature. Sherman and Parrish devised one classification system to describe shotgun wounds according to their distance. Specifically, their system was based on the number of yards/meters from muzzle to target. In type I wounds, the distance is greater than 7 yards, and such wounds tend to involve the subcutaneous tissue and deep fascia. (See Figure 15-21.) In type II wounds the distance is between 3 and 7 yards, and they show deeper pellet penetration of tissue. In type III wounds, the distance is less than 3 yards and these wounds have dramatic soft and hard tissue injuries and avulsion of tissue.[6,8] (See Figure 15-22.) Glazer and colleagues described the second classification system for shotgun wounds. Their system is based on pellet scatter. The pellet scatter in type I is within an area of 25 cm^2, type II 10 to 25 cm^2, and type III <10 cm^2.[6]

Wound Ballistics

Wound ballistics is the study of a missile's effect on living tissue. Knowledge of wound ballistics is essential to determine the extent and type of injury from a missile. Velocity has the largest impact on KE.[10,11] Both missile and tissue characteristics determine the nature of the wound. The degree of injury is primarily dependent on the mass and velocity of the missile.[14] In addition, the bullet's orientation and whether it fragments or deforms affect the nature of the wound. Understanding the mechanisms by which the projectile disrupts tissue provides more information for the surgeon evaluating and treating GSWs.[9,14]

The various types of bullets produce a variety of tissue injuries. Furthermore, similar bullets can also produce a wide variety of wounds that range from minor to lethal. The severity will vary depending on characteristics of the missile, the weapon, and the tissues struck. The bullets are shaped or composed differently for a variety of purposes. The "round-nose" bullet is blunted at the end. The "hollow-point" has a hole in the bullet that creates expansion when a target is struck, creating greater damage. In the "jacketed" bullet, the soft lead is surrounded by another metal, usually copper, that allows the bullet to penetrate a target more easily. The "wad cutter" has a flattened front end. The "semi-wad cutter" is an intermediate between round-nose and wad cutter. Tissue damage is dependent on the characteristics of the firearm firing the projectile (rifle vs. handgun); the nature of the projectile—for example, fully jacketed versus expanding bullet; and the attributes of the target tissue—for example, tis

[11]

fee

high-velocity (>2000 feet/second).[5,7] The tissue injury is dependent on the efficiency of energy transfer; the projectile's physical characteristics, including deformation and fragmentation, KE, stability, entrance profile, and path traveled through the body; and the biologic characteristics of the tissues.[11] A velocity of 50 m/sec is required on impact to penetrate skin and 65 m/sec to fracture bone. However, any bullet is capable of inflicting serious or lethal injury if a vital structure (e.g., heart or brain) is involved.[14] In high-velocity

wounds there is more damage by production of shock waves and temporary cavitation in addition to laceration and crushing injury.[11,14]

Gunshot injuries are categorized as follows: (1) penetrating, where the missile strikes the victim without exiting the body; (2) perforating, with entrance and exit wounds without appreciable tissue loss; and (3) avulsive injuries, where there is an entrance and exit wound with an acute loss of tissue associated with the passage of the projectile out of the victim.[10]

The Physics of Ballistics

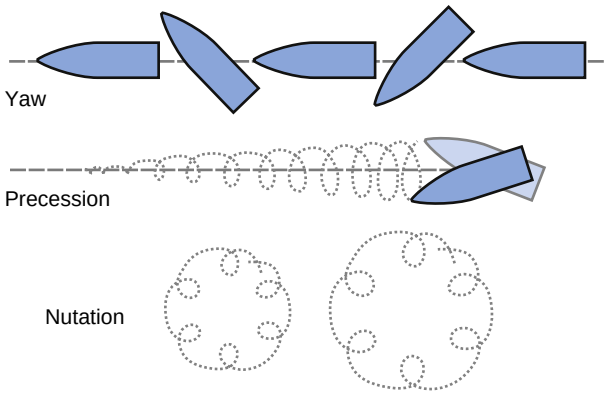
The motion of a projectile, from the instant of firing until propellant's ignition until the projectile exits the gun barrel; (2) external ballistics deals with the phase of unpowered free flight of the projectile from the time it exits the gun until it reaches the target; and (3) terminal ballistics deals with the effect of the projectile on the target.[15]

There are three basic determinants of the external ballistics of the bullet: (1) mass of the bullet (the greater the mass of the bullet, the harder it is to propel with the same amount of gunpowder), (2) the amount of gunpowder in the cartridge (the larger the amount of gunpowder, the greater the explosion), and (3) the length of the barrel (the longer barrels, for example, the rifle, are able to attain significantly higher bullet velocities than handguns).[15]

Three key terminologies are important in understanding external ballistics: yaw, precession, and nutation. Yaw refers to the rotation of the nose of the bullet away from the line of flight. It is the deviation of a forward-moving aerodynamic object from its longitudinal axis (generally less than 1 to 2 degrees).[10] Precession is an angular force applied to a rotating object caused by its torque rotation of the bullet around the center of mass. Nutation refers to small circular movements at the bullet tip or the opposing force in a rotating object that gradually "normalize" along the longitudinal axis during projectile flight[7,10] (Figure 15-1).

A short, high-velocity bullet begins to yaw more severely and turn, and even rotate, upon entering tissue. This causes more tissue to be displaced, increases drag, and imparts more of the KE to the target. A longer, heavier bullet might have more KE at a longer range when it hits the target, but it may penetrate so well that it exits the target with much of its KE remaining.[11] Although these terms have practical applications in weaponry, the clinical significance in maxillofacial ballistic trauma is minimal.[10]

Three physical parameters have been used to explain and predict the damage caused by a bullet upon impact: KE, power, and momentum.[14] Once discharged from the weapon, the bullet's energy decreases throughout its flight. The bullet dissipates the remainder of its energy when it collides with a target.



• **Figure 15-1** Movements of a bullet. The classic movements of yaw, precession, and nutation are diagrammed. (From Powers DB, Delo RI: Characteristics of ballistic and blast injuries. *Atlas Oral Maxillofac Surg Clin North Am* 21:15-24, 2013. Reprinted from U.S. Government Printing Office, *Emergency war surgery*, rev. 3, 2004.)

The projectile's wounding capacity is directly related to the amount of KE transferred to the tissue. Kinetic energy (KE) is equal to half the product of the mass (M) and velocity squared (V^2): $KE = \frac{1}{2}MV^2$. Doubling the mass doubles KE, but doubling the velocity quadruples KE.[5,11]

The total energy released to the target can be represented by:

$$\text{Change in KE} = \text{KE entry} - \text{KE exit}$$

Higher KE, which is increased by increasing bullet mass or velocity, has higher potential for wounding. However, if the exit KE is still high, then relatively minor tissue damage may result. A bullet that passes cleanly through the target and exits with significant velocity will not cause as much damage as a bullet with similar KE that completely decelerates and comes to rest within the target.[11]

A low-velocity bullet wound causes laceration and crushing of tissue. In addition to lacerating and crushing tissue, high-velocity bullet wounds cause cavitation and produce pressure and shock waves. There is rapid energy release upon penetration, and as energy is absorbed, the tissue starts to flow forward with the projectile. A large cavity is formed that may be 30 to 40 times the diameter of the bullet in a few milliseconds. The cavity produced is vapor filled, with a sub-atmospheric pressure, and is pulsatile in nature, expanding and collapsing repeatedly with decreasing amplitude. The target tissue comes to rest, leaving a permanent cavity.[14]

KE is not a predictor of injury. It reveals nothing about the magnitude, type, and location of tissue disruption or the forces that cause tissue disruption. One must determine if the mechanism of injury is predominantly one of crushing, such as a .71 caliber traveling 500 to 800 feet per second, or is predominantly tissue tearing from being displaced and stretched beyond its elastic limits by temporary cavitation, such as a .24 caliber traveling 3000 to 3300 feet per second.[14]

Handguns and shotguns are low to medium velocity. Tissue damage attributed to a low-velocity projectile is less

predictable. The bullet's tendency to deflect off the tissue results in bone and soft tissue damage. Some of the ballistic energy may be transferred to bone fragments, teeth, and dental prostheses, converting them to secondary projectiles that cause additional injuries. High-velocity GSWs are rarely seen in the emergency room because of the high fatality of such injuries.[5] Two major mechanisms of wounding occur: the crushing of the tissue struck by the projectile, forming a permanent cavity, and the radial stretching of the projectile path walls, forming a temporary cavity.[9]

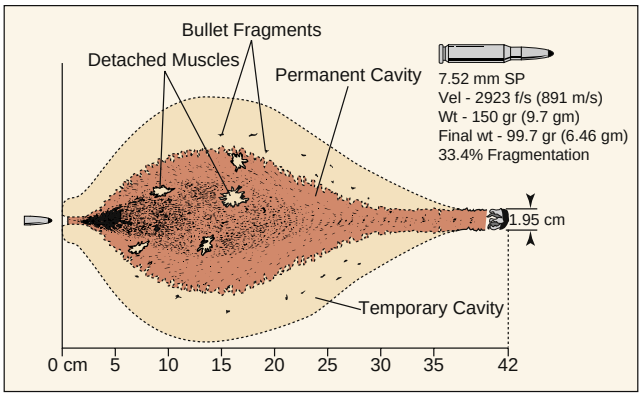
Three tissue phenomena are noted upon impact: sonic wave formation, permanent cavitation, and temporary cavitation. There are two types of pressure waves produced by penetrating objects. The first wave is the sonic pressure wave or "shock wave" that precedes the projectile through tissue at the speed of sound (~4800 feet per second). The sonic pressure wave that was reported by Harvey in 1947, reaching pressure up to 117 atm and lasting only a few microseconds, forms a hemispherical arc ahead of the advancing bullet when a bullet enters soft tissue. No temporary cavity is formed with the sonic pressure wave, and it has no damaging effects on tissue. This is a finding confirmed by clinical experience with sonic pressure wave lithotripsy. In lithotripsy, the tissue receives sonic pressure waves two to three times greater than that produced by a supersonic rifle bullet, and as many as 2000 waves might be used during a single treatment of renal stones. These sonic waves do not significantly harm the surrounding tissues.[9,10,14]

A permanent cavity is created as the missile penetrates the wound and crushes the stricken tissue. The track made by the diameter of the bullet (cavity plus change in size through deformation) consists of crushed tissue and cellular debris. As the tissues recoil, hot gases dissipate, and soft tissue collapses inward, leaving a permanent cavity defect.[16] Adjacent to this track is the temporary cavity, a region in which the pressure wave created by the bullet causes outward stretching and shearing forces that produce tissue contusion.

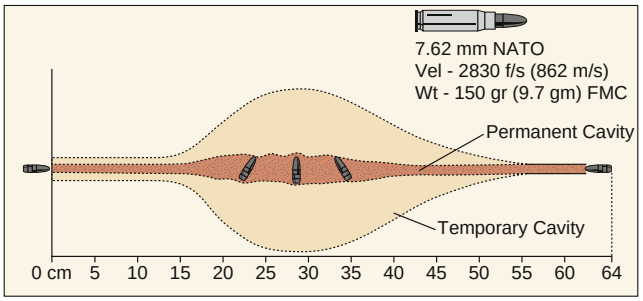
The secondary pressure wave or the temporary cavity is created behind the path of the bullet, with pressures between 4 atm and sub-atmospheric pressure when the penetrating projectile strikes tissue. The wave radiates laterally away from the permanent cavity of the projectile path. This wave injures tissues such as muscle, vessels, and organs.[10] The maximal size of the temporary cavity occurs several milliseconds after the bullet has passed through the tissue[9] (Figure 15-2).

Bullets that display greater yaw will be associated with increased temporary cavitation. Velocity is another factor that increases the temporary cavity size. The higher the velocity of the bullet, the greater the KE, which may increase the temporary cavity by more than 10 times the caliber of the bullet in a few milliseconds[11,14] (Figure 15-3).

The effect and damage of the temporary cavitation can vary greatly depending on the elasticity of the injured tissue, the size of the cavity, and its anatomic location.[11,14] These forces can rupture blood vessels. The extracellular tissue matrix with collagen, reticular, and elastic fibers can also



• **Figure 15-2** Cavity, soft-point bullet. As the bullet strikes the underlying structures, there is an almost instantaneous increase in temporary and permanent cavity. This occurs because the soft tip deforms and fragments. (From Powers DB, Delo RI: Maxillofacial ballistic and missile injuries. In Fonseca RJ, Barber HD, Walker RV, et al, editors: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

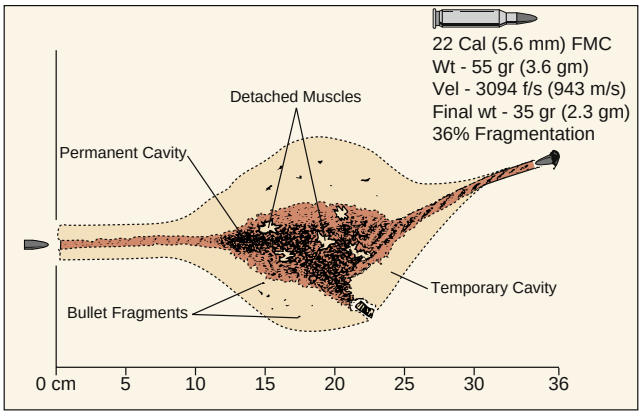


• **Figure 15-3** Cavity formation, high-velocity bullet. This figure depicts a 7.62-mm round from an M16 rifle. Note the relatively small permanent cavity and large temporary cavity. The bullet tumbles after 20 cm; thus in the maxillofacial area this bullet would not be very destructive if it traversed, for example, the bilateral buccal mucosa soft tissues. (From Powers DB, Delo RI: Maxillofacial ballistic and missile injuries. In Fonseca RJ, Barber HD, Walker RV, et al, editors: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

be disrupted. At first, the projectile crushes structures along its track, similar to other forms of penetrating injury. Temporary cavitation, which follows the path of least resistance, causes shearing and compression, sometimes tearing structures or stretching inelastic tissue similar to blunt trauma.[14] Less elastic tissues (e.g., brain, liver, or spleen) fluid-filled organs (heart, bladder, gastrointestinal tract), and dense tissue (e.g., bone) may be severely damaged when they are contacted by a large temporary cavity. The cavity formed by most expanding handgun bullets is about 9 cm in diameter.[14] This 9-cm diameter cavity is likely to be absorbed in highly elastic tissues, such as the lung or muscle, which can easily accommodate the stretching created by the temporary cavity. These highly elastic tissues, therefore, are less affected or damaged by the formation of the temporary cavity.[9] In contrast to this, the temporary cavity has a very damaging effect on inelastic organs such as the liver, and in the cranial cavity, where the brain tissue is unable to move aside due to the restraint by the cranium. Thus, this 9-cm cavity will cause instant death.[14]

The following factors influence the degree of injury: yaw, deformation, and fragmentation of the bullet upon striking the target. The process of tumbling or yaw within the target significantly increases the destructive capacity of the projectile. When the yaw of the bullet is 90 degrees, the maximum effective diameter, the entire long axis of the bullet strikes the tissue and the amount crushed may be three times greater than that at zero degree yaw.[15] Two bullets of similar KE can have different wounding potentials. The ratio of bullet size to velocity also has a significant effect on tissue injury. A large, slow projectile tends to crush tissue in its path and creates little radial dispersion of energy (temporary cavity formation). A small, fast bullet tends to crush little tissue; however, it creates more transient radial tissue stretching.[15]

An expanding soft-point or hollow-point bullet causes more tissue disruption than a similar but non-expanding bullet.[14] Soft-point and hollow-point bullets deform into a mushroom shape, which increases the surface area and wound severity. If the mushroom diameter is 2.5 times the initial diameter of the bullet, the area of the tissue crushed is 6.25 times greater than for a non-deformed bullet. Bullet fragmentation increases the volume of tissue crushed by increasing the surface area of the bullet.[9] Bullets that fragment create much larger permanent cavities and cause extensive damage because of the production of secondary missiles.[14] Understanding the mechanism by which bullets disrupt tissue can help in evaluating and treating maxillofacial GSW victims' injuries and wounds. The nature of the wound is determined by both the missile and tissue characteristics. The elasticity and density of a tissue and the thickness of the body part wounded strongly affect the wound produced. The key factors in determining the wounding potential of a missile are mass, construction, tendency to fragment or yaw, and the missile's velocity. A bullet can cause more damage to tissue by fragmentation and yaw than by high velocity[9] (Figure 15-4).



• **Figure 15-4** Cavity, small-caliber bullet. This figure depicts a small 22-caliber full-metal case round striking hard and soft tissues. The bullet deforms and creates both a large permanent cavity and another trajectory. Thus the wounding potential of a small-caliber bullet can be significant. (From Powers DB, Delo RI: Maxillofacial ballistic and missile injuries. In Fonseca RJ, Barber HD, Walker RV, et al, editors: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

Treatment of Maxillofacial Gunshot Wound Injuries

Gunshot wounds to the maxillofacial region present the treating surgeon with a myriad of challenges. The highest priorities in treatment are the well-being of the GSW victim and excellent communication among all of the treating colleagues. The assigned trauma team members may vary depending on the needs of various acute care facilities. Nonetheless, a well-organized trauma team should be expected to evaluate all maxillofacial GSW patients. There are many components of care that happen concurrently when treating maxillofacial GSW victims. As primary assessment of the patient is occurring, there are acute issues that are a priority in treatment. The most urgent treatment needs for these patients are basic life support, including acute airway issues and all the components of shock management. These issues are treated concurrently and include the following:

1. Initial Treatment, GSW Maxillofacial Region—Treatment Sequence

1. Basic life support (BLS)
2. Advanced Trauma Life Support (ATLS)—primary and secondary survey/continuous patient resuscitation
3. Evaluation/treatment plan—trauma team
4. Ophthalmology/neurosurgery evaluation
5. Completion of head and neck exam and location of missiles
6. Initial procedures in operating room
7. Patient-specific therapy/surgery and further data collection; intravenous antibiotic therapy, including *Staphylococcus aureus* and *Streptococcus* coverage; admit to ICU or Close Observation Unit—monitor for expanding hematomas and airway compromise, obtain computed tomography (CT) of bony windows face and mandible, 0.5-mm cuts, reformat into 3D images and medical 3D modeling if needed.

2. Initial Treatment, GSW Maxillofacial Region—Treatment Sequence

The points previously listed specifically include these further components:

1. BLS:
   - 1A. Acute airway needs
   - 1B. Hemorrhage control intraorally, extraorally; removal of foreign bodies, initial stabilization of alveolar segments. Determine the amount of floor of the mouth and oropharyngeal swelling in acute ER setting and estimate short-term expected edema? Intubation? Surgical airway?[17]
2. ATLS: amount estimated blood loss, treatment of shock, hypovolemia, secondary evaluations.
3. Evaluation and treatment plan with trauma team—including plan to manage analysis of zones of the neck the missile traversed and associated damage, imaging

studies, immediate versus delayed operation, and anesthesia plan/consultation.
4. Early ophthalmologic assessment—visual acuity, retrobulbar hematoma, ophtho consult. Assess neurologic injury—open or closed intracranial injury, presence of cerebrospinal fluid (CSF), neurosurgical consultation.
5. Completion of head and neck exam and location of missiles:
   Including: evaluate cranial nerves, especially trigeminal and facial nerves, parotid flow—presence of saliva on the face? (See Figure 15-26.)
   Locate bullet fragment(s) —Follow flowchart figure for location of displaced missile (bullet). (See Figure 15-10, *C.*)
6. Initial procedures in operating room
7. Patient-specific therapy/surgery and further data collection

1A. Initial Assessment of the GSW Face Victim

Maxillofacial GSW victims presenting with cervical collars in place represent a challenge, as comfortable positions the patient can be placed in are limited by the concerns for a cervical spine injury. Moreover, the initial providers are often eager to manipulate the conscious patient's position. Patients maintaining their airway should only be repositioned with great caution as doing so may cause a rapid deterioration in their ability to maintain the airway. The conscious patient with an extensive GSW crossing one or more anatomic zones of the neck and maxillofacial region will often find a comfortable position to sustain life. Depending on the extent of the soft tissue damage to the face and airway, these patients will often be comfortable sitting up erect or positioned with the head forward. One may need to place the patient in the prone position for forward traction in order to keep the airway patent in the acute care setting.[18] These patients, whether sitting up, erect, or prone, can participate in maintaining their airway temporarily by maintaining traction on a suture tied to their anterior tongue. Very often these GSW patients have a soft tissue flap in their airway that may close their airway opening when they are repositioned against their will by a health care provider.[19] Similarly, patients with extensive mid-face comminution and floating maxillofacial segments may have compression of vascular components resulting in control of bleeding. These vessels can open again and cause hemorrhage when the segments are capriciously manipulated and result in loss of the airway in an otherwise conscious patient with a patent airway (Figure 15-5).



• **Figure 15-5** **A,** Sitting position. **B,** Semi-erect position. **C,** Prone position. Three different positions of the conscious maxillofacial gunshot-wound patient. They are all maintaining their own airways. These patients do not do well with sudden jostling or insistence that they reposition themselves. (Courtesy Dr. R. S. Sadda.)



• **Figure 15-6** Airway distress, zone III injury. Patient appears with posterior zone III wound extending across base of tongue. He has an obvious protruding tongue, excessive drooling, and an appearance of exhaustion with impending respiratory arrest. The urgency of this clinical appearance can be dismissed by the novice who is not impressed by any avulsive or displaced tissues as seen in many other injuries that have patent airways despite their gross appearance. This patient is treated with an urgent surgical airway if nasal intubation is not possible. (Courtesy Dr. R. S. Sadda.)

In addition to this, the clinical presentation of a prolapsed tongue in a maxillofacial GSW victim results in airway compromise secondary to a displaced anterior mandible fracture caused by the missile. This prolapsed tongue can be relieved by physically bringing the anterior mandibular segments, associated teeth, muscles and tongue forward by simple interdental wiring using 24- or 26-gauge stainless steel wire. This is done by grossly reducing the fracture, by connecting the traumatized, displaced anterior segments to the intact segments posterior to the fractures. This results in bringing all of the structures forward and thus the tongue away from the oropharynx.

An acute loss of the airway may result in the need for a rapid-sequence intubation or emergency airway in the ER setting. These situations are often met with chaos and may result in catastrophic results (Figure 15-6).

Many authors recommend a non-urgent surgical airway be placed in the OR setting where all hands and equipment are available to deal with any complications that may arise.[20] Furthermore, it is important for the consulting surgeon to be aware that many of the other practitioners evaluating the patient may not be accustomed to looking for tooth fragments and foreign bodies in the airway simply because they are not as experienced at finding foreign bodies in the various pouches and vestibules of the mouth or oropharynx. It is not uncommon to see a maxillofacial region GSW victim speaking fairly well although they have tooth fragments, whole teeth, and foreign bodies displaced throughout the airway. An early finding of any of these objects in the airway will help prevent laryngospasm, aspiration, pneumonia, and subsequent morbidity.

When the trauma team deems an acute surgical airway is necessary for an adult, the first choice is cricothyrotomy, followed by a conversion to a traditional tracheostomy in the OR under controlled conditions. The treatment of choice for an acutely needed surgical airway in a child is a tracheostomy.[20,21]

1B. Hemorrhage Control in the Acute Setting of the Maxillofacial GSW Victim

The surgical consultant is reminded to use universal precautions when examining these patients. These patients often present with bulky dressings, and unwrapping the dressings often reveals large, damaged vessels and exposes the health care providers to gross amounts of blood from pressurized areas. Immediate direct pressure is essential. Random clamping of tissues and vessels that have not been clearly isolated and identified is not recommended. This injudicious clamping may lead to permanent facial and trigeminal nerve injuries. Bulky moist pressure dressings are useful for a short time to stop arterial and venous bleeding.[18]

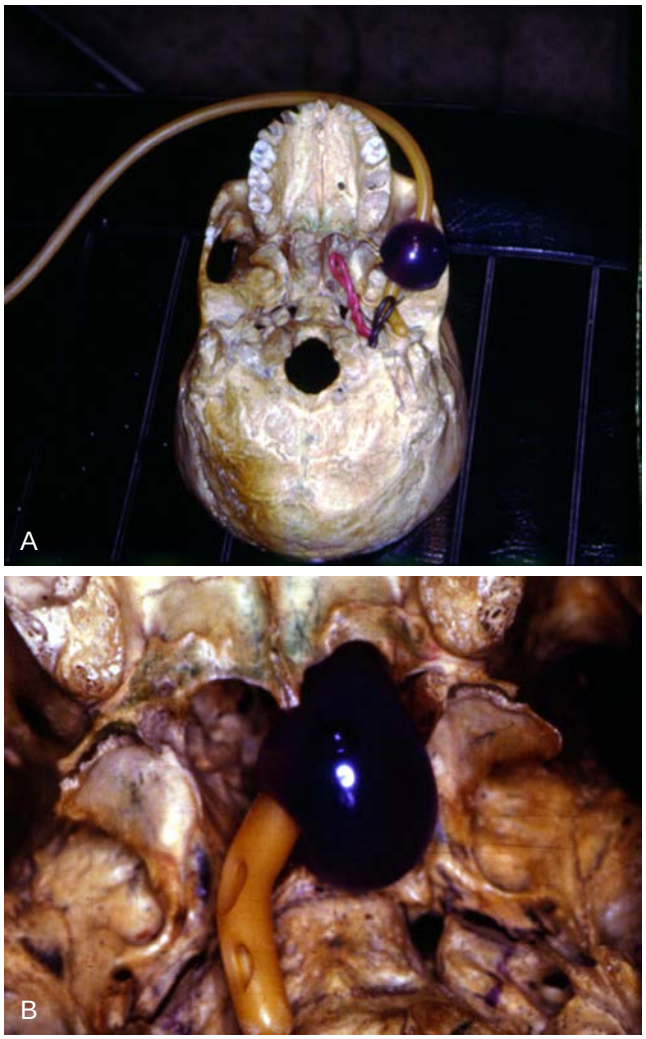
Mid-face bleeding that clinically appears to originate from the posterior nose or maxilla can be controlled by the use of 20 French Foley catheters carefully placed along the floor of the nose or the nasal remnants that are present and then inflated. The two Foley catheters usually require inflation with approximately 20 mL each of normal saline. They can then be secured together anteriorly to help maintain the posterior pressure and position of the catheter bulbs and thus curtail the bleeding. These catheters can be left in place until bleeding is curtailed or until angiography localizes and embolizes those vessels that may contribute to the hemorrhage.[22]

Foley catheters can also be used in deep wounds and the base of the skull, pterygoid plexus areas to help tamponade bleeding (Figure 15-7).

Floor of the mouth bleeding and bleeding from the base of the tongue can be controlled in the acute setting by a health care provider holding the tongue with his/her fingers and gauze or a suture through the tongue, and displacing it anteriorly to compress the vessels.

Exploration of any wound can easily be done with digital examination as well as a sterile cotton-tip applicator. This exploration will yield information on the path and structures the bullet may have encountered. Many of the maxillofacial GSW patients who have uncontrolled bleeding will need angiography to assess vascular damage and embolization of needed areas of the vascular tree, which is often a branch of the external carotid artery. Ligation of branches of the external carotid artery is not recommended, as collateral circulation will contribute to continuous bleeding. Complex multi-trauma patients also often develop mas-

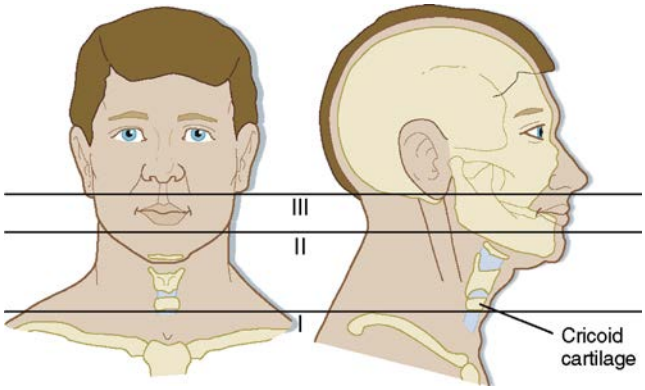
coagulation factors.



• **Figure 15-7** **A,** Base of skull Foley catheter and **(B)** posterior nasal Foley catheter. Foley catheters are useful in areas that have numerous vascular plexuses, such as the pterygoid plexus of veins in the infratemporal space and posterior nasal/maxilla regions, zone III locations. Foley catheters have been used to control bleeding temporarily in vascular injuries to the chest as well.

2. ATLS—Primary and Secondary Survey/ Continuous Patient Resuscitation and 3. Evaluation/Treatment Plan—Trauma Team

The clinical reality is that the components included in 2 and 3 happen simultaneously. Often a maxillofacial GSW victim presents to a smaller community hospital and is stabilized and consequently transferred to a Level I or Level II trauma facility for definitive care. Communication in these situations is essential to a good result for the patient. For example, the maxillofacial GSW patient may have a wound that entered the right maxilla and exited the left angle of the mandible. The patient is stable, and it appears there is no risk in transferring the patient to another facility for definitive care. This is an example of an occurrence that may be encountered in accepting a transfer of a maxillofacial GSW trauma patient. Incomplete information



• **Figure 15-8** Zones of the neck. This is essential for the treating surgeon, as misdiagnoses can have poor outcomes for the patient. (From Adams J: *Emergency medicine*, ed 2, St Louis, 2013, Saunders.)

and communication of the areas the missile traversed and a thorough assessment of vascular or aerodigestive tract injury may lead to poor outcomes for these patients.

The zones of the neck that the missile traveled through should be documented and the information discussed with the treating trauma team. The management of penetrating neck trauma has changed over the past three decades from mandatory exploration of all wounds that penetrate the platysma muscle to selective nonoperative management of certain injury patterns.[23-25]

Historically the anatomic zones of the neck have been delineated into three areas known as zone I, zone II, and zone III (Figure 15-8). The anatomic zones and recommended studies are as follows:

- Zone I: Boundaries are between the clavicles and cricoid cartilage; contains lung, trachea, great vessels, esophagus,
- daries are between the cricoid cartilage and the angle of the mandible. Invasive studies recommended: none
- Zone III: Boundaries are from the angle of the mandible commended:

g neck injuries to zone II has traditionally been exploration of the neck and wound.[23] Clinically many maxillofacial GSWs may cross more than one zone of the neck. In clinical assessment it is important to look, feel, and listen. The clinician should look at the zone or zones of the neck involved, assess the apparent depth of the wound, look for bubbling or bleeding, and assess for presence of a hematoma. The clinician should feel for subcutaneous emphysema and listen for bruits. One prospective study showed that physical examination is reliable for identifying those patients with penetrating injuries to the neck who require vascular or esophageal diagnostic studies.[23]

injuries that did not correlate with the anatomic zone they entered superficially. Their study shows that the anatomic location of the superficial injury may be of questionable use in guiding treatment. Low and co-workers emphasized that treatment should be guided by soft signs, hard signs, or no signs.[24]

Soft signs include:

1. Venous oozing
2. Non-expanding or non-pulsatile hematomas
3. Minor hemoptysis
4. Dysphonia
5. Dysphagia
6. Subcutaneous emphysema

Hard signs include:

1. Active hemorrhage
2. Expanding or pulsatile hematoma
3. Bruit or thrill in area of injury
4. Shock unresponsive to initial fluid resuscitation
5. Massive hemoptysis or hematemesis
6. Air bubbling through injury site

Their recommendation is to use multidetector computed tomographic angiography (MDCTA) and hard signs to make decisions as to when surgical intervention is needed. They found 90% of injured patients with hard signs had true injury.[24] The surgical consultant should communicate expediently with the trauma team to establish a comprehensive plan for acute and long-term treatment. Doppler ultrasound, a useful adjunct, has been shown to be impractical in evaluation of penetrating neck injuries as a result of the interpretation variability and the need for an experienced technician.[24]

Nevertheless, exploration of all neck wounds deep to the platysma muscle leads to a significant number of unnecessary operations and extra cost. However, the consequences of a missed injury are potentially high. To what extent clinical examination can be relied on, and which diagnostic adjuncts should be employed, remains a subject of some debate. The actual management plans will depend not only on the specific patient and the injury sustained, but also on available staffing, expertise, monitoring, and diagnostic modalities.[23-25] Furthermore, late effects of penetrating trauma to the head and neck vessels can result in pseudoaneurysms requiring treatment.[26]

4. Early Ophthalmologic Assessment and Neurosurgery Evaluation and Consultation

Eye injuries are not uncommon with GSWs to the maxillofacial region. The surgeon should be familiar with a basic screening for VA (visual acuity) and the presence of light perception. As a general rule, loss of the patient's ability to perceive a bright red object and perceive it instead as dark or crimson in color is an indication of developing optic nerve damage and vision loss. Early consultation with the ophthalmologic service early on is essential[27] (Figure 15-9). Neurosurgery consultation usually occurs early on in treatment and is done in coordination with the trauma team.



• **Figure 15-9** Ophthalmologic considerations. Patient presents with an anterior maxillofacial gunshot wound with no acute airway loss. Clinically he has significant periorbital ecchymosis. One of the priorities is to evaluate for retrobulbar hematoma: palpate the right eye for firm hardness in comparison to the left eye, feel for pulsations in the ecchymotic eye, visually inspect the amount of proptosis of the eye, and separate the lids to check for visual acuity. (Courtesy Dr. V. J. Perciaccante.)

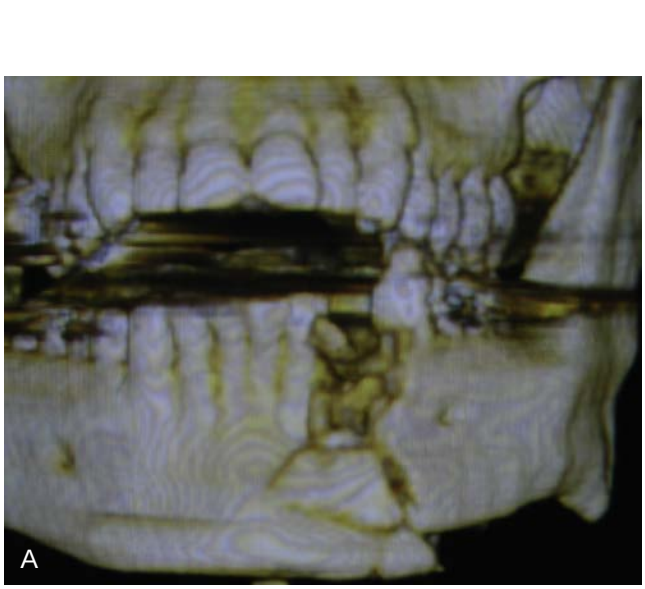
5. Completion of Head and Neck Exam and Location of Missiles

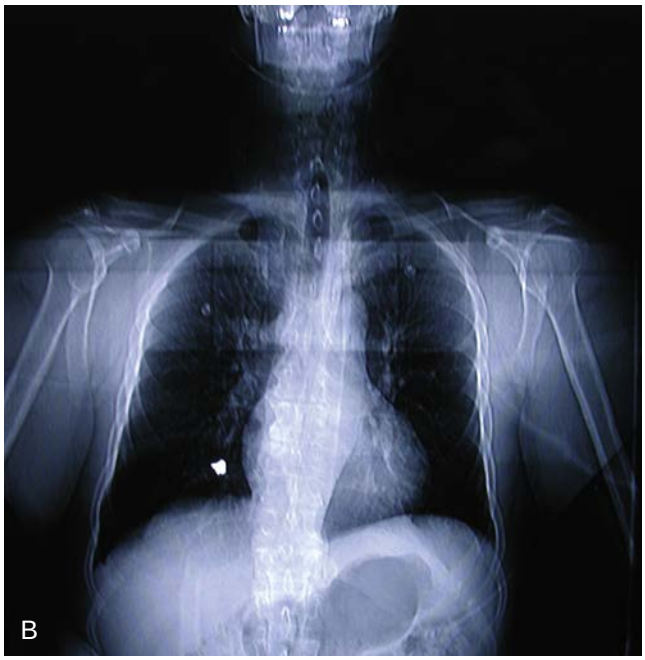
Complete assessment of the wound and accounting for all bullet fragments is also essential in the treatment of maxillofacial GSW patients. Low-velocity wounds can be expected to have an entrance wound and often no exit wound. Furthermore, these GSW victims may have a bullet fragment traverse into the chest and/or below the diaphragm[28] (Figure 15-10).

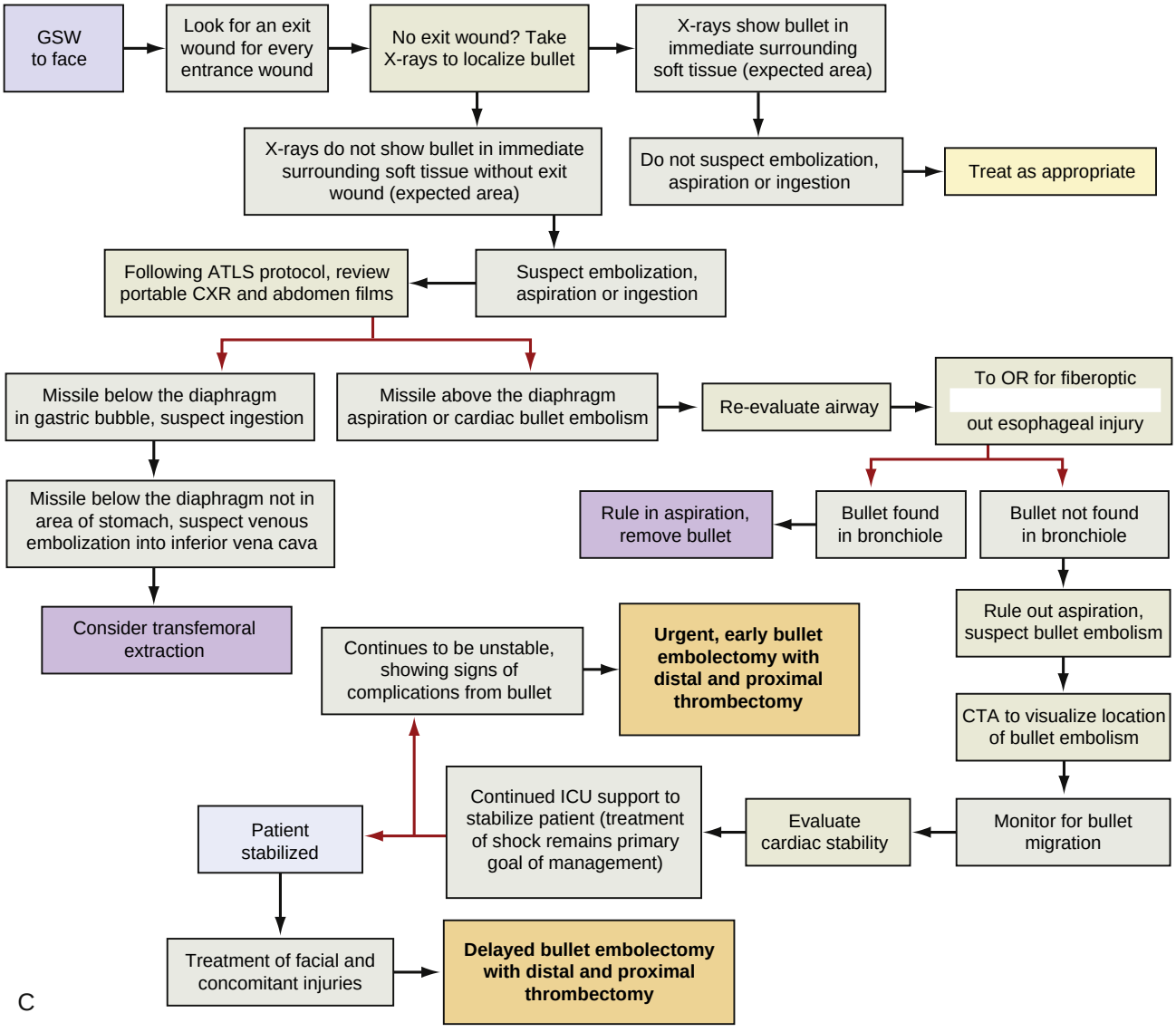
The point of the algorithm is that when an exit wound is not found and plain film head and neck radiographs do not reveal the missile in local tissues, then another occurrence such as aspiration, ingestion, or embolization should be suspected. The diaphragm is the landmark dividing the chest from the abdomen. When the bullet fragment is located above the diaphragm, aspiration or embolization is suspected, and when it is found below the diaphragm in the gastric air bubble, we would suspect ingestion. Careful assessment and determination of the path of the bullet from the maxillofacial GSW victim is essential to comprehensive treatment.[28] Proper assessment, consultation, and communication with other members of the trauma team will help decrease morbidity for the patient.

6. Initial Procedures in the Operating Room and 7. Patient-specific Therapy/Surgery and Further Data Collection

Once the patient has been stabilized and is in the operating room with a secured airway, the wounds can be explored and initial treatment and debridement can be done. This part of the treatment plan—6 and 7—includes many elements.







• **Figure 15-10** The patient had sustained a gunshot wound (GSW) to the anterior mandible **(A),** and the bullet traversed into the pulmonary artery to create a bullet embolus **(B). C,** Flowchart for bullet embolus. Diagram of management strategy for GSWs to the face involving retained missiles. (**B** From Jo C, Steed M, Perciaccante VJ: Bullet embolus to the pulmonary artery after gunshot wound to the face: case report and review of literature, *J Oral Maxillofac Surg* 68:504, 2010. **C** Courtesy Dr. V. J. Perciaccante.)

The treating surgical team at this point determines which techniques will be needed to eventually bring the patient to the reconstructive phase of treatment months later. There is a large difference between the planning and number of operations needed for the single, non-avulsive wound in Figure 15-13 versus the complex, avulsive wounds in Figure 15-15.

Primary Wound Treatment

Historically a great amount of time and energy was spent by treating surgeons on differentiating low-velocity GSWs from high-velocity GSWs. Contemporary treatment of GSW management is that the caliber of the projectile essentially makes little difference in the treatment of the patient.[29] Low-velocity bullet wounds from handguns (100-150) are often confined to the wound track. High-velocity bullet wounds (2000-3000) include missiles and assault rifle bullets. The most recent data and reporting of high-velocity wounds shows that tissue damage in excess of this projectile does not occur until approximately 15 cm into the body of the target. Thus, depending on the site of impact, this high-velocity projectile could exit the body before breakage and result in minimal tissue damage.[29,30] The high-energy wounds cause laceration and crush injuries to adjacent structures as well as have the potential to inflict injuries remote from the wound track. These high-energy wounds have an increased morbidity for the victim as they may involve kidneys, liver, and spleen.[29]

General Guidelines for Wound Treatment

Debridement of Wound

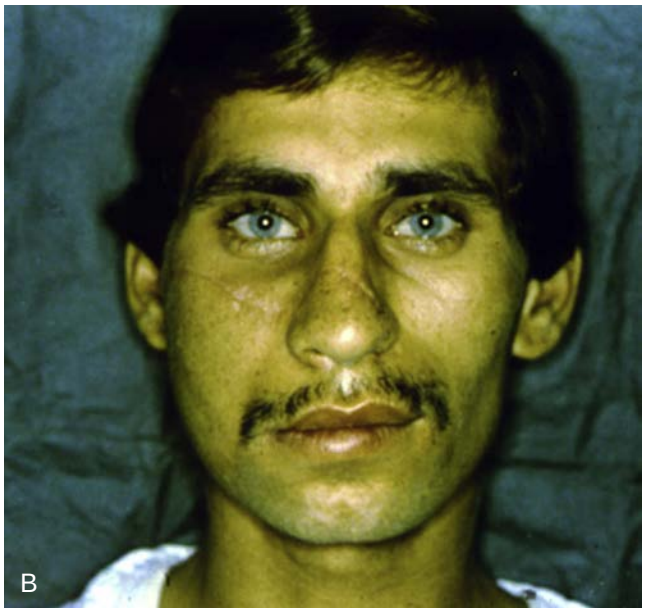
- Copious irrigation with warm, normal saline with bacitracin solution (4-6 L)
- Exploration of wounds under general anesthesia—unfolding and exploration
- Removal of any skin contaminants and road-rash-type debris that may cause permanent tattooing; may need to scrub skin[18]
- Assessment of regional neurovascular bundles, arteries, veins
- Assessment of parotid duct (see Figure 15-26)
- Assessment of nasolacrimal duct
- Early surgical debridement of devitalized tissue
- Removal only of bony fragments smaller than 1 cm, free floating, without periosteal attachment
- Use of Penrose drains—hematoma evacuation, delayed closure of wounds

Although a wound may initially appear to be avulsive, careful evaluation often reveals little or no tissue loss and thus primary closure is possible[31] (Figure 15-11).

However, when the avulsed facial soft tissue wound is large, it is preferable to suture the oral mucosa to the facial skin mucosa to decrease shrinkage.[18] Avulsed lower lip wounds also benefit from using the tongue as a source of soft tissue and muscle. The tongue is used as a tongue flap and sutured to the skin. The flap is checked for vascularity in 2 weeks by pinprick testing for bleeding and then separated, leaving the anterior tongue flap tissue to fill the avulsed lip defect (Figure 15-12).

Penrose drains are usually not needed for wounds treated and closed in the first 24 hours. Wounds treated after 24





• **Figure 15-11** **A,** Open displaced wound. **B,** Wound, postoperative. The patient sustained a tangential wound that originally appears avulsive. Once the wound and flaps are explored, debrided and re-approximated in the operating room, it is obvious the nose and maxilla were grossly displaced to the right posterior face. This wound has a good prognosis, as the upper lip and nasal complex were intact as seen in the postoperative photo. These wounds benefit from suspension sutures. (Courtesy Dr. R. S. Sadda.)



• **Figure 15-12** Tongue to avulsed lower lip. These patients usually have advanced maxillofacial wounds requiring a tracheostomy. Use of a nasogastric tube (NGT) and NPO diet for a short period may be needed to allow the intraoral wounds to close. Use of the masticatory apparatus as soon as possible will contribute to healing and functional recovery. (Courtesy Dr. R. S. Sadda.)

hours are best treated by delayed closure and placement of a Penrose drain. Complex mandibular wounds that have extensive bony involvement and wounds involving the submandibular space will benefit from the placement of a Penrose drain.[7]

Wound edge debridement of nonviable tissue should preferably be limited to removing 1 to 2 mm of skin. This margin should be non-beveled. When needed, skin flaps can be mobilized by undermining the edges, permitting primary closure of the wound. When using this technique, the extent of undermining should be less than 5 cm, and deep subcutaneous sutures should be placed to reduce skin tension and premature opening of the healing wound. Rotational flaps can be cautiously used to close large, full-thickness soft tissue defects. The design of these flaps must be well planned. The rotational flap should not be brought from an area of the donor that appears unhealthy. Poor choices for donor flaps include dusky appearance and a flap edge that was part of the GSW cavitation. When soft tissue defects cannot be closed primarily using sterile fine mesh, moist gauze may be gently packed into the defect. The gauze is changed daily to successively smaller gauze as the wound begins to heal by secondary intention. A split-thickness graft can be used either initially or in a delayed fashion once the wound that has been packed with gauze begins to reepithelialize.[31]

Small pieces of bone fragments that are attached by periosteum should be left in place. These segments can be gently aligned with 0-chromic gut suture. In the maxilla when the anteromedial or lateral wall bone along with the underlying soft tissue is mobile and fractured, but the sinus drainage is patent, it is recommended to leave the Schneiderian membrane lining in place. Pseudopolyps will occur and then decrease in size, allowing the sinus mucosa to become continuous with the oral mucosa. This process will provide a more cleansable defect than having a split-thickness graft placed acutely to a denuded sinus wall.[18]

Nerve injury repair is done in a delayed process. When the ends of the trigeminal or facial nerve are found during debridement, a tag suture can be placed and the area revisited in a month to repair the defect. Open intraoral wounds will take several days to close. Once the wounds are closed, if the patient's neurologic status and swallowing are intact, they can advance to a liquid diet in addition to intravenous fluids. Extensive soft tissue losses and oral wounds are best treated with a nasogastric tube (NGT), such as a Dobhoff tube, for feedings while these wounds close.

Through-and-through wounds are treated by closure from inside first, then outside once hard tissues and fractures are initially reduced so as not to open closed wounds.[7]

Case Varieties and Management

Many practitioners will plan on definitive surgery for low-velocity, confined GSW's to the maxillofacial region. An example is shown in Figure 15-13, a low-velocity GSW to left lower face with a comminuted mandible fracture and no vascular injury. Such an injury can usually be treated in one or two surgeries.

These fractures can be treated in a multitude of ways. The rationale for open reduction via the simplification method should be discussed. The surgeon is faced with deciding how to stabilize and reduce mandible fractures that are extensively comminuted. Over the past several decades it has stripping comminuted bone may compromise an already compromised blood supply and result in further morbidity for the patient. Historically many of these surgeries resulted in significant osseous loss and morbidity. In fact, surgeons have recently shown that many of these fractures can do well with proper exposure and stabilization. Interestingly, Ellis and colleagues showed a 13.7% complication rate for open reduction of these types of fractures when there were more than five fragments. The complication rate for moderately and minimally comminuted fractures was 6.9% and 4.5%, respectively.[37] Their results showed a statistically significant relationship with non-occlusal complications ($P < 0.01$). Furthermore, the fractures treated with external pin



• **Figure 15-13** **A,** Gunshot wound (GSW), zone III left face and jaw. Patient sustained a single GSW through the anterior face. entering anatomic neck zone III and causing a left comminuted mandible fracture. **B,** GSW, 3D, lateral mandible. **C,** GSW, left mandible. This is an axial computed tomographic view. No hard signs of vascular injury were noted on clinical exam. Note the presence of the impacted third molar in the comminuted fracture. Initial exam of this patient should pay special attention to airway edema and tongue swelling. **D,** Simplification and open reduction of fractures demonstrated. (Courtesy Dr. V. J. Perciaccante.)

stand functional forces.

The technique for open reduction of this comminuted mandible fracture from a GSW is as follows: First, the teeth are rigidly held together by any means the surgeon chooses. Second, the fractured comminuted mandible is accessed via a transcutaneous approach for large fractures. The key point in exposure of the comminuted segments is to maintain lingual periosteum wherever possible. The small segments are brought together using miniplates and lag screws.[33] This part of the treatment is the "simplification" of the fracture in preparation for the locking reconstruction plate. Small stainless steel wires are sometimes utilized as well to stabilize small segments of comminuted bone. (See Figure 15-13, *D*.) The locking reconstruction plate ideally should have three or four bicortical locking screws on each side of the most posterior fracture. The locking reconstruction plate allows several benefits in these cases. Essentially the locking reconstruction plate is similar to an external fixator in the sense that the large reconstruction plate or fixator bar is suspended from the fixation screws or locking implants locked into the reconstruction plate. Thus the plate is not being compressed onto the bone surface, but suspended from the fixation implants that are locked into the double lead threads of the locking plate. This design allows stabilization of the fracture with a plate that is not perfectly adapted to the mandibular bony contour. This is a big advantage, as adapting large reconstruction plates are difficult, and a great deal of experience and time are required to master the technique. The locking reconstruction plate has also been shown to cause less bony deterioration, as it does not compress itself on the bony surface and thus avoids some vascular compromise to the existing and healing bone.[41] Last, the locking screws are unlikely to cause inflammation when they are still present after bone resorbs around the screw because the screw is locked into the plate, unlike conventional AO techniques where the loose screw eventually causes bony

resorption and/or chronic inflammation. These reconstruction plates can be pre-bent preoperatively with the aid of virtual surgical planning and medical modeling. This process can save the surgeon a great deal of operative time.

Repair of Facial Fractures and Low-velocity GSW Injuries

The treating surgeon has many choices for fixation techniques to treat isolated mandibular fractures, avulsive injuries, or a combination of facial fractures all caused by maxillofacial GSWs. Fixation points for dentate segments traditionally include Erich arch bars and Ivy loops. These allow the surgeon to eventually establish maxillomandibular fixation (MMF) occlusion, the first step in the bottom-up method of repair of multiple facial fractures. Establishing accurate occlusion is also used in the inside-out method of facial fracture repair.

More recently, new fixation devices have been used for establishing MMF whether there are teeth present or absent, also known as edentulous segments. Surgeons with experience in rigid fixation or TADs (tissue-anchored devices), or IMF (intermaxillary fixation) screws may be more proficient with these techniques, or even the SMARTLock Hybrid fixation arch bar (an arch bar that is connected to rigid fixation screws; Stryker, Kalamazoo, MI) for the mandible or maxilla. These devices provide rigid fixation to bony structures rather than fixation to dental structures. Thus they provide fixation similar to skeletal wires without the complexities of using skeletal wire fixation. Also, skeletal wires may have tendency to stretch and need retightening of the skeletal wire as well as the maxillomandibular fixation (MMF) during the healing period to maintain stability of the bony segments. Skeletal fixation wiring includes circumzygomatic wires, zygomatic buttress wires, anterior nasal spine wires, pyriform rim wires, peri-alveolar wires, and circummandibular wires. The stainless steel wires used are usually 24-gauge wire for the skeletal fixation and 26-gauge wire for the interconnecting wire. These techniques of skeletal fixation are useful; however, it is unlikely that many institutions are consistently teaching these techniques. The treating surgeon must insist on excellent soft tissue mucosal care for all devices traversing the oral mucosa, as there is a potential for all of these devices to stimulate varying degrees of chronic tissue trauma, hyperplastic tissue, and patient discomfort at the sites of these devices. The peri-alveolar wire technique involves using a hollow spinal needle with a wire driver and air-controlled trigger release to drive the spinal needle through the alveolus. A stainless steel 24- to 26-gauge wire is placed through the hollow bore of the needle, the needle is removed, and then the wire is tightened over a hemostat to create a loop that can be used for fixation.

In addition to these techniques, the use of a 2-mm K-wire for stabilization of the bilateral mandibular interrami combined with circummandibular wires has been described by Shuker.[42] After routine irrigation and debridement, two holes are drilled using No. 6 round burs into the retromolar fossa at the level of the alveolar ridge. Shuker suggests that the maxilla be used as a guide for locating the retromolar fossa drilling sites in cases that have a severely disrupted mandibular arch. He recommends shaping the K-wire into a horseshoe anteriorly. The posterior of the K-wire is made about 1 cm wider to provide a springing action against the muscle pull medially. The ends of the wire are placed into the prepared holes and inserted about 1 cm deep. Proper seating may require gentle tapping to seat the K-wire correctly. He then uses 0.5-mm stainless steel circumferential wires suspended from the K-wire to the larger segments of the mandible. Shuker describes this technique as superior to an arch bar and a replacement for an external fixator because this K-wire device allows stabilization of the fractured body and rami segments of the mandible.[42] Application of the K-wire at the inferior border of the mandible is also useful for avulsive mandibular anterior wounds. In addition, the K-wire will provide a landmark for future dissection during reconstruction of the continuity defect (Figure 15-14).

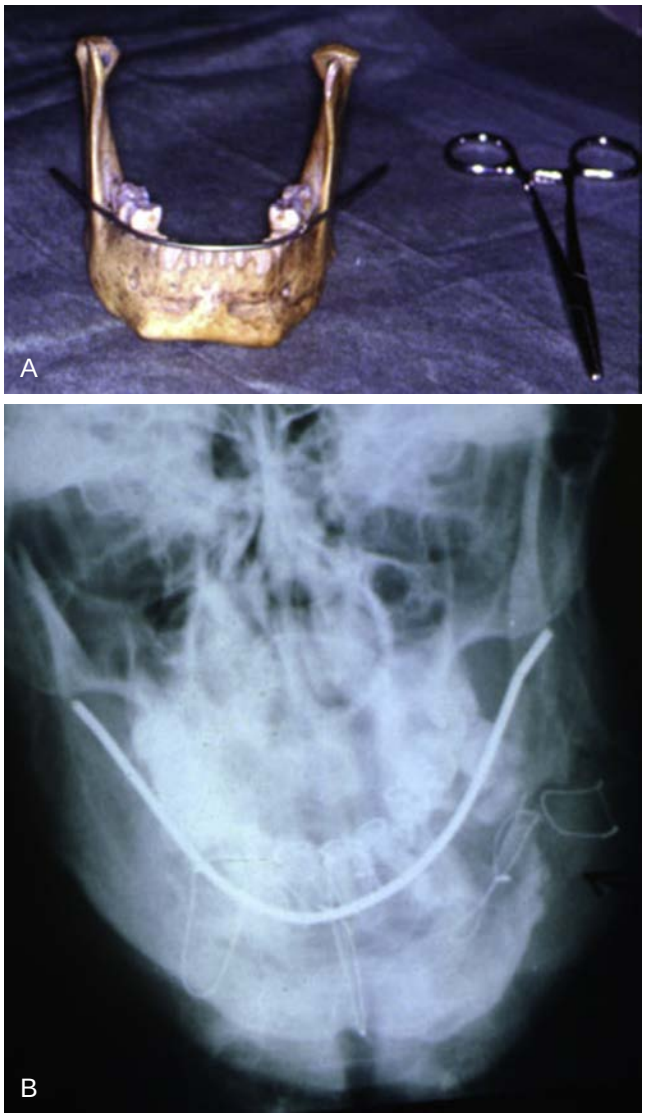
Preparation of the correct curve of the K-wire is essential so the bilateral rami are not excessively splayed laterally. This technique is completed in a short time period and is very useful for initial treatment to allow the patient's soft tissue wounds to be supported by a correctly established three-dimensional structure. This technique is also gentle to the existing soft tissues. The radiograph in Figure 15-14 shows an example of a satisfactory placement of a K-wire in and a mandibular posterior comminuted mandibular fracture.

The K-wire technique has also been a useful and expedient treatment for large avulsive mandibular wounds as seen in Figure 15-15 (avulsive wound) and Figure 15-23 (large avulsive wound).

External Fixators for Maxillofacial GSW Injuries

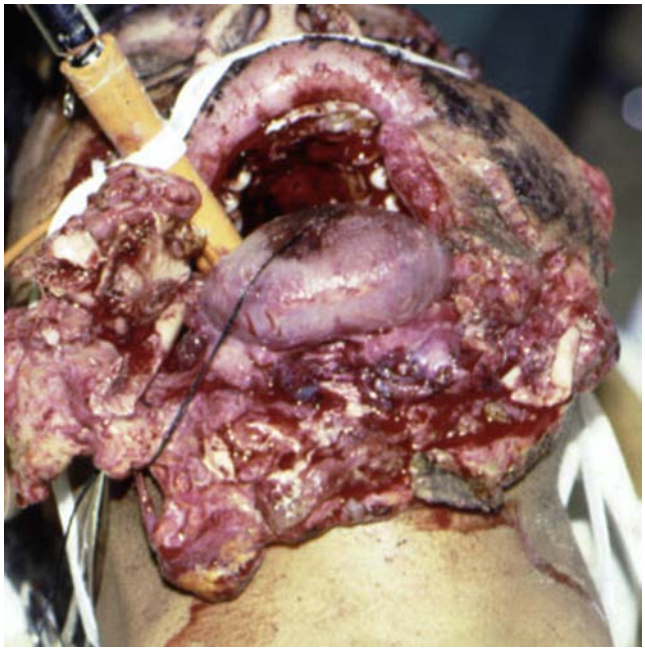
There are generally two types of external fixators that are useful for maxillofacial GSW injuries. The technique is gentle to the soft tissues. Both fixators involve essentially the same primary adjustable metal splint. The primary splint is placed once the facial dimensions—anteroposterior, vertical, and transverse—have been realigned and the occlusion is fixed with any combination of intermaxillary fixation where possible. It is important to note that the bilateral rami will often be splayed laterally and will need to be properly reduced where possible to prevent posterior facial widening. This technique is obviously facilitated when there are condyles attached to the proximal segments. The bone screws can then be placed in preparation for the primary splint that will hold the mandible in place while the secondary splint is placed as either a metal device or an acrylic bar[43] (Figure 15-16).

Key points in using any external fixator include making sure that the surgeon has checked and familiarized himself



• **Figure 15-14** **A,** K-wire preparation. **B,** K-wire radiograph. (Courtesy Dr. R. S. Sadda.)

or herself with all of the necessary armamentarium to place the fixator. A preoperative trial run outside of the operating room manipulating the fixator parts and reviewing the set is recommended. Also, the novice surgeon will often place the primary splint on the superior part of the face rather than under the mandible. This is easily remedied by a simple realignment of the primary splint. The bone screws are different for the ramus and body of the mandible sites. The ramus bone screw has a broad flat base that tapers as it goes away from the bone contact. This allows the ramus bone, which is very flat and cortical, to engage a wide area of the bone screw, thereby preventing displacement. The mandibular body bone screws are narrow at the base and relatively parallel as they move away from the bony contact area. The mandibular body has more cancellous bone in most cases, and this allows more bony contact with a wider area of combined cancellous and cortical bone.[43]



• **Figure 15-15** Avulsive wound and large avulsive wound (see Figure 15-23). Both are examples of large avulsive wounds, loss of mandibular bone, and soft tissue with mobile bilateral rami that benefit from repositioning and fixation. This technique is gentle on the soft tissues and does not require excessive stripping of the bilateral rami to place the K wire. (Courtesy Dr. R. S. Sadda.)

Advantages of the Joe Hall Morris external fixator include the following:

1. Enables the surgeon to establish continuity in very comminuted fractures that are often difficult to reduce with rigid fixation.
2. Decreased surgical time for surgeons skilled in the use of acrylic.
3. Less metal hardware to manipulate as the secondary splint is acrylic.
4. Allows the surgeon to cut the acrylic bar weeks after surgery and "test" the continuity of the bony union. The acrylic can be replaced and the patient left in fixation for continued bony healing, or the surgeon may decide that clinically there is a fibrous union present, and then the patient can be prepped for debridement of the fibrous union and preferably placement of an autogenous iliac bone graft or tibial, cancellous bone graft.
5. Bone screws remain relatively stable to the acrylic bar in comparison to the metal second-stage attachments that often require regular tightening.

Potential disadvantages of the Joe Hall Morris external fixator include:

1. The technique may be cumbersome for the first-time user, especially in complex multi-segmented mandibular GSWs.
2. The fixator may be difficult for the patient to tolerate in warm climates.
3. Bone screws, when few in number, may loosen at the point of bone contact and cause loss of stability of reduced fractures.



• **Figure 15-16** **A,** External pin fixator metal. The metal here is for the second stage attached to the bone screws. Note the dressings of iodoform around the fixation screws. These screws often require repeated tightening during the healing phase. **B,** Joe Hall Morris fixator. Note the acrylic bar and the intraoperative procedure using dressings on top of the skin and under the acrylic bar to decrease any injury from the exothermic reaction of the setting acrylic.[43] **C,** Joe Hall Morris fixator. Fixator is successfully in place even in the setting of significant buccal facial swelling.[7] (**A** Courtesy Dr. V. J. Perciaccante; **B** from Morris JH, Hipp BR: Biphasic pin fixation. In Williams JL, editor: *Rowe and Williams' Maxillofacial Injuries,* Vol. 1, 2, New York, 1994, Churchill Livingstone, p. 337; **C** from Osborne TE, Bays RA: Pathophysiology and management of gunshot wounds to the face. In Fonseca RJ, Walker RV, editors: *Oral and maxillofacial trauma*, vol 2, Philadelphia, 1991, Saunders.)

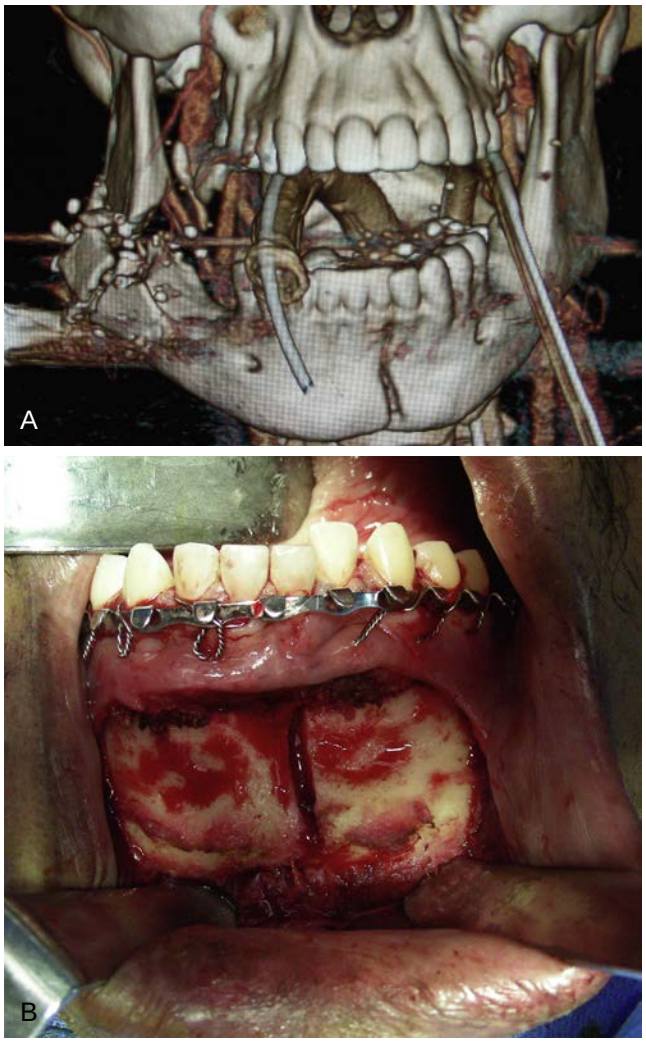
4. Very often the novice surgeon will not manipulate the acrylic correctly over the threads of the fixation pins, and premature setting leads to a large block of wasted operative time during removal of excess acrylic from the bone-screw threaded heads with a burr. There is an inset area at the end of the antitorque wrench that allows the acrylic to be pushed off the top of the threads and thus ease placement for the fixation nut over the acrylic bar.[43]

Complex lower-face GSWs as seen in Figure 15-17 require a combination of techniques to treat the bony fractures. In this case, the patient sustained a zone III injury that resulted in a grossly displaced and comminuted right mandible fracture as well as a symphysis fracture. These fractures were treated by a metal external pin fixator on the right mandible and an open reduction of the anterior mandibular fracture with locking reconstruction plates.

Treatment Phases: Surgical Treatment of Mandible/Maxilla/Mid-face/Upper-face High-energy GSWs

Traditionally, high-energy GSWs to the face were commonly from rifles. Today, high-caliber handguns and IEDs (improvised explosive devices) are common causes of high-energy injuries. High-energy wounds pulverize soft tissues and bone (Figure 15-18).

Management of these complex maxillofacial injuries requires several considerations. Initial treatment is as previously discussed. These complex wounds are demanding because of tissue and bone loss. In addition to this, ophthalmologic and intracranial injuries are common with these complex injuries. Treatment planning for reconstructive procedures is facilitated by production of medical models.



• **Figure 15-17** **A,** Comminuted mandible fractures. Anterior fracture seen as well in 3D reconstruction of computed tomography scan. Note gross flaring and displacement of right posterior mandible. The use of the external pin fixator metal (see Figure 15-16, *A*) allowed the area to be stabilized without gross periosteal stripping of the multiple comminuted segments to place a reconstruction plate. The fixator also allowed for some molding of the bony comminuted fracture that is also grossly flared laterally. This is likely not possible with a simple closed reduction. **B,** Anterior open reduction. Locking reconstruction plates were adapted and applied. This is often difficult in the anterior mandible, as the convexities of the symphysis may cause difficulty in adapting a reconstruction plate. This problem can be alleviated by some bony osteoplasty with a large pineapple-shaped burr to reduce the irregularities before adapting the reconstruction plate.



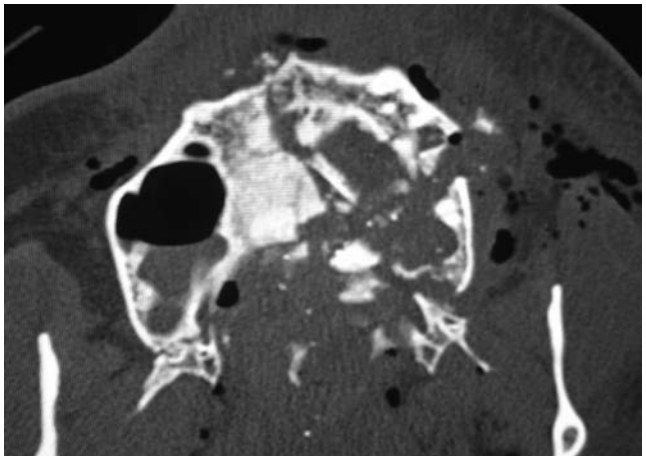
• **Figure 15-18** Characteristic facial injuries caused by an improvised explosive device (IED). Note concomitant burns, tissue loss, shrapnel injuries, ruptured right globe, and avulsed soft tissues. Only a small portion of the left side of the patient's lateral nasal complex was unaffected by this injury. (From Powers DB, Delo RI: Maxillofacial ballistic and missile injuries. In Fonseca RJ, Barber HD, Walker RV, et al, editors: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

These models allow treatment planning conferences and measurements to be more efficient and accurate. The medical models can also be supplemented by 3D CT scanning and virtual surgical planning, such as is commonly done with orthognathic surgery planning and the treatment of dentofacial deformities.

Loss of mandible, lips, nose, and other midfacial tissues requires several tissues to reconstruct these defects. First, of utmost importance is the timing for grafting of onlay bone grafts; for example, calvarial grafts and costochondral grafts to the mid-face or mandible should be postponed until all salivary fistulas have been closed and all intraoral wounds have closed.[44] Contemporary treatment of these complex maxillofacial defects with microvascular free flaps and a skin paddle allows for coverage of the intraoral soft tissue defects and provides a stock of bone that is well perfused. Free flaps used in reconstruction of the hard palate include the scapular, fibular, radial forearm, rectus abdominis, iliac crest, and latissimus dorsi flap. These complex wounds often require many surgeries over several years. Tissue expansion has been used by many reconstructive surgeons and is often fraught with complications.[45]

Special considerations for these complex cases include preparing a problem list for each patient, diagramming all areas of craniofacial fractures and trauma, and a detailed anesthesia plan. Before a discussion with the anesthesia team, the surgical team should discuss with the trauma team the patient's current status, an updated history and physical, and a reasonable idea of how much surgery the patient can reasonably and safely tolerate. Many surgeons will stage complex injuries over several visits to the operating room. Surgical staging for this case may include, for example, placement of a tracheostomy and arch bars as the first surgery followed by definitive treatment of

injuries at another time. Of primary importance in all of these cases is management of the airway and possibilities of nasal intubation versus submental intubation versus tracheostomy. Once this information has been determined, the surgical team should make a detailed surgical plan and a list of needed equipment. One useful item for treating comminuted maxillary fractures is the formation of rigid occlusal surgical splints to establish occlusion and cross-arch stabilization in complex cases (Figure 15-19).



• **Figure 15-19** Comminuted maxillary fracture. When possible, impressions of the comminuted maxilla and mandible will assist in formation of a rigid surgical splint. These splints should have a palatal strap of acrylic that does not contact the soft tissue of the hard palate, and the splint should have buccal holes placed buccal to the contact points of the teeth. These holes will allow wire fixation of the splint to the arch bar.

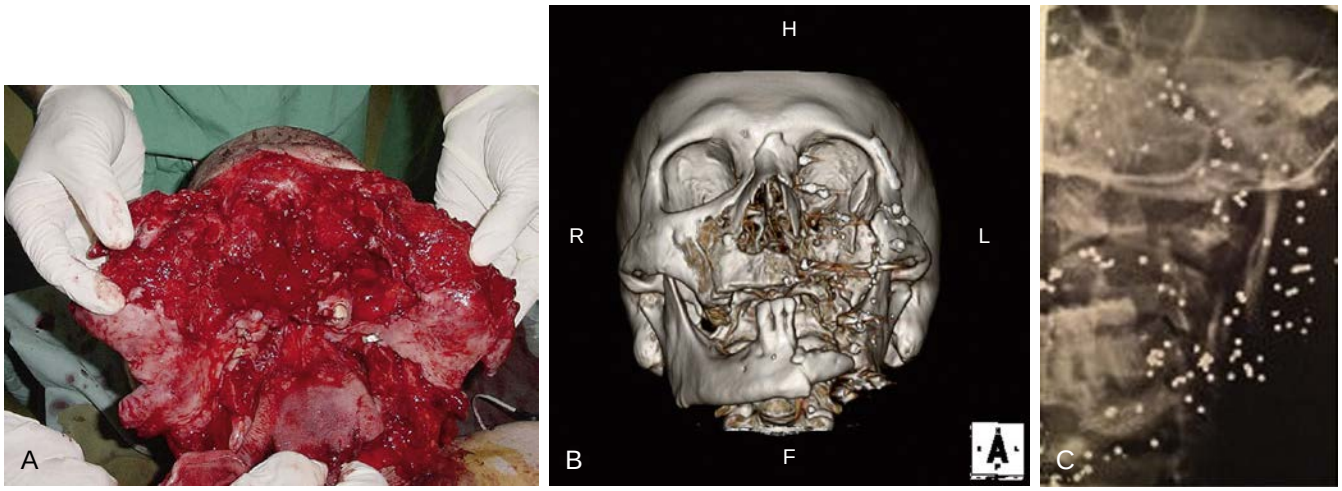
Shotgun Injuries

Type I: long-range, greater than 7 yards, penetration of subcutaneous tissue or deep fascia.
Type II: short range, 3 to 7 yards, penetration of body cavities.
Type III: point-blank range, less than 3 yards, extensive tissue destruction.[46]
(See Figures 15-20 and 15-21.)

Self-inflicted Gunshot Wounds

Maxillofacial GSWs attributed to shotguns have been shown to be suicide attempts in an estimated range of 20% to 76% of cases.[18,46,47] In 2000, the most common method of successful suicide was self-inflicted gunshot wounds (SIGSWs). Furthermore, more than 75% were SIGSWs to the head.[48] Surviving a SIGSW is relatively rare and makes up only 1% of all failed suicide attempts.[49] A poor prognosis for survival includes a Glasgow Coma Scale (GCS) of less than eight.[48,49]

Also, missiles traveling in a sagittal direction are less likely to be lethal as compared to those traveling in a coronal direction. Long-barreled firearms placed submentally may cause a hyperextension of the neck and thus a trajectory that does not enter intracranially. Furthermore, a handgun placed submentally may cause a jerk reflex that also hyperextends the neck and causes the trajectory to miss the intracranial structures.[1,13] Trauma to the periorbital region is a major concern and requires immediate ophthalmology

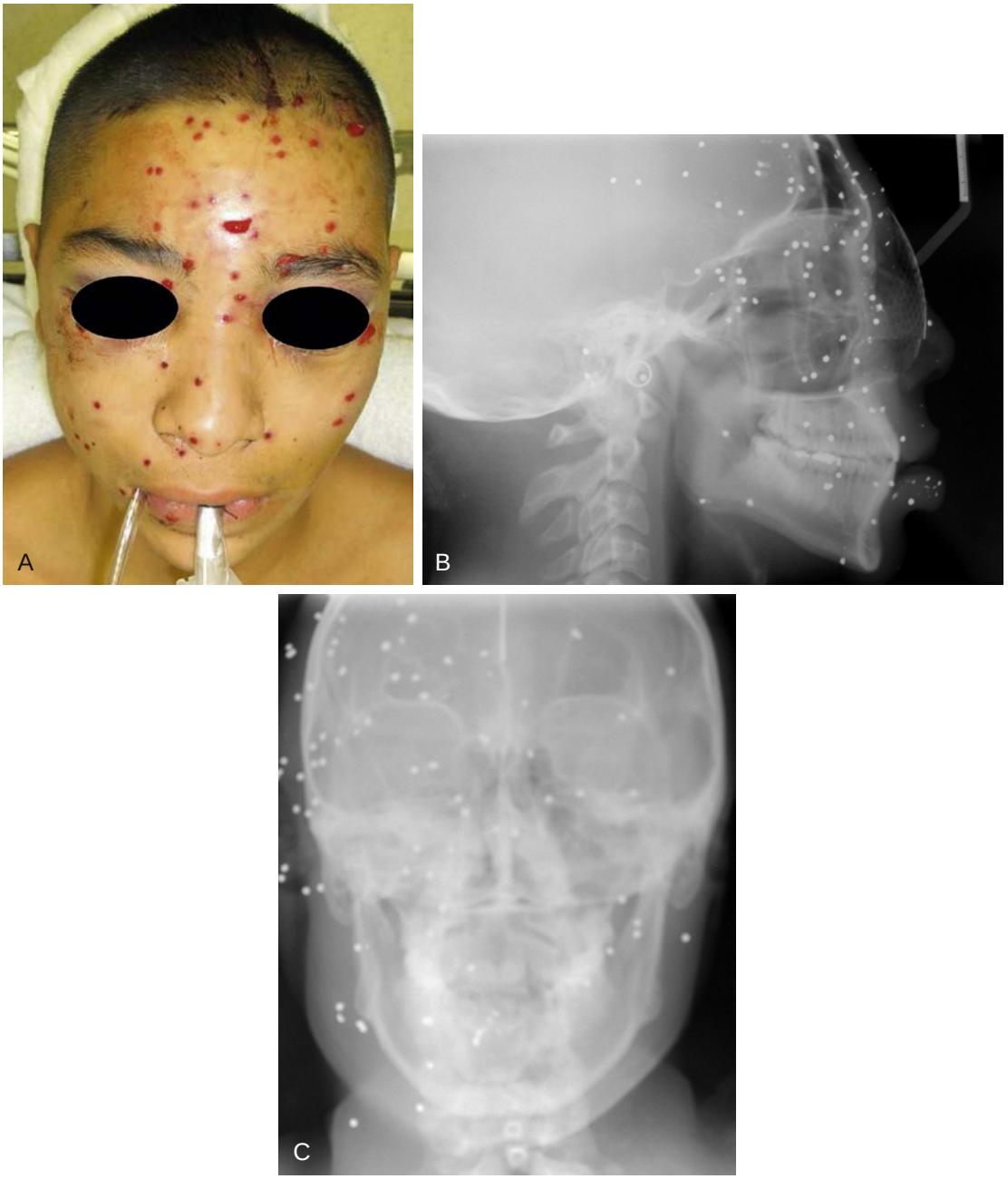


• **Figure 15-20** **A,** Self-inflicted shotgun wound in a suicide attempt. Note significant hard and soft tissue disruption and avulsion (Sherman and Parrish, Class III; Glezer, Class III). **B,** Three-dimensional reconstruction of computed tomography scan showing the degree of hard tissue loss experienced in a suicide attempt with a high-energy weapon. **C,** Class III shotgun wound, lateral plain film. Note hard tissue injury as well as concentrated shrapnel. (**B** From Powers DB, Delo RI: Maxillofacial ballistic and missile injuries. In Fonseca RJ, Barber HD, Walker RV, et al, editors: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders. **C** From Osborne TE, Bays RA: Pathophysiology and management of gunshot wounds to the face. In Fonseca RJ, Walker RV, editors: *Oral and maxillofacial trauma*, vol 2, Philadelphia, 1991, Saunders.)

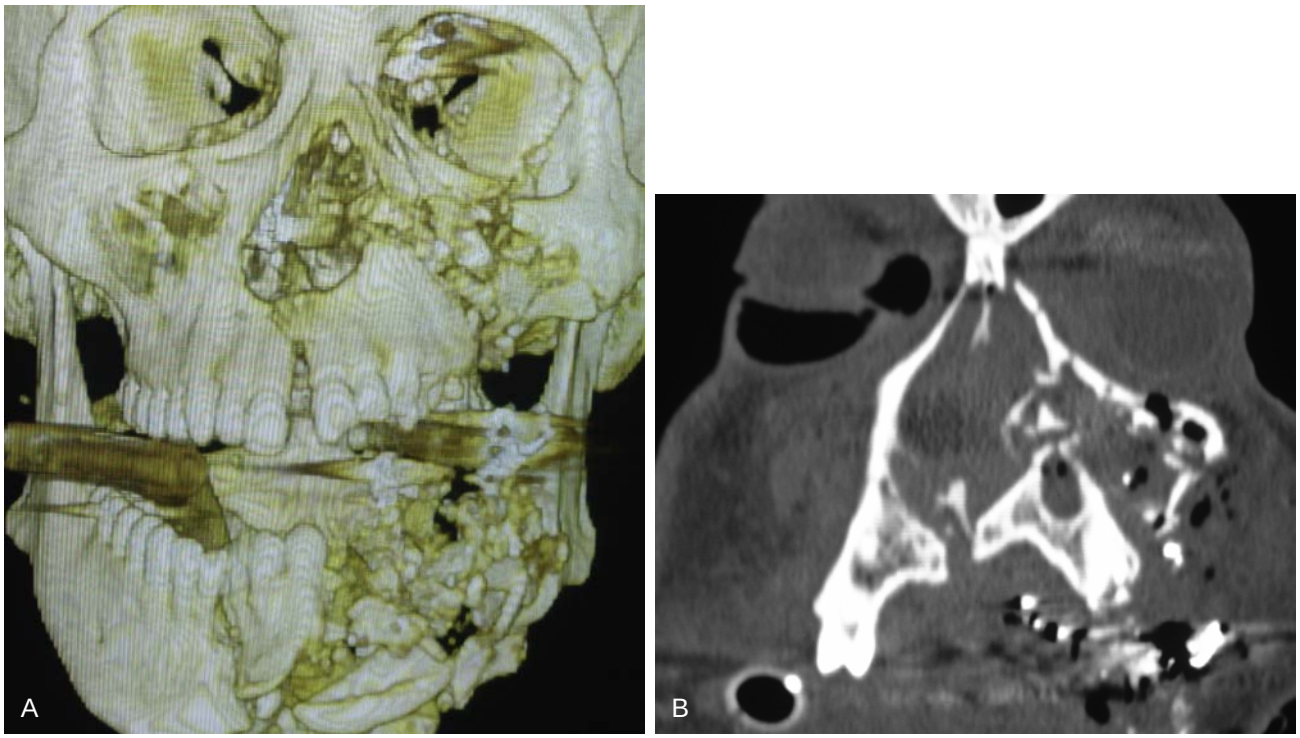
examination; needed reconstructive procedures must be performed promptly. Many of these patients can be restored to functional vision despite the apparent devastation that may be seen during initial examination[50] (Figure 15-22).

These GSW victims sustain injuries that cause gaping wounds and extensive comminuted facial fractures. Shotgun wadding and pellets are often found scattered in the facial soft tissue wounds. In general, if a maxillofacial GSW victim arrives alive in the emergency room, there is a high survival rate in the absence of intracranial wounds.[29] These wounds will require several debridements until all nonviable tissue is removed and flap advancement or other techniques can be used to provide proper tissue bulk.[18]

The general treatment sequence for maxillofacial shotgun GSW injuries includes all of the previous listed treatments. In addition to these items, wadding and pellets just under the skin should be removed. Those that are deeply embedded should be left in place, as their



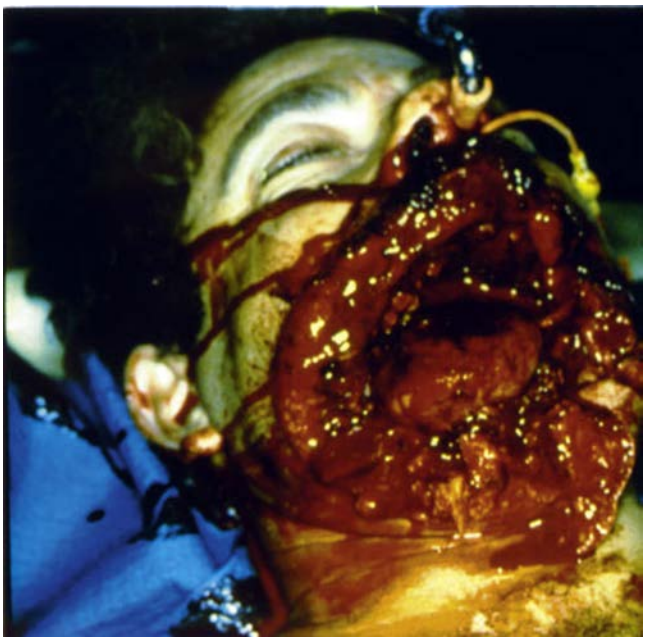
• **Figure 15-21** **A,** Characteristic facial appearance of a patient sustaining a shotgun wound from a distance. (Sherman and Parrish, class I; Glezer, class I). Note the presence of multiple punctate entry wounds, but no significant disruption of the facial features. **B** and **C,** Classic radiographic appearance of a patient sustaining a shotgun wound from a distance (Sherman and Parrish, class I; Glezer, class I). Note the presence of multiple shotgun pellets on the radiographs. (From Powers DB, Delo RI: Maxillofacial ballistic and missile injuries. In Fonseca RJ, Barber HD, Walker RV, et al, editors: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)



• **Figure 15-22** **A,** Self-inflicted gunshot wound (SIGSW), hemifacial and left frontal lobe. 3D reconstruction computed tomography: This patient sustained a comminuted mandible fracture, maxillary fracture, orbital fracture, and anterior cranial fossa trauma from a SIGSW. **B,** SIGSW coronal view CT.

removal may be destructive and cause iatrogenic injury. These wounds are not to be closed primarily in the early post-injury period, as abscess and soft tissue infection may occur. When there is an ensuing infection, it is treated by opening, draining, and debriding the wadding and pellets. Occasionally through-and-through drains may be needed for continuous irrigation of a grossly infected wound. Appropriately directed antibiotic treatment directed by culture and sensitivity results is prudent. Contemporary medicine suggests that the surgeon should adhere to a treatment protocol for judicious use and overuse of antibiotics.

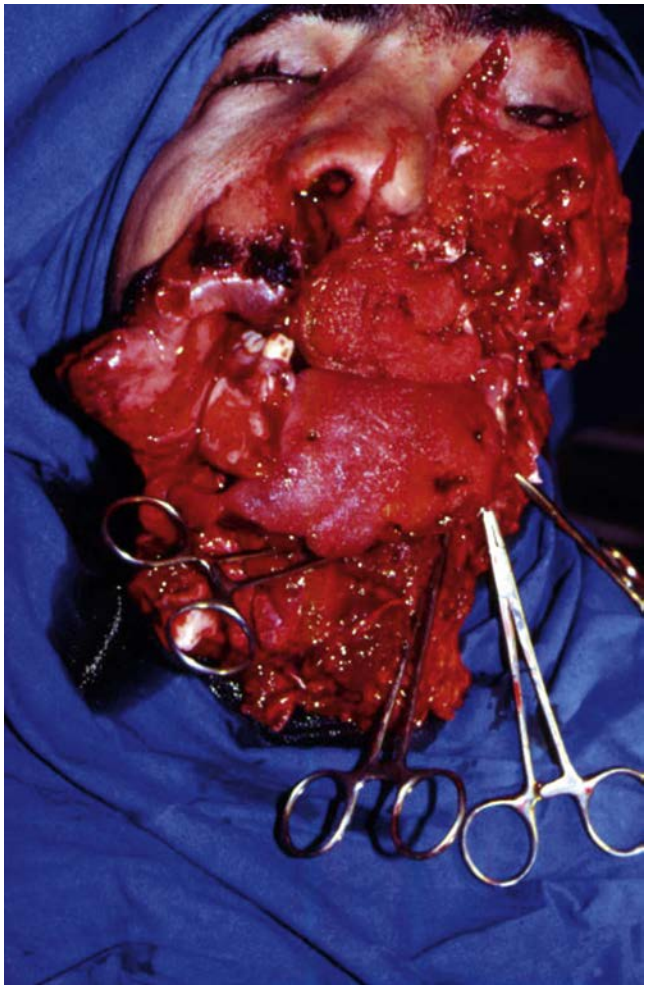
A suicidal person who uses the shotgun in a submental position often blows off the anterior face and avoids intracranial injury. These patients will have excessive anteroposterior facial dimension loss due to bony and soft tissue destruction. Moreover, these cases will involve several surgeries before all of the nonviable soft tissue can be removed. These "second look" explorations help to avoid complications by using judicious, definitive debridement to avoid tissue loss and infection. The surgeon should not be focused on defining the areas of extent of damage at the first exploration, as sequential explorations will confirm the expectation that the wound is a high-energy injury by the obvious pattern of evolving tissue necrosis over time. This first look will also allow the surgeon to set the threshold for future re-exploration. Major issues are large losses of the mandibular and maxillary bone. One study showed that



• **Figure 15-23** Large avulsive wound. This patient has gross soft tissue and bony loss of the lower face and mandible. Nasal intubation was possible to secure the patient's airway.

27% of the avulsive tissue loss in these injuries is the mandible[47] (Figure 15-23).

Debriding loose, non-periosteal attached bone, debriding and irrigating the wounds, and allowing for reduction and establishment of correct facial dimensions must be a



• **Figure 15-24** Avulsive flap. This is a complex gunshot wound to the maxillofacial region. The patient received a tracheostomy urgently. Gross displacement of the naso-orbito-ethmoid on initial exam is significant. Unfolding and evaluation in the operating room will likely reveal deeper damage extending to the frontal bone. Cerebrospinal fluid leaks are likely in these wounds. (Courtesy Dr. R. S. Sadda.)

priority.[18] If the mandible is involved with a major, multifragmented, comminuted mandible fracture (including damaged intraoral lining), approximately 35% of patients will have failed primary, immediate grafts and develop localized sepsis, persistent fistulae, wound breakdown, and graft loss. The key point many surgeons miss is that they underestimate the need for replacement of vascularized lining before nonvascularized bone grafting. Some surgeons also recommend post-grafting soft-tissue rest, a brief period of intermaxillary fixation, in patients with severe soft tissue injuries.[47]

These complex injuries often reveal deeper skull base injuries when the tissues are unfolded and explored in the operating room. For example, a complex deep injury may have obliterated bone extending into the anterior cranial fossa (Figure 15-24).

These injuries may present with cerebrospinal fluid (CSF) leaks due to damage through the cribriform plate. Neurosurgical consultation and surgical intervention by way of frontal bone bloc osteotomy and pericranial flaps are often used in conjunction with a lumbar drain to treat the CSF leak originating from damage to the dura at the cribriform plate and crista galli. The frontal bloc osteotomy gives the reconstructing surgeon the opportunity to use the inner table of the calvarium to harvest an inner cortex bone graft to reconstruct the nasal dorsum. Another key clinical pearl is that these complex naso-orbito-ethmoid (NOE) and deep fractures are best reconstructed in one surgery when possible—it is very difficult to reconstruct the adjacent structures in multiple sequential surgeries because of scarring and difficult access.

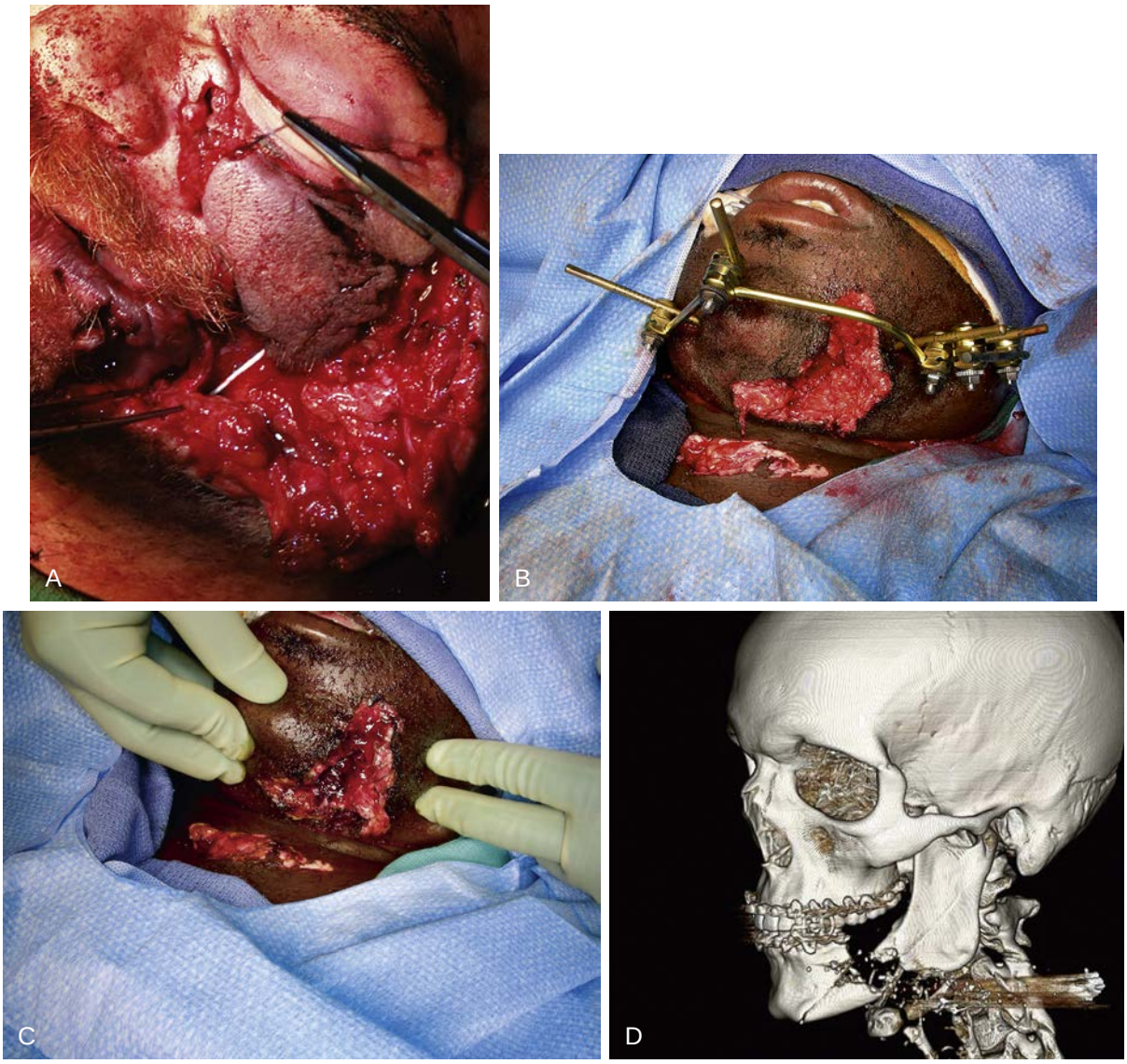
Reestablishing the intercanthal width in complex NOE trauma is difficult. These procedures require multiple surgical access incisions. Using C-shaped 2.0-mm flexible plates to connect structures high and low enables the surgeon to manipulate and narrow the radix area, thus correcting the traumatic telecanthus. Holton recommends a goal of 22 mm of bony reduction at the radix. The 22 mm, plus 5 mm on each side for the length of the medial canthal ligament, yields an intercanthal distance of 32 mm. The nasofrontal, nasolacrimal, and salivary ducts should be assessed and repaired as early as possible (Figure 15-25).

Furthermore, suspension of the facial muscles and tissues in the infraorbital region is done with suspension sutures. This technique uses a 1.2-mm titanium screw into the infraorbital rim to suspend and prevent sagging of the repaired issues.[51]

Intermediate Phase

A definite intermediate phase of treatment for maxillofacial GSWs may meld into the reconstructive phase. This is largely determined on an individual case basis. Regardless of the individual case, some of the components of the intermediate phase include supportive care and the prevention of complications. Supportive care includes nutritional needs and dealing with the challenges the maxillofacial GSW victim is faced with, including dysphonia, dysphagia, mucosal moisture changes, and neurosensory changes. Early function of these patients and use of the masticatory system enables increased blood flow and improved healing with increased presence of oxygen and nutrients to the healing tissues. Included with the masticatory function is maintenance of oral health, increased range of motion of the mandible, and decreased pain. Other supportive care includes ongoing psychological care, as many of these patients are victims of violence and frequently SIGSWs. In addition to this, ophthalmologic care must be continuous, as functional vision should be a priority. Neurologically improving the patient's cognitive function in those with brain injuries is essential. Many of these patients will require both occupational therapy and physical therapy for an extended amount of time.[7]

Prevention of complications includes monitoring for hemorrhage, infection, and further wound breakdown and



• **Figure 15-25** **A,** Cannulation of the severed parotid duct with Silastic tubing. All ballistic injuries to the craniomaxillofacial complex should undergo evaluation under some form of magnification for potential remnants of the salivary ducts and cranial nerves because primary repair is best accomplished at the time of initial injury. **B,** High-energy gunshot wound to the anterior mandible. Note the presence of soft tissue disruption and a second gunshot wound across the anterior neck, glancing off the surface epithelium and providing only superficial injury to the platysma. **C,** Initial stabilization of the patient was accomplished with an external fixator secondary to the presence of other life-threatening gunshot wounds that were sustained

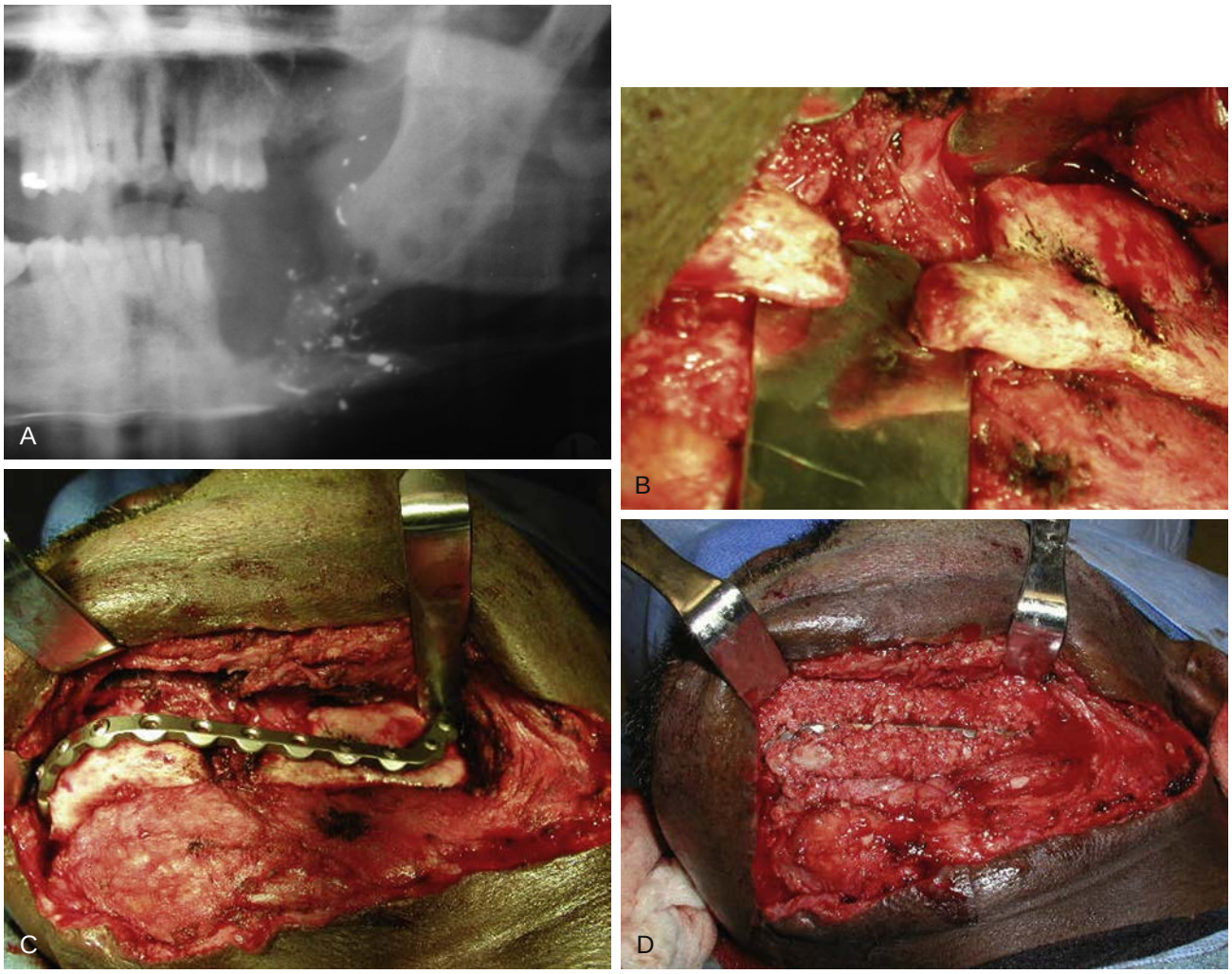
reconstruction plate and corticocancellous bone graft from the anterior ilium. **D,** Three-dimensional reconstruction of computed tomography (CT) scan indicating the degree of comminution and avulsive bone loss associated with this gunshot wound. The projectile can easily be identified at the bottom right of the CT scan. (From Powers DB, Delo RI: Maxillofacial ballistic and missile injuries. In Fonseca RJ, Barber HD, Walker RV, et al, editors: *Oral and maxillofacial trauma*, ed 4, St Louis, 2013, Saunders.)

bony sequestration. Wound care is essential, and for the patient who goes home with dressings, it is essential they receive immaculate wound care in a timely fashion.

Looking forward to the preparation for the reconstructive phase of treatment, it is essential that the patient's updated condition be continually documented, with consultations obtained as necessary. Imaging should be updated and medical models prepared as necessary. The overall goal is eventual reconstruction with adequate hard and soft tissues as well as a functioning dentition.

Reconstructive Phase

Traditionally the bony reconstructive phase for these wounds has been delayed several months, as nonvascularized grafts require watertight, sealed soft tissue margins. Continuity



• **Figure 15-26** **A,** Panograph of post–gunshot wound defect. Continuity defect, left body mandible. Note shrapnel in wound and superior rotation of proximal ramus segment. Control of the proximal segment is easier once a coronoidectomy is completed on the ipsilateral side. **B,** After debridement. Note removal of all soft tissue from proximal and distal bony stumps. Copious irrigation with normal saline is done in preparation for the corticocancellous graft. **C,** Locking recon plate. Immobility of the graft is essential for bony healing. Alternative technique to recon plate: One should cautiously use the correct titanium mesh crib when restoring continuity defects. It is essential that the crib be rigid enough to prevent micromovement that may lead to a failed attempt at bony consolidation and thus not allow a bony union with the native mandibular stumps. **D,** Graft in situ. Note the overpacking of bone graft. This is a useful technique, as some resorption of the bony graft is expected. (Courtesy Dr. V. J. Perciaccante.)

and large defects are primarily grafted simultaneously when the overlying tissue is healthy.[52] To review, healthy tissue includes closed intraoral wounds, lack of infection, and lack of fistulae. The bone grafting material of choice is autogenous bone, as it revascularizes rapidly and is relatively resistant to infection. The tibial bone is recommended by many as the preferred site for harvesting copious amounts of marrow.[33] Many surgeons successfully use corticocancellous iliac grafting, both anterior and posterior, with a reconstruction plate or a titanium mesh crib for reconstruction of maxillofacial GSW continuity defects. These grafts will consolidate well in 6 months and allow reconstruction of the defect with dental implants and subsequently oral reconstruction. Many of these defects will also need soft tissue revision and vestibuloplasty as well as soft tissue grafting procedures because of inadequate firm tissue at the recipient dental implant site (Figure 15-26).

Key points in reconstruction of jaw injuries:

- Maturation of involved tissue should precede reconstruction or correction.
- Sufficient soft tissue cover, extra and intraoral, must be provided to permit adequate bone contour restoration. This is also called "lining" in many references written on GSW.
- Skin graft shrinkage will happen, and when the scar defect is released, it usually assumes proportions larger than initially visualized.
- Facial bone loss benefits from iliac grafting.
- Fixation and immobilization are essential for successful bone grafting.[18,47]

Each reconstruction case is managed on an individual basis. Mid-face and upper-face avulsive bony and soft tissue loss reconstruction will involve many surgeries over a span of time. Traditionally, reconstruction procedures have included calvarial grafts, costochondral grafts, iliac grafts, cranioplasty, and oculoplastic reconstructive surgeries.[47] Many injuries that will be planned for vascularized soft and hard tissue reconstruction may be reconstructed before the intraoral lining has completely healed, as providing soft tissue with the vascularized graft corrects for this problem. Also, defects involving the anterior of the mandible and defects larger than 10 cm often do well with vascularized osteocutaneous free fibula grafting. This technique allows a soft tissue paddle attached to a significant stock of bone to restore both bony and soft tissue defects. This bone can be used for immediate or delayed dental implant placement. When necessary, the free fibula can be used as a double barrel to provide additional height that mimics the shape of the mandibular alveolus. A reconstruction plate similar to the one used to stabilize the bilateral remaining mandible is used to attach the fibula graft. The graft is anchored with smaller diameter screws, placed monocortically, than fixation screws used to fixate the reconstruction plate to the existing native mandibular stumps. A combination of costochondral grafting attached to a rigid fixation reconstruction plate is possible, although it may be difficult to stabilize the soft costochondral graft. The costochondral graft is insufficient in bulk when used to restore the mandibular body region in combination with dental implant reconstruction.

A costochondral graft to restore the ramus and condylar segments has been used with a reconstruction plate. Also, a custom-made alloplastic implant has been employed, attaching a custom-made mandible seated into a custom-made fossa implant. A less commonly used technique to restore mandibular continuity in GSW defects is osteogenic distraction, also known as distraction osteogenesis. In 2005, Labbé and colleagues reported a series of 11 cases of mandibular continuity defects treated by osteogenic distraction.[53] On average their patients achieved nearly 8 cm of linear bone growth by way of the osteogenic distraction technique. Their recommendation is to use the trifocal technique. This technique involves one bone segment mobilized on each side, and thus two distracted foci and one consolidation focus. Osteogenic distraction can be used to reconstruct several different tissue types. In addition to bone elongation, it results in the formation of new skin, muscles, and subcutaneous tissues. All the tissues from skeleton to skin are elongated simultaneously without the inconvenience of skin expansion and with optimal aesthetic results. As distraction proceeds, the superficial tissues are elongated considerably more than the bone. This technique has disadvantages, such as the need for at least two surgeries. One surgery is for corticotomies and distractor placement, and the other is for at least removal of the distractor. At the time of distractor removal, a reconstruction plate and additional bone grafting may be needed. Very often the chin area requires additional grafting for esthetic purposes in these distraction cases. Another disadvantage can be the unsightly scars from the distractor fixation pins.[53]

Severe avulsive GSWs of the maxillofacial region have been treated with near-total face transplantation. One near-total face transplantation was done at the Cleveland Clinic in 2009. A 41-year-old woman had sustained a shotgun GSW to the maxillofacial region approximately 5 years prior to the face transplantation. Her injuries included severe damage to her mid-face, which included amputation of her nose, cheeks, upper lip, right globe, upper jaw, and maxillary alveolus and associated teeth. She was left with 20/200 vision in her left eye, and she had no function of smell because of a blocked nasal passage. Her main nutrition was by a percutaneous endoscopic gastrostomy tube. She had bony defects of her palate, maxilla, bilateral zygomas, bilateral orbits, and nasal bones. During a 5-year period she had more than 20 reconstructive surgeries. These surgeries still left her with a tremendous tridimensional defect of the craniofacial skeleton. It is estimated that soft tissue coverage of a full facial/scalp deficit would require more than 1200 cm^2 of autologous tissue provided in one flap. The largest autologous flap available from the human back by a scapular-parascapular flap is less than half of the total needed for a full facial/scalp defect. This patient successfully underwent the near-total face transplantation and did well. She was truly dedicated to engaging in the required physical therapy, speech therapy, and facial reanimation. As a result she was able to regain most of her missing facial functions of nasal breathing, sense of smell, drinking from a cup, eating solid foods, and speaking intelligibly. Sensory healing in the facial region provided a 7-mm two-point discrimination upon neurosensory testing.[54] Overall, this was an incredible accomplishment for a tremendous problem; however, this therapy was only made possible by an enormous effort of the patient, the appropriate location of a donor, the formation of an exceptional harvest and transplant team, an exceptional health care system/institution, and substantial funding. Perhaps this therapy will be used more in the future for other extremely complex craniofacial defects secondary to GSWs.[53]

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16

Oral and Maxillofacial Pathology: Available Diagnostic Techniques and Surgical Interactions

J. MICHAEL McCOY

Introduction

Surgical pathology is the specialty of medicine/dentistry that deals with the pathologic characteristics of hard and soft tissue removed from the living patient. The tissue removed includes not only the solid tissue seen in biopsy material, but also the cells seen in smears, aspirates, and tissue core biopsies. The surgical pathologist must be proficient in the evaluation of all types of cellular tissue. This includes normal as well as abnormal.

Unlike autopsy pathology, the decisions made by the surgical pathologist are often rapid and occasionally immediate. The rendered diagnosis frequently precedes the patient's treatment and, in many cases, influences or even dictates the exact nature of this treatment. In addition, the surgical pathologist also functions as a teacher or consultant. Such consultations should always benefit the patient as well as the clinician, even though the surgical pathologist works in a laboratory without true patient contact.

Historical Perspective

In times past, the surgical pathologist was situated in a division of surgery or at least closely affiliated with such a clinical department. Oftentimes, the examination of tissue removed from the living patient was relegated to the pathology resident. With such assignment came delays of pathology reports, and in some cases the report only stated "benign" or "malignant." Under such conditions the clinical surgeon's diagnoses and treatment recommendations were often much more appropriate than those of the undereducated and occasionally uninterested pathology resident. Even so, it was almost impossible to be a competent clinician and a skilled pathologist simultaneously. Yet, during these earlier times, there were those exceptional individuals who not only were skilled pathologists but, in addition, introduced numerous important contributions to their respective surgical disciplines.

In the first half of the 20th century, the technology of tissue fixation, staining procedures, and microscopic discrimination progressed rapidly. Immunostaining was initiated in the 1960s. Enzymatic immunochemistry and monoclonal antibody staining became widely used in the as many others allowed the surgical pathologist the ability to help recognize and categorize a multitude of human pathologic disease states.

Even though the title *surgical pathology* implies surgery, the surgical pathologist is actually closely related to all medical/surgical disciplines. These medical and/or dental professionals have the unique position of seeing both the beginning of a disease and the end point of many pathologic processes. The oral and maxillofacial surgical pathologist must have an extensive background in clinical medicine/surgery, but must also be quite thoroughly familiar with his or her own specialty. With the utilization of all the available diagnostic modalities comes the surgical pathologist's obligation to correctly discern among such testing methods, thus leading to a useful definitive diagnosis rather than just a myriad superfluous esoterica.

Surgeon/Pathologist Interaction

In order for any pathologic test to be *successful* (i.e., beneficial for the patient), the pathologist and the surgeon must communicate well. The importance of such a cohesive relationship cannot be stressed enough. It is imperative that each professional recognize the other's skills well enough that the

ultimate outcome will be exceptional patient care. Guided interaction should be the norm rather than the exception.[1]

A predicament that always appears to accompany laboratory analysis is a reasonable timetable for results. Several pathologic studies such as the frozen section must render an immediate diagnosis. Many others, such as the culture of an acid-fast bacillus, may take several weeks. During this longer time frame, the surgeon often becomes quite anxious, as these surgical clinicians are the ones who must ultimately deal with the patient and the related family. Realistic expectations should arise from prior reporting of earlier patient studies as well as turnaround times routinely published by the laboratory. The surgeon should always stay attuned to the needs of the pathologist. If the surgeon considers lymphoma as the diagnosis, tissue should routinely be submitted fresh for immunologic assays. Tissue that needs a bacterial or fungal culture should not be submitted in formalin. Technical advances must be followed closely by both the surgeon and the pathologist. In this way, such improper specimen handling will be discouraged.

Biopsy Techniques

A biopsy is defined as the removal of a small piece of tissue from a larger mass or tumor. This small fragment is then analyzed under a microscope in order to determine a specific diagnosis. The basic technique of tissue biopsy and its subsequent handling has undergone very few changes since its introduction many years ago. The handling, processing, and pathologic evaluation of this biopsy material are without a doubt the most important duties of the surgical pathologist. The surgeon should always remember that the pathologist cannot diagnose a specific disease entity if the biopsy material is not representative of that disease.

knife are often unsatisfactory because of the cellular cautery artifact seen under a microscope. If the patient presents with a large aggregate of lymph nodes, a biopsy of a peripheral node may not be as representative as one from the central portion of the mass. Biopsies removed from a tumor near an ulcerated area can frequently show only necrosis and inflammation. If a lesion is ulcerated, the biopsy should include both normal tissue and the ulcer. Although it is oftentimes not the ideal tissue fixative, 10% formalin is the fixative solution most often used today. The biopsied tissue should be placed immediately into this fixative and transported to the pathology laboratory within 24 hours.

The choice between an incisional or an excisional biopsy should be carefully considered before the biopsy procedure. The biopsy of an oral malignancy should not be of an excisional type, as such a procedure may leave no remaining visual landmarks of the original tumor. At the time of resection, the oncologic oral and maxillofacial surgeon may then be left with inadequate information regarding sufficient tumor margins.

Frozen Section

In the early 1900s, the frozen section, also known as the cryosection, was first discussed in the medical literature as a means to rapidly identify biopsy specimens. An instrument known as a freezing cryostat was later used to rapidly prepare biopsy material for the pathologist to evaluate. A reliable cryostat must be able to cut tissue specimens 5 to 10 μm in thickness after the tissue is flash-frozen to −20° to −30° C. The development of the freezing cryostat in the late 1950s led to the extensive use of the frozen section in today's hospital pathology departments. It was during this same latter time period that the frozen section was accepted as a valid diagnostic test.[2]

A frozen section should be accurate, rapid, and reliable. The use of this interpretive tissue assessment demands that the surgical oral and maxillofacial pathologist have a well-balanced clinical background as well as be proficient in the needed microscopic analysis. Before viewing the frozen tissue, the pathologist must be thoroughly briefed on the clinical nature of the patient's problem. While viewing the gross biopsied tissue, he or she should ask the surgeon's advice on the correct area of tissue to be microscopically examined. As often as not, complete sampling of large tissue specimens is limited because of time and equipment constraints. Consequently, judicious tissue sampling is of paramount importance. Similar, although not identical, problems arise in the sampling of smaller tissue biopsies. If at all possible, some of the biopsied tissue should be saved for permanent microscopic examination and only a tiny fragment used in the frozen section diagnosis. Once again, discussion of the case with the involved oral and maxillofacial surgeon can often create a tremendous difference in the ultimate outcome of the biopsy material.

The frozen section can be of great value to the oral and maxillofacial surgeon, but the surgeon and pathologist both should agree that such a test should only be used when the interpretation can provide information of immediate or ultimate value in the patient's management. A diagnostic frozen section generally should not be used if a more definitive surgery is contemplated at a later time. For such surgery, the classic biopsy using tissue fixation would be more appropriate. The surgeon should remember that the examination of frozen tissue is a great deal more difficult than examining properly fixed tissue. Examples of noncontroversial indications for the use of a frozen section during surgery include:

1. The diagnosis may influence immediate surgical management
2. The lesion is not accessible or the patient not amenable to preoperative biopsy
3. Preoperative biopsy attempted but was not successful
4. Staging of malignant neoplasms
5. Assessing the adequacy of excision
6. Procuring tissue for ancillary studies

The frozen section type of tissue examination should *not* be used in order to facilitate immediate discussion with the

patient or patient's family. One should always remember the fragilities of the frozen section's diagnostic abilities and thus the possibility of an inaccurate or incorrect immediate diagnosis.[3] In addition, it should be kept in mind that in this new age of medical care and its reimbursement, the frozen section not only raises the cost of the procedure but also increases the time the patient will be placed under a general anesthetic.

The surgeon and the pathologist should carefully consider all the viable options before considering the frozen section. At this time, the surgical pathologist should confirm the following conditions are met: (1) There is no risk of compromising the tissue specimen, (2) there is significant tissue for all ancillary studies, (3) there is a high probability of rendering the correct diagnosis, and (4) there is little risk of conveying incorrect diagnostic information. Then and only then should the frozen section examination proceed.

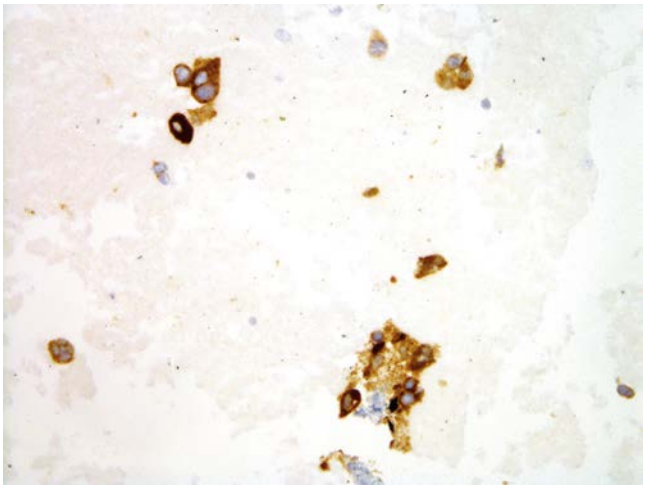
Aspiration Biopsy Techniques

The fine needle aspiration biopsy (FNA, FNAB) has enjoyed a clinical rebirth in the past 15 to 20 years. As an extremely cost-effective procedure, the FNA is now a commonly used method of diagnosis when dealing with neoplastic disease.[4] This procedure is performed not only by surgeons and pathologists, but also by many other medical/dental specialists such as internists, endocrinologists, and gastroenterologists. The recent advent of various imaging modalities such as computed tomography (CT) and ultrasound has stimulated radiologists to commonly perform FNA biopsies as well.

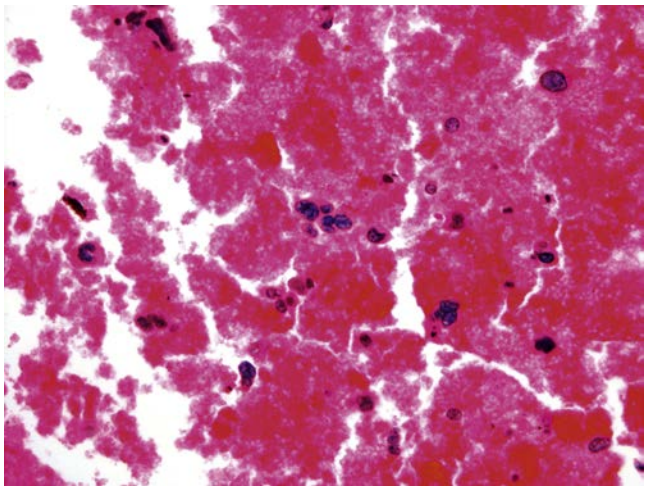
The crucial factor in the use of FNA is that, regardless of which medical or surgical specialist performs the procedure, he or she must be adequately trained in all aspects of lesion sampling and cell/smear preparation. Various stains of the cytopathology specimen are available, including routine hematoxylin and eosin (H&E), Papanicolaou (Pap), and Wright-Giemsa (Figure 16-1). In recent years, immunofluorescent and immunoperoxidase stains have proven to be quite useful in the determination of tumor tion with the cytopathologist is essential.[5]

Exfoliative Cytology

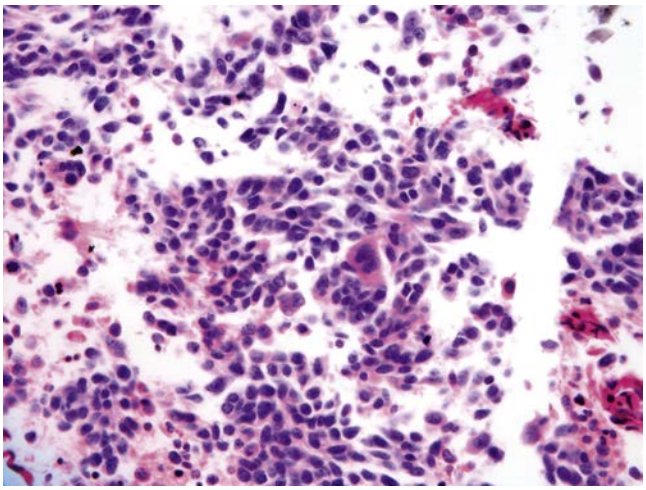
Oral exfoliative cytology has become extremely popular in the United States during the past 25 years. There is no doubt that the clinical brush biopsy technique and the Papanicolaou stain used by medical/dental generalists and specialists alike have resulted in the marked increase in the detection of early-stage oral/oropharyngeal cancers. This variation has also been successful because of the relatively long pre-invasive phase of oral squamous cell carcinoma.



• **Figure 16-2** These same cells proved positive with a chromogranin immunostain that commonly stains neuroendocrine cells (400×, chromogranin).



• **Figure 16-1** This represents a fine-needle aspiration (FNA) biopsy obtained from a patient with a solitary neck mass. Note the numerous cohesive islands of rather bland, monotonous, relatively round tumor cells (400×, Pap).



• **Figure 16-3** After review of the fine-needle aspiration seen in Figures 16-1 and 16-2, the primary tumor was found to be a carcinoid tumor of the small bowel as seen here, metastatic to the neck. Note the similarity of the small round cell population of both tumors (400×, H&E).

Some authorities believe that exfoliative cytology has little use in areas such as the oral cavity that are readily accessible for an open biopsy. It also makes little sense to use such a diagnostic technique as an oral screening tool in asymptomatic patients except under special circumstances. Still, evaluation of red, white, or mixed oral lesions using brush biopsy (cytologic) technique is a tool easily mastered by non-surgeons such as dentists, internists, or family medicine physicians.[6]

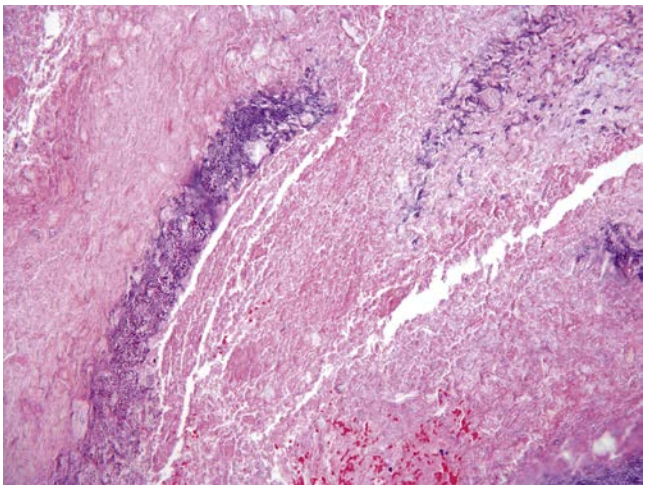
Even though the brush biopsy (cytologic) technique alone is not overly sensitive, when combined with nuclear DNA analysis, its sensitivity and specificity both can reach 98% to 100%. Cytology smears from all visible oral lesions are cheap, practical, noninvasive, painless, and safe screening methods for the detection of oral cancerous and precancerous lesions. When DNA image cytometry is added to the brush biopsy, this combined method is a very sensitive, highly specific, and reproducible tool for the identification of neoplastic cells in oral smears.

Special Histochemical Staining Techniques

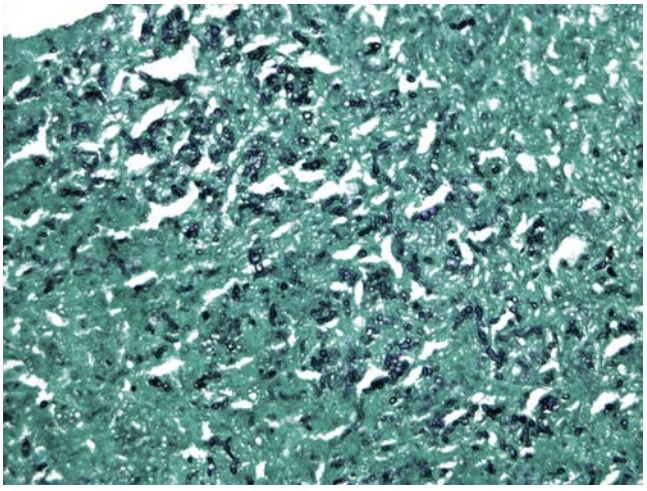
The clinician often encounters the term *special stains* when discussing a specific case with a pathologist. He or she then wonders, "What is a *special* stain?" The *routine* or *usual* stain used in pathology laboratories today is the H&E. This specific stain has been used in surgical pathology for well over 150 years and has stood the test of time. Hematoxylin stains tissue a deep blue color while eosin staining produces a deep red. Depending on the exact tissue being studied, the majority of all cells will demonstrate an almost infinite number or combination of colors and/or patterns. These staining qualities are fairly reproducible regardless of the submitted tissue. Examples of such reproducibility include the facts that all sections of skeletal muscle will stain red with the H&E stain, while the nuclei of most cells will stain some hue of blue/black with the same stain.

It is unclear when and why the term *special* stains arose, but in the world of histology and pathology, this term refers to the empirical and histochemical staining techniques that have significantly contributed to both of these scientific fields beginning in the late 19th century. These stains are different from the usual or routinely used H&E stain. In other words, *special* stains are the stains other than either the H&E or immunoperoxidase stains that are used in pathology today. For the most part, these special stains are used for a single purpose only. Some of the more commonly used special stains are: (1) periodic acid–Schiff (PAS) and Grocott's methenamine silver (GMS) stains for fungi, (2) Gram stain for bacteria, (3) Congo Red stain for amyloid, and (4) the Fite stain for acid-fast bacilli (Figures 16-4 and 16-5).

Immunofluorescence Studies



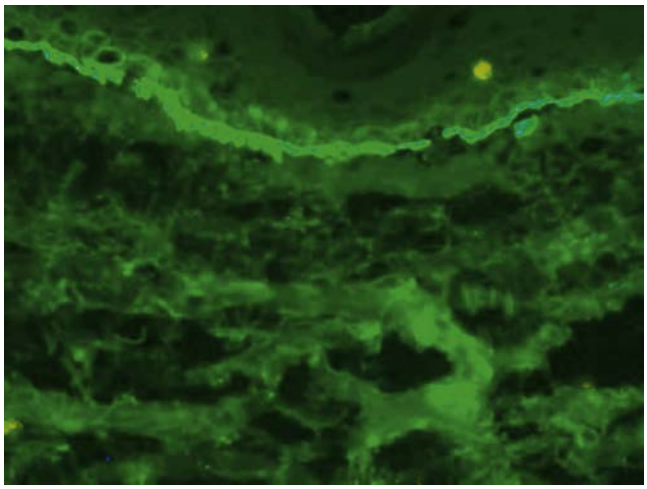
• **Figure 16-4** This biopsy material is from a large necrotic mass of the maxillary sinus clinically thought to be a mucocele. Note a few calcifications within the areas of necrosis (200×, H&E).



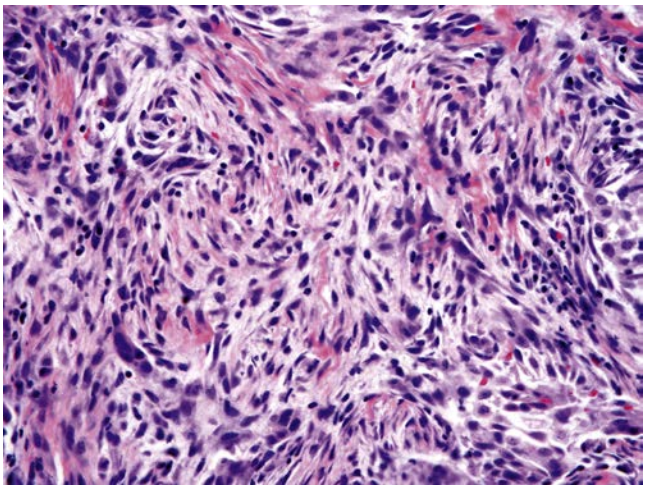
• **Figure 16-5** Special (non-immunohistochemistry) stain is of the sinus mass in Figure 16- 4. This GMS special stain demonstrates the septated hyphae of a fungus. In this case, *Aspergillus* was cultured from the surgical specimen (400×, GMS).

against tissue sites located within or just below the mucosal surface. Direct immunofluorescent studies allow today's clinicians to better diagnosis, treat, and understand such clinical problems. The most commonly encountered of these ailments include benign mucous membrane pemphigoid, pemphigus vulgaris, linear IgA disease, epidermolysis bullosa, and other similar disease entities that occur within the mucosa of the oral and head and neck area.

Surgical oral and maxillofacial pathology laboratories use a special fluorescent microscope to examine mucosal biopsy material from patients demonstrating such clinical presentations (Figure 16-6). In order for mucosal tissue biopsies to be accurate, the oral and maxillofacial surgeon must be aware of the pathologist's special needs in such cases and thus collect the biopsy material in a specially prepared fixative and transport media known as Michel's solution. Each laboratory will have such material readily available for the clinician.



• **Figure 16-6** Seen is a direct immunofluorescent study of a biopsied gingival ulceration. Note the labeled IgG antibody deposited at the basement membrane area strongly suggesting benign mucous membrane pemphigoid (400×, Immunoglobin G-Immunofluorescent stain).



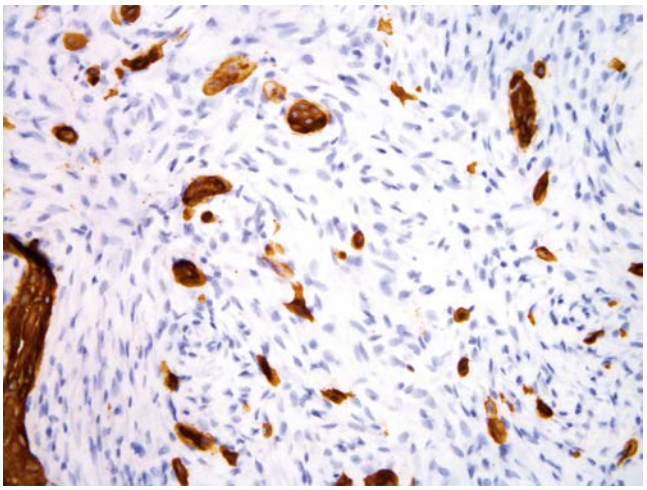
• **Figure 16-7** This biopsy demonstrates a poorly differentiated mass of tongue base. Note the spindle cells as well as the large multinucleated cells and the numerous atypical cell features. With routine H&E staining, this lesion could represent either a sarcoma or a carcinoma (400×, H&E).

Immunohistochemistry

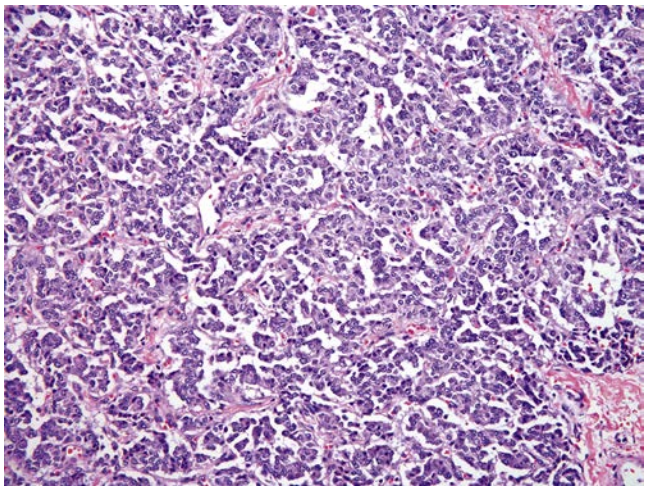
For many years, surgical oral and maxillofacial pathologists have relied almost exclusively on their ability to characterize cell morphology under the light microscope. These same pathologists have long recognized the fallibility or imperfection of such methodology. More objective means of validating microscopic judgments have long been sought. Unique histochemical stains have been used for decades to depict specific cell arrangements and origins. These stains have been quite useful but lack the absolute ability to identify specific cell lineage or the biologic potential of individual cells. The use of immunohistochemistry (IHC) allows the identification of specific antigens associated with the pathologic cells. This methodology has allowed surgical pathology to become a much more objective science while still using the light microscope and the diagnostic rapidity that it possesses (Figures 16-7 and 16-8).

Immunoperoxidase stains came into relatively common use during the middle and late 1970s and even more so in the 1980s. Such stains have revolutionized the practice of diagnostic surgical pathology during this same time frame.[7] Immunoperoxidase or IHC stains are in fact a form of monoclonal antibodies, raised against specific proteins. These antibodies are then labeled with a marker that usually stains brown with a counterstain. There are many specific antibody kits available today, with new ones being produced almost monthly. Depending on the exact antibody being used and the biopsy tissue being examined, the pathologist can develop a working differential diagnosis or confirm an earlier impression by the use of these IHC stains (Figures 16-9 and 16-10).

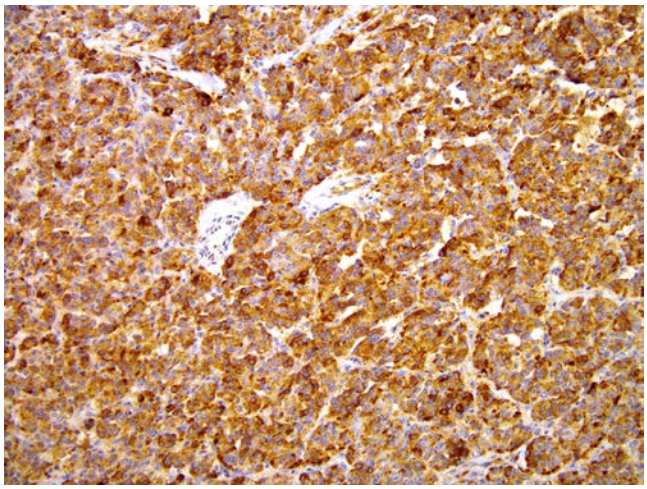
The primary use of immunohistochemistry in surgical pathology is as a diagnostic tool to determine the cytologic lineage of tumor cells and thus, often, the primary site of the tumor itself (Figures 16-11 and 16-12). In recent times, this technique has demonstrated much success in selecting



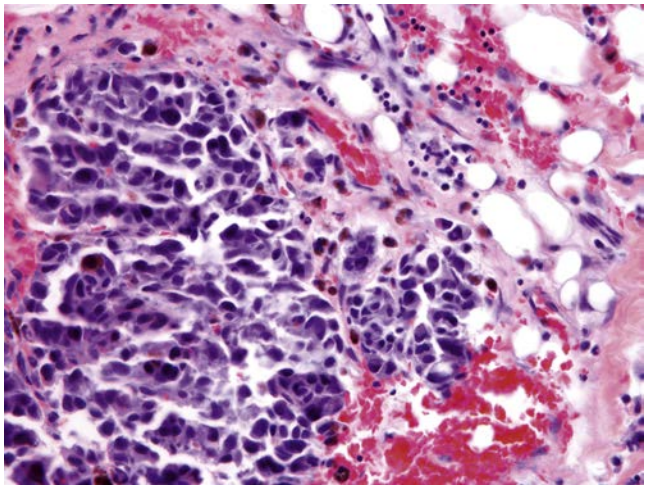
• **Figure 16-8** Seen is the same tongue base tumor as Figure 16-7 but now stained with a pancytokeratin (PanCK) immunostain. This lesion is now accurately characterized as a spindle cell carcinoma (400×, PanCK).



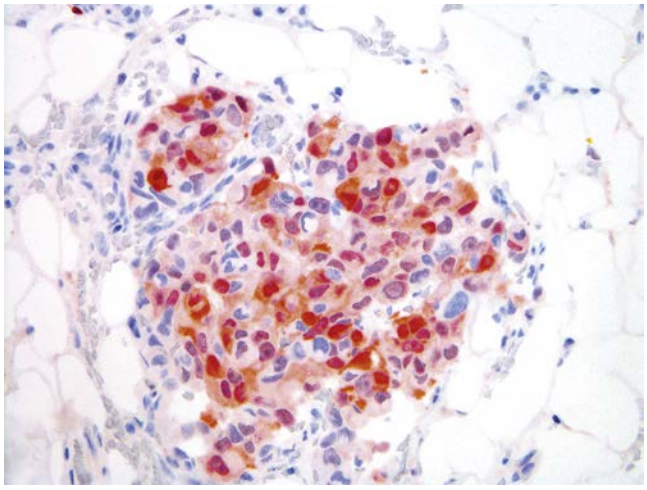
• **Figure 16-9** This biopsy is of a large deep neck mass near the carotid artery. Note the uniform cells suggestive of glandular origin (200×, H&E).



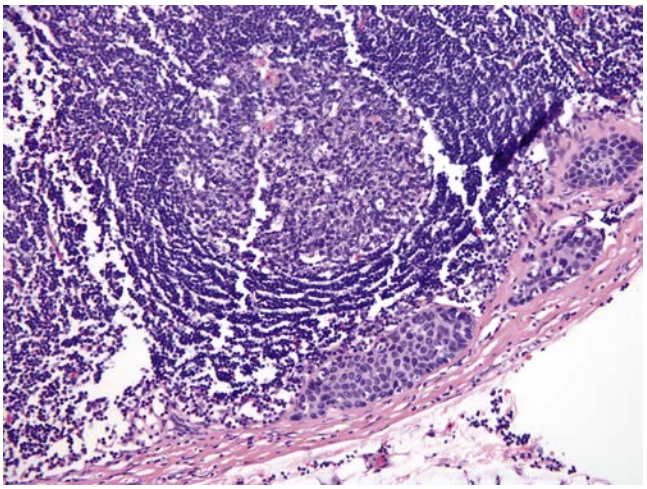
• **Figure 16-10** This represents a chromogranin immunostain of the neck mass seen in Figure 16-9. Note the uniform positive staining with this immunostain. Such findings are consistent with a lesion of neuroendocrine origin suggesting a paraganglioma—in this case, a carotid body tumor (200×, chromogranin).



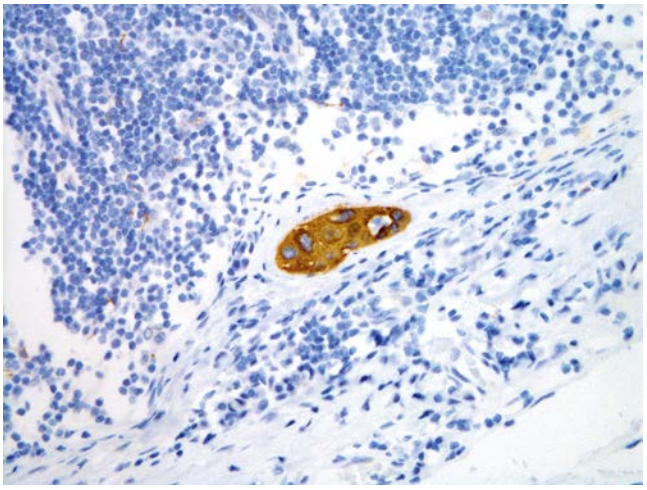
• **Figure 16-11** This biopsy is of a nodule in the skin just below the mandible. The malignant cells appear to be epithelial, but no history of oral/head and neck or skin cancer was ever identified (400×, H&E).



• **Figure 16-12** Represented is an IHC stain of specimen in Figure 16-11. In this case an S-100 stain was used to demonstrate melanin-producing cells; thus this patient's biopsy is now representative of a metastatic melanoma (400×, S-100).



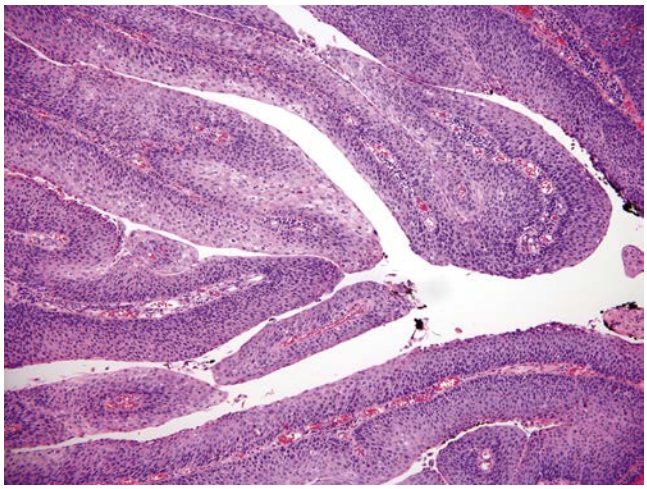
• **Figure 16-13** This is a cervical lymph node removed during a neck dissection in a T1N0M0 squamous cell carcinoma of the lateral tongue. Note the tiny island of unusual cells at the very periphery of a single small node (400×, H&E).



• **Figure 16-14** Seen here is the same node as in Figure 16-13 but now stained with a pancytokeratin (PanCK) immunostain that commonly stains squamous epithelial cells. Such staining allows the staging of this rather small tumor as a T1N1M0, thus altering the patient's therapeutic course and ultimate prognosis (400×, PanCK).

specific treatment regimens (Figures 16-13 and 16-14).[8] Another application of immunohistochemistry that is gaining popularity is its use as a predictor of disease progression and prognosis.[9] A working example of such ability is the p16 immunostain. Recent publications have established the p16 IHC stain as a faster and less expensive alternative to a papillomavirus polymerase chain reaction (HPV-PCR) in the identification of a high-grade papillomavirus. For this reason, the p16 immunostain is often used in the determination of a pathologic papillomavirus within the cells of specific oropharyngeal squamous cell carcinomas (Figures 16-15 and 16-16).[10]

It is a certainty that immunohistochemistry has the real potential to transform surgical pathology from a subjective art to an objective science, based principally on the microscopic recognition of immunostained cells.[11]

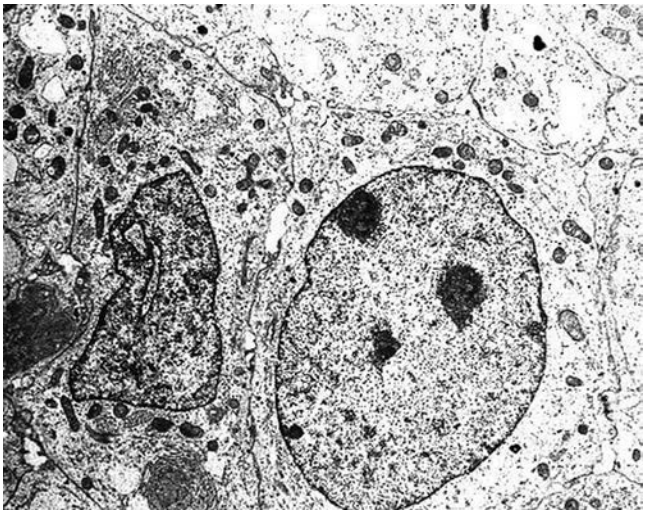


• **Figure 16-15** This biopsy specimen is from a soft palate lesion that clinically appears to represent a large and possibly very aggressive oral cancer. This biopsy is interpreted as a relatively rare papillary squamous cell carcinoma. Such lesions commonly denote an aggressive lesion with an extremely poor prognosis (200×, H&E).



• **Figure 16-16** This microphotograph represents a p16 immunostain of the lesion seen in Figure 16-15. Note that the entire tumor is composed of p16-positive cells. It is now recognized that such staining properties define the papillomavirus origin of this tumor and thus allow the patient's prognosis to become much more favorable (200×, p16).

pathology by the application of immunohistochemistry and cytogenetics. TEM was very popular in the 1970s and early 1980s and was often used as an adjunctive diagnostic procedure to determine the cell of origin within many tumors of unknown derivation. Pathologists now have the option of choosing from a myriad ancillary diagnostic procedures to aid in the determination of such findings. These include immunohistochemistry, cytogenetics identification of specific reciprocal chromosome translocations, gene rearrangement studies, fluorescent in situ hybridization, and



• **Figure 16-17** This photo represents a transmission electron micrograph (TEM) of the lesion seen in Figure 16-3. Note the very large nucleus and nucleolus of the tumor cell. Also view the intracellular filaments and desmosomes that characterize this lesion as a carcinoma rather than a sarcoma (6000×, TEM).

many others of these studies are incapable of solving all the diagnostic problems seen in tumor recognition and diagnosis. This realization in turn has caused a resurgence of interest in the use of TEM as a diagnostic tool.

Time and expense are very real constraints when using TEM. Initially, the diagnostic tissue must be fixed in a specific manner (buffered glutaraldehyde) so that the cell membrane and cytoplasmic organelles can be preserved. The tissue preparation and ultimate TEM examination usually take 3 to 4 days, which makes such diagnostic studies anything but routine. The surgical pathologist must be well-versed in the review of diagnostic electron microscopic features to take full advantage of the assets of TEM. Such studies have proven to be exceptional in certain lesions such as soft tissue tumors, Langerhans cell histiocytosis, and various undifferentiated neoplasms of the head and neck area (Figure 16-17).

Flow Cytometry

For over 15 years flow cytometry (FCM) has been used by the surgical pathologist to aid in the analysis of cellular DNA content as well as in the determination of specific cellular antigens.[12] Cell preparations from both cytology smears and surgical pathology specimens can be used by FCM processes.

FCM allows the detection of altered cell ploidy. It can also evaluate the excess or deficiency of chromosomal DNA within the cell. The methodology involves the measurement of the fluorescent intensity of cellular dyes that have been excited by a laser, usually of an argon-ion type. The dye-labeled cells pass in single file through a light beam. Thousands of such particles can be measured in a few seconds

depending on the flow rate. The collection of labeled particles of interest is then placed on a computer-generated histogram according to specific windows or gates. These graphs subsequently are interpreted by the surgical pathologist and presented to the clinician.

As stated previously, both tissue and cytologic cells are acceptable for FCM studies. Fresh tissue allows a much more accurate analysis, but processed tissue from paraffin blocks can also be used. Flow cytometric DNA ploidy has turned out to be a significant predictor for survival in oral squamous cell carcinoma. Only recently has FCM been identified for its contribution in assisting histopathology in the identification of potentially malignant salivary gland lesions.[13]

Molecular Biology

There have been tremendous advances in the field of molecular biology during the past 20 years. This knowledge has contributed immensely to our understanding of human disease. These advances have slowly become integrated into the practice of surgical pathology. Many methods are available to view molecular products and thus expand the traditional light microscopic analysis of tissue specimens. Some of the technologies available today include in situ hybridization, polymerase chain reaction, fluorescent in situ hybridization, and southern blot hybridization. At the present time, the use of such techniques has been limited primarily to large academic medical centers. There is no doubt that in time these laboratory principles will become available to all pathologists and thus can be used by all patient caregivers.

Once a diagnosis has been made, the surgical pathologist's next task is to provide the surgeon with information regarding the lesion's behavior, disease progression, and the ultimate prognosis of the particular disease state. The majority of molecular biologic tests help determine specific cellular factors or molecular abnormalities that have clinical relevance for treatment or prognosis. As an example, in cases of breast cancer, HER2-neu is frequently examined. Its presence is often a poor prognostic indicator. Another common use of molecular pathology is found within the field of gynecologic oncology. The number of human papillomavirus (HPV) genotypes is extensive, with more than 150 subtypes identified.[14] It has been determined that there are specific high-risk types (HPV 16, 18, 31, 45, and 56) that are associated with cervical cancer. Recently HPV was implicated in several squamous cell carcinomas of the head and neck. In addition, at present time, various oncogenes are recognized as having prognostic significance in cancer of the head and neck. Some of these include p53 (tumor suppressor gene products), bcl-2 (apoptosis inhibitor), Ki-67, and PCNA (cell proliferation markers). Only through the use of molecular biologic testing have these prognostic markers been identified. There is no doubt that as we learn more about the genetic events that determine biologic behavior, the list of these molecular markers will only increase.

Summary

By its very nature, surgical oral and maxillofacial pathology depends on the input of various clinicians. These dentists and physicians should be well aware of the abilities and limitations of our specialty. Surgical pathology is for the most part a very subjective specialty. As such, it relies on the interpretation of glass slides, gross tissue examination, laboratory studies, radiographs, and imaging studies as well as information from the supplied patient history. Unless the evaluation of all of this information is undertaken by the surgical pathologist, the microscopic evaluation may be in vain.

Presented are the majority of diagnostic methods available to the oral and maxillofacial surgical pathologist in his or her quest for diagnostic accuracy. A great number of oral and maxillofacial pathology cases do not need all of these available studies. In fact the majority need only a very few of them. Still, such methods are available today, and with the passage of time, even more sophisticated studies will become available. It is the hope of this author that the reader will now have a better understanding of the oral and maxillofacial surgical pathologist and as such avail themselves of the diagnostic skills of such a person.

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17

Cysts of the Oral and Maxillofacial Region

NABIL A. ABAZA, SAMIR K. EL-MOFTY, ANDREW D. MILLER

Definitions

To thoroughly understand the biology of any lesion and, therefore, render the appropriate management, clear and accurate definitions are a prerequisite. This task may not be easily achieved for all the lesions discussed in this chapter.

For cysts of the oral and maxillofacial region, several terms need to be defined in order to provide both the treating surgeon and the patient with a clear understanding of the outcome and expectations.

Grossly, a cyst is a saclike mass or lesion containing luminal fluid or semi-fluid substances. By imaging, a cyst is a well-delineated area of different contrast to the surrounding tissue. A true cyst, however, is a histologic diagnosis in which the cyst wall is lined by epithelium regardless of its subtypes. The type and the biologic nature of the epithelium, however, have a significant impact on the lesion prognosis and recurrence rate. The major classifications have thus far been based on the origin of the epithelium—either from the processes of odontogenesis (odontogenic cysts) or from the embryogenesis of the head and neck region (non-odontogenic cysts). Frequently a lesion is described as cystic, which implies only a clinical or imaging feature; therefore the term is nonspecific. Occasionally the term *pseudocyst* may be used, which describes a collection of fluid or semi-solid material in a non-epithelialized tissue compartment that has been compressed to simulate the clinical cystic designation. For the purpose of this chapter, the specific definitions of odontogenic and non-odontogenic cysts are subsequently described in some detail.

General Surgical Considerations

In the surgical management of these cysts, it is critical that the physician submit any tissue that is surgically removed, regardless of the size, for microscopic examination by a pathologist familiar with the region. There is also an important role for fine-needle aspiration (FNA) biopsy in establishing the diagnosis of cysts of the oral and maxillofacial region.[1,2] The input of a cytopathologist is essential.

As this chapter details, most lesions under discussion are histologically benign, but the biologic behavior and recurrence rates differ from one cyst to the other. Therefore it is prudent that the treating oral and maxillofacial surgeon be aware of these differences. Then the patient and the surgeon can be on the same level of expectations, and repeated surgical intervention, if required, does not constitute misunderstanding. The initial surgical treatment and the subsequent follow-up of cysts of the oral and maxillofacial region depend on several factors:

1. The patient's age and overall health condition
2. Size and location of the cyst
3. Histologic diagnosis of the lesion gained by excisional, incisional, or FNA biopsies

Surgical procedures fall on a spectrum that includes marsupialization (unroofing of the cyst); enucleation; a two-stage surgery that consists of marsupialization with delayed enucleation thereafter; marginal or en bloc resection, with or without immediate reconstruction; and hemimaxillectomy or hemimandibulectomy, again with or without immediate reconstruction with grafting of bone and/or soft tissue. In all procedures, adjunct therapy including chemical cauterization, cryotherapy, or peripheral ostectomy with burrs has been reported, particularly if the diagnosed cyst is known to have a high recurrence rate. These surgical considerations are discussed in more detail in conjunction with individual lesions.

Odontogenic Cysts

Inflammatory

The process of odontogenesis is a unique histogenic and morphogenic phenomenon in human embryogenesis. After

complete formation of the two sets of dentition, deciduous and permanent, the embryogenic soft tissue remnants are widely accepted as the origin of both odontogenic cysts and tumors. The epithelial rests of Malassez and Serres, documented to be histologically present in the periodontal ligament and gingiva, respectively, are widely implicated in the pathogenesis of odontogenic cysts. The rests of Serres are remnants of the dental lamina, and the rests of Malassez are remnants of epithelium from the involution of the enamel organ.[3]

Table 17-1 summarizes suggested origins of these lesions. Currently there is no single classification that is universally accepted, and proposals for revisions are being [4-7]

cates that a proliferation of tissue occurred in the enamel organ before any calcification was initiated; therefore the cyst replaces a tooth, usually of the permanent dentition with no history of extraction. This is an old classification system that emerged before the understanding of the odontogenic keratocyst. Neville et al[8] concluded that a cyst clinically considered to represent a primordial cyst, in the older terminology, almost always is an odontogenic keratocyst microscopically.

The dentigerous cyst, a fairly common lesion, indicates proliferation of the remnants of the enamel organ after formation and calcification of a crown, most commonly the third molars and canines. This cyst can be around or lateral to the crown. The lateral periodontal cyst is epithelial proliferations lateral to the root of an erupted tooth, commonly a lower premolar. It is believed to result from proliferative activity of the periodontal rests of Malassez. The very common radicular or periapical cyst represents proliferation of epithelial remnants in the apex of a nonvital tooth, secondary to caries or trauma, and the subsequent inflammatory stimulation of the periapical tissues. Cysts that are present

TABLE 17-1 1985 WHO Classification of Cysts of the Jaws

Classification	Site	Suggested Origin
1. Developmental		
a. Odontogenic		
Odontogenic keratocyst	Usually mandibular angle or ramus	Dental lamina or tooth germ
Follicular cyst	Around crown of unerupted tooth	Follicle and reduced enamel epithelium
Eruption cyst	Around crown of unerupted tooth	Follicle and reduced enamel epithelium
Lateral periodontal cyst	Periodontal ligament	Dental lamina rests or reduced enamel epithelium
Gingival cyst of adults	Gingiva	Dental lamina rests or reduced enamel epithelium
Alveolar cyst of infants	Gum pads	Dental lamina
b. Non-odontogenic		
Nasopalatine duct cyst	Incisive canal and foramen	Oronasal duct epithelium
Nasolabial cyst	Soft tissues of buccal sulcus adjacent to upper canines	Nasolacrimal duct epithelium
Mid-palatal cyst of infants	Midline palate	Palatal process epithelium
2. Inflammatory		
Radicular cyst	Root apex	Rests of Malassez
Residual cyst	Edentulous alveolus	Rests of Malassez
Inflammatory lateral periodontal cyst	Periodontal ligament	Rests of Malassez
Paradontal cyst epithelium	Adjacent to partially erupted tooth involved by pericoronitis	Rests of Malassez or reduced enamel
Inflammatory epithelium	Follicle of unerupted permanent tooth below an infected deciduous tooth	Follicle and reduced enamel

Modified from Tinkler S: The jaws. In McGee JO, D'Isaacson PG, Wright NA, editors: *Oxford textbook of pathology: pathology of systems*, vol. 2a, Oxford, UK, 1992, Oxford University Press. Based on Main DMG: Epithelial jaw cysts: 10 years of the WHO classification, *J Oral Pathol* 14:1, 1985

after history of extraction of a tooth or the inadequate removal of associated soft tissue during a previous procedure are called residual cysts.

This chapter discusses in detail commonly encountered odontogenic cysts and, for completeness, briefly mentions less frequently encountered lesions.

• BOX 17-1 1992 WHO Classification of Cysts of the Jaws

Developmental

Odontogenic

Gingival cysts of infants (Epstein pearls)
Odontogenic keratocyst* (primordial cyst)
Dentigerous (follicular) cyst
Eruption cyst
Lateral periodontal cyst
Gingiva cyst of adults
Glandular odontogenic cyst; sialo-odontogenic cyst

Non-odontogenic

Nasopalatine duct (incisive canal) cyst
Nasolabial (nasoalveolar) cyst

Inflammatory

Radicular cyst
Apical and lateral cysts
Residual cyst
Paradental (inflammatory collateral, mandibular infected buccal) cyst

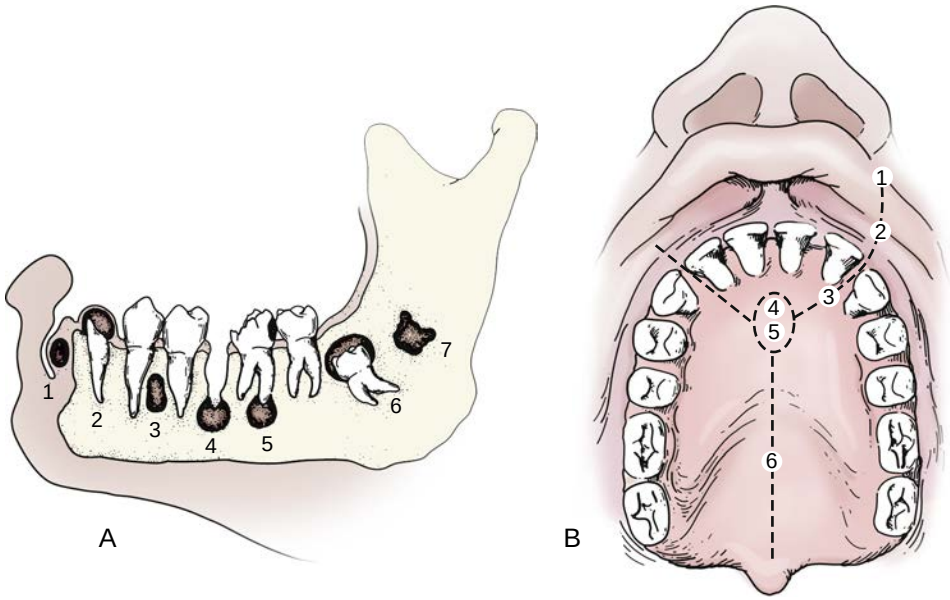
*WHO renamed odontogenic keratocyst to keratocystic odontogenic tumor in 2005.[24]

From Kramer IRH, Pindborg JJ, Shear M: *Histological typing of odontogenic tumors*, ed 2, Berlin, 1992, Springer.

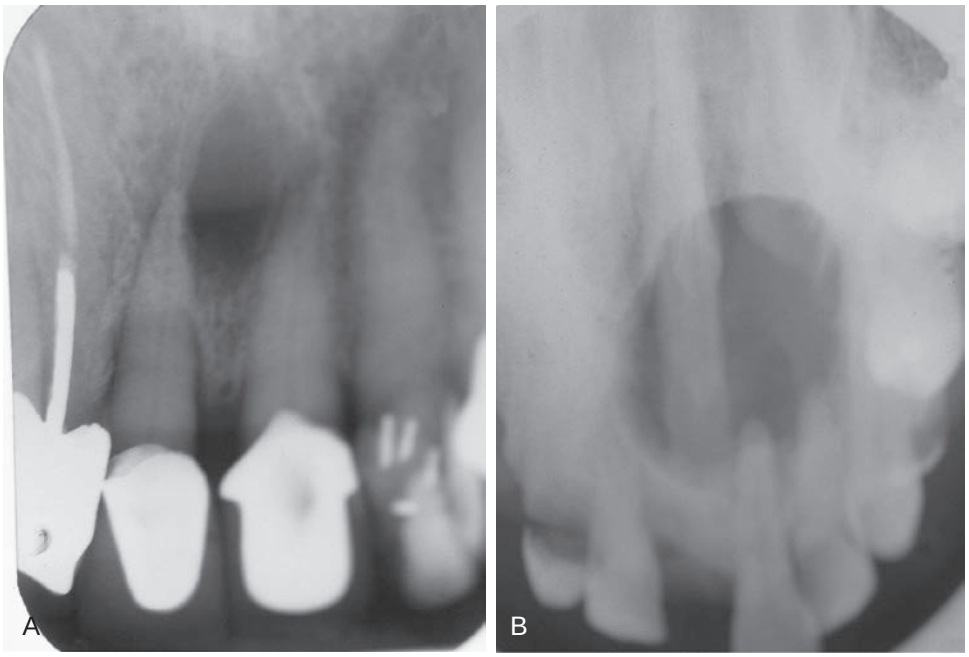
Radicular Cyst

Clinical Features

Frequently referred to as a periapical cyst, it is the most common lesion encountered secondary to caries or trauma. Bacteria initiate inflammation in the pulp and the surrounding periapical tissues; the secreted chemical mediators of inflammation then induce proliferation of periapical soft tissues and stimulate osteoclastic activity. This inflammatory process also stimulates proliferation of the rest of Malassez, which is present in the periodontal ligament. As the proliferating islands of epithelium enlarge, their centers degenerate and/or liquefy, resulting in microcysts. The latter ultimately coalesce to form a fairly well-defined periapical bony rarefaction (Figure 17-2). If the offending tooth is not treated or extracted, the lesion continues to enlarge via the hyperosmolarity created by the cellular breakdown and the resulting osmotic gradient that favors the transudation of fluids into the lumen of the lesion.[8,9] There is long-standing discussion of the clinical, radiographic, and even histologic differentiation between the small periapical lesions—that is, whether they are radicular cysts or periapical granulomas. Several views have been expressed to differentiate the two lesions.[9] The authors believe this issue is of limited clinical value. Conceptually, if the tooth in question is salvageable, root canal, with or without apicoectomy, may be the treatment of choice. Follow-up is required to monitor the regression of the lesion. If the lesion continues to expand after root canal therapy or if the tooth is extracted, the lesion should be enucleated and submitted for microscopic examination.



• **Figure 17-1** Diagrams of the site of odontogenic **(A)** and fissural (non-odontogenic) cysts **(B)** in the mandible and maxilla, respectively. **A**: *1,* gingival; *2,* eruption; *3,* lateral periodontal; *4,* residual; *5,* periapical (radicular); *6,* dentigerous; *7,* primordial. **B**: *1,* nasolabial cyst; *2,* nasoalveolar cyst; *3,* globulomaxillary cyst; *4,* nasopalatine cyst; *5,* cyst of palatine papilla; *6,* median palatal cyst. (From Batsakis JG: *Tumors of the head and neck; clinical and pathological considerations*, ed 2, Baltimore, 1979, Williams & Wilkins.)



• **Figure 17-2** **A,** Periapical radiograph of maxillary anterior teeth showing a well delineated bony rarefaction at the apices of non-vital maxillary anterior teeth. **B,** An occlusal film of a radicular cyst of a traumatized maxillary central incisor. Differential diagnosis from incisive canal duct cyst is necessary.

Imaging Features

The apical radiolucency and the associated non-vital tooth are easily recognized by periapical radiographs. In large cysts, other plain films may be useful to delineate the lesion. In rare cases, a computed tomography (CT) scan may be useful. In all cases, the lesion is a well-delineated and corticated radiolucency that is confluent with the periodontal ligament of the associated tooth.

Pathologic Features

The radicular cyst is usually small, measuring 1 or 2 cm in diameter. However, on occasions, especially in patient populations with limited availability of oral health care, the cyst can attain several centimeters in diameter. The cyst contents are brown serosanguineous fluid with glistening cholesterol crystals commonly present. If the cyst has communicated with the oral cavity, the fluid may be suppurative.

Microscopically, the connective tissue wall varies in thickness and degree of inflammatory cell infiltrates (Figure 17-3, *A-C*). The epithelium is made of non-keratinized stratified squamous cells with varying thickness. In actively inflamed cysts, the epithelium is thicker with marked proliferation of the rete pegs into the cyst wall. Frequently, the epithelial lining is focally ulcerated. Histiocytes and foreign body giant cells are frequently present (see Figure 17-3, *D*). When the lesion drains into the oral cavity, the epithelial lining becomes attenuated and the cyst wall shows a marked decrease in the inflammatory cell infiltrate (see Figure 17-3, *E*). Cholesterol clefts and Rushton bodies are frequently seen. The origin of the latter has been debated and has yet to be settled.[5,6,9] These hyaline bodies can calcify and change the lesion's staining property from eosinophilic to basophilic.

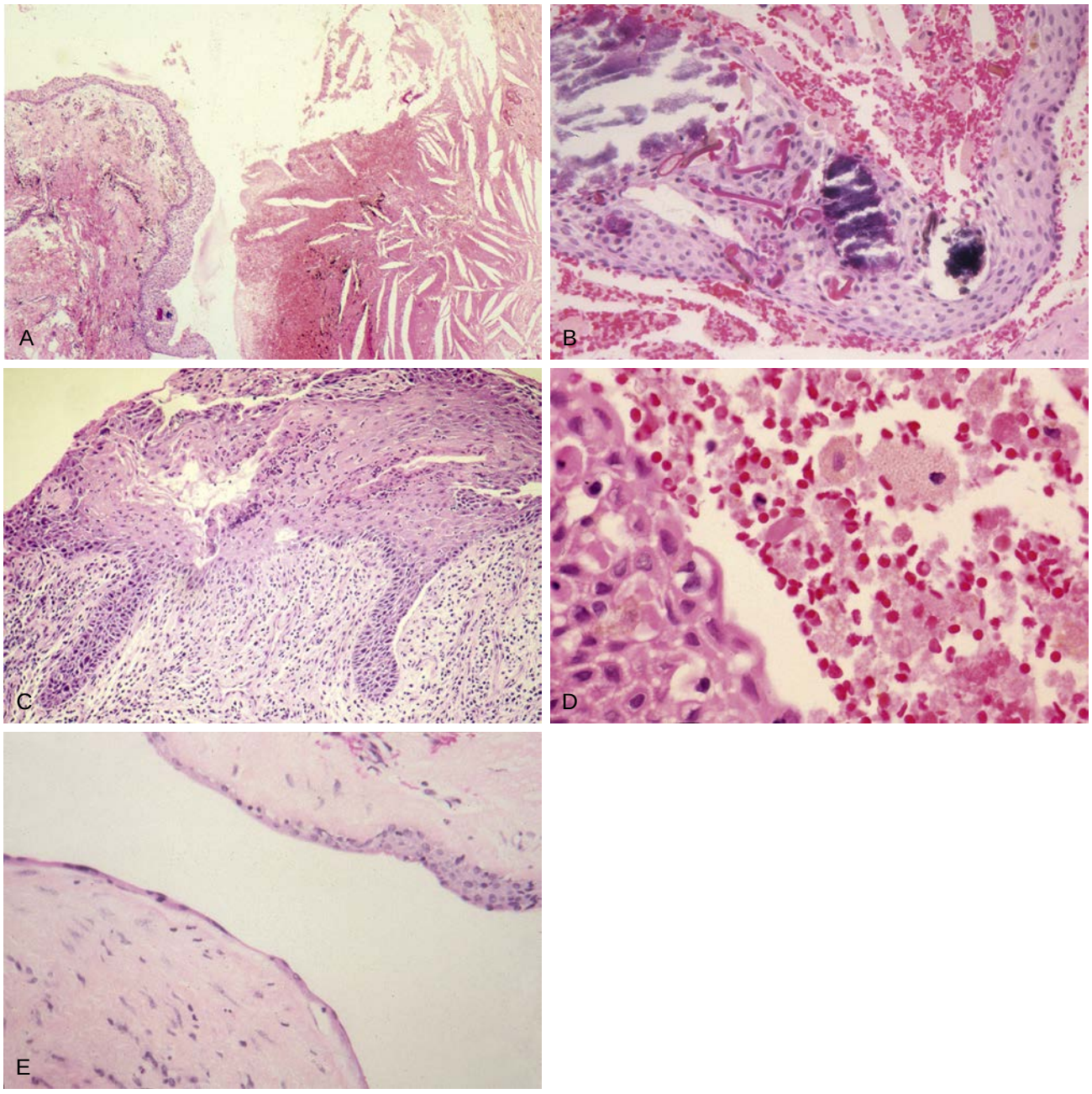
Surgical Management

As previously mentioned, if the tooth in question is salvageable, root canal therapy with or without apicoectomy and retrograde filling is recommended. The progress of healing is then monitored. If the tooth is extracted, the lesion should be thoroughly enucleated. In small lesions, enucleation can be undertaken through the socket. In large cysts, an independent incision and bone removal are necessary to have adequate exposure of the lesion. Every attempt should be made to enucleate the lesion in total (Figure 17-4, *A*). A semilunar incision at the junction of the free and attached gingiva, with the curvature toward the crown of the tooth, is preferred, with care to extend the incision 5 to 10 mm beyond the anticipated resulting bony defect. The surgeon may elect to have the incision around the cervices of the teeth involved in the site. In the absence of exuberant acute inflammation and when the bony defect is significant, immediate bone grafting with autogenous or allogeneic material, or a mixture of the two, will enhance healing and facilitate early placement of an implant if the tooth in question has to be extracted (see Figure 17-4, *B*).

Residual Cyst

Clinical Features

Simply defined, a residual cyst is a retained radicular cyst or periapical tissues that are left behind after removal of an associated tooth.[6,8,10] History of extraction is important to help differentiate the lesion from primordial odontogenic keratocysts, which arise from epithelial elements of the enamel organ before any calcification (Figure 17-5, *A*).



• **Figure 17-3** Photomicrographs of the radicular cyst showing **(A)** stratified squamous epithelium with cholesterol clefts **B,** Rushton bodies and calcification. **C,** Marked inflammatory cell infiltrate of the connective tissue wall with hyperplastic proliferation of the epithelial lining. **D,** Significant presence of histiocytes in the cyst lumen. **E,** Attenuated epithelial lining with obvious lack of inflammation when cyst drains to oral cavity.

Imaging Features

The cyst is usually small (1 to 3 cm in diameter) but may assume a large size if not treated (see Figure 17-5, *B* and *F*). The lesion is well delineated and may even be a corticated radiolucency.

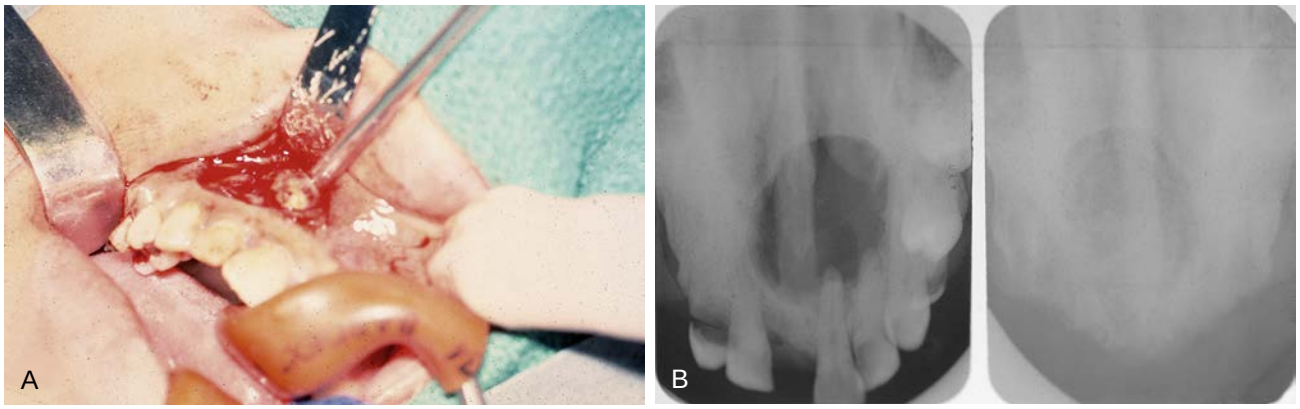
Pathologic Features

The gross and microscopic features are similar to those of the radicular cyst. The degree of inflammation of the cyst capsule and its epithelial lining is variable. Presence of cholesterol clefts is common (see Figure 17-5, *D* and *E*).

Examination of the specimen is necessary not only to confirm the clinical diagnosis, but also to ensure that the lesion is not an aggressive keratocyst or other odontogenic tumor.

Surgical Management

Enucleation of the cyst is curative. Because ossification of the extraction socket has probably occurred, an independent incision is required. Routine follow-up radiographs reveal the healing progress.



• **Figure 17-4** **A,** Enucleation of a maxillary radicular cyst in one piece. **B,** Two occlusal films; compare preoperative film shown in Figure 17-2, *B*, with postoperative film a few months after enucleation of cyst, extraction, and allogeneic bone grafting.

Paradental Cyst: Buccal Bifurcation Cyst

Overview

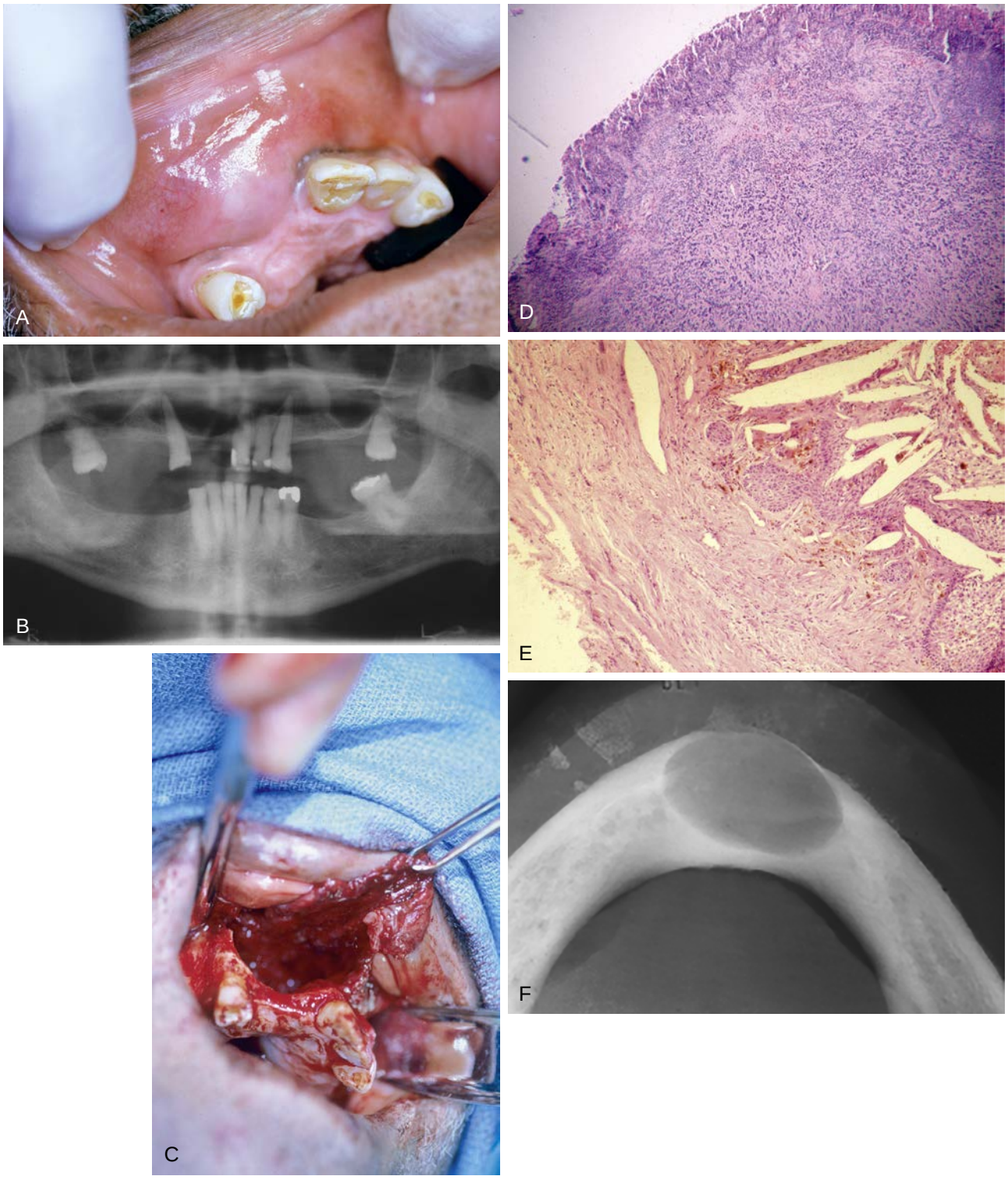
Paradental, buccal bifurcation, and mandibular infected buccal cysts are good examples of a lack of generally accepted and clear classification of cysts of the oral and maxillofacial region. The WHO classification describes a paradental cyst as an inflammatory collateral or mandibular infected buccal cyst.[4,6] The lesion is defined as a cyst near the cervical margin of the lateral aspect of a vital tooth, usually erupted mandibular molars (most commonly the third molars), with associated pericoronitis.[6] Other authors consider the paradental cyst as a variant of the dentigerous cyst.[9] Neville and colleagues[8] define the buccal bifurcation cyst as an uncommon inflammatory odontogenic cyst on the buccal aspect of the mandibular first molar, usually associated with enamel extensions into the bifurcation. These cysts are associated with the buccal surface of the mandibular molar in 5- to 11-year-old children.[6,8,11-13] The odontogenic epithelium in the superficial part of the periodontal ligament responds to the inflammatory stimulus and forms these lesions. Slight to moderate tenderness may be elicited. The histopathology of these lesions is nonspecific, with a cyst lining of non-keratinizing stratified squamous epithelium.[6,8,9] Inflammation is prominent. Extraction of associated third molars, particularly if not in function, and enucleation of the associated cyst are curative. In the buccal bifurcation lesion, enucleation without extraction of the associated tooth is adequate with reduction of the pocket depth and bone refill.[8,11-13] It has been reported that this cyst can resolve without surgery.[8,11]

Developmental

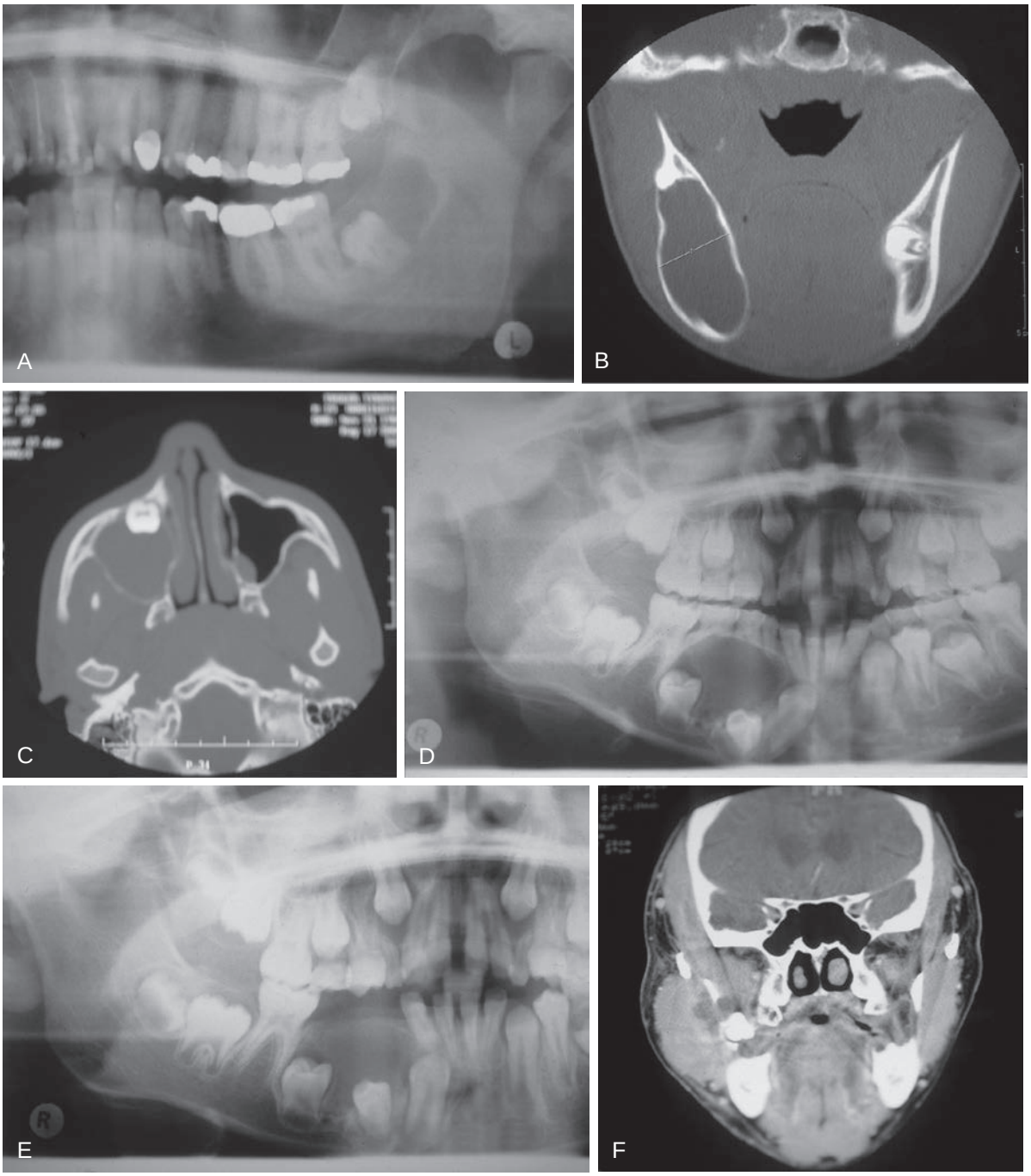
Dentigerous Cyst

Clinical Features

This is the second most commonly encountered odontogenic cyst in the oral and maxillofacial region. Frequently it is associated with third molars followed by maxillary canines. Lower premolars are also frequent sites (Figure 17-6, *D* and *E*). On a daily basis, oral and maxillofacial surgeons remove countless numbers of impacted teeth that have radiographic and gross evidence of cystic degeneration around part of or the whole crown of a tooth. The following question then arises: When do you call the lesion a dentigerous cyst versus an expanded follicle? Differentiation is clinically insignificant, although a lesion of 2.5 mm or larger has been reported as a requirement before a diagnosis of dentigerous cyst can be made.[14] The diagnosis is better supported by microscopic examination showing the cystic cavity to be lined by a confluent epithelial lining. A practical definition, therefore, is a lesion arising from the dental follicle of an unerupted or developing tooth with the latter projecting into the lumen. Depending on the location and the extent of the cystic degeneration in relationship to the crown of the associated tooth, the cyst can be described as central, lateral, or circumferential.[8] The degeneration of cells, with its subsequent hyperosmolarity and fluid transudation, has been theorized either to occur between the reduced enamel epithelium and the crown of the tooth or to be a result of the breakdown of the stellate reticulum, between the inner and outer enamel epithelium.[5,6,8,10] The cyst is usually small and may be discovered during routine radiographic examination of the jaw (see Figure 17-6, *A*). However, these cysts can assume large sizes and displace the associated impacted teeth to remote sites in the maxillofacial complex such as the ascending ramus in the mandible or the superior and posterior areas in the maxilla (see Figure 17-6, *B* and *C*). These large lesions can cause marked expansion of the cortices of the jaw with clinical evidence of their resorption evident by an "eggshell-crackling" or "frog-belly" phenomenon upon palpation. Root resorption of adjacent teeth does occur, but neurosensory deficits are not common. The cyst may be asymptomatic, but if it communicates with the oral cavity, it can become infected and pain is elicited. Painless facial swelling is also clinically apparent in larger lesions (see Figure 17-6, *F*).



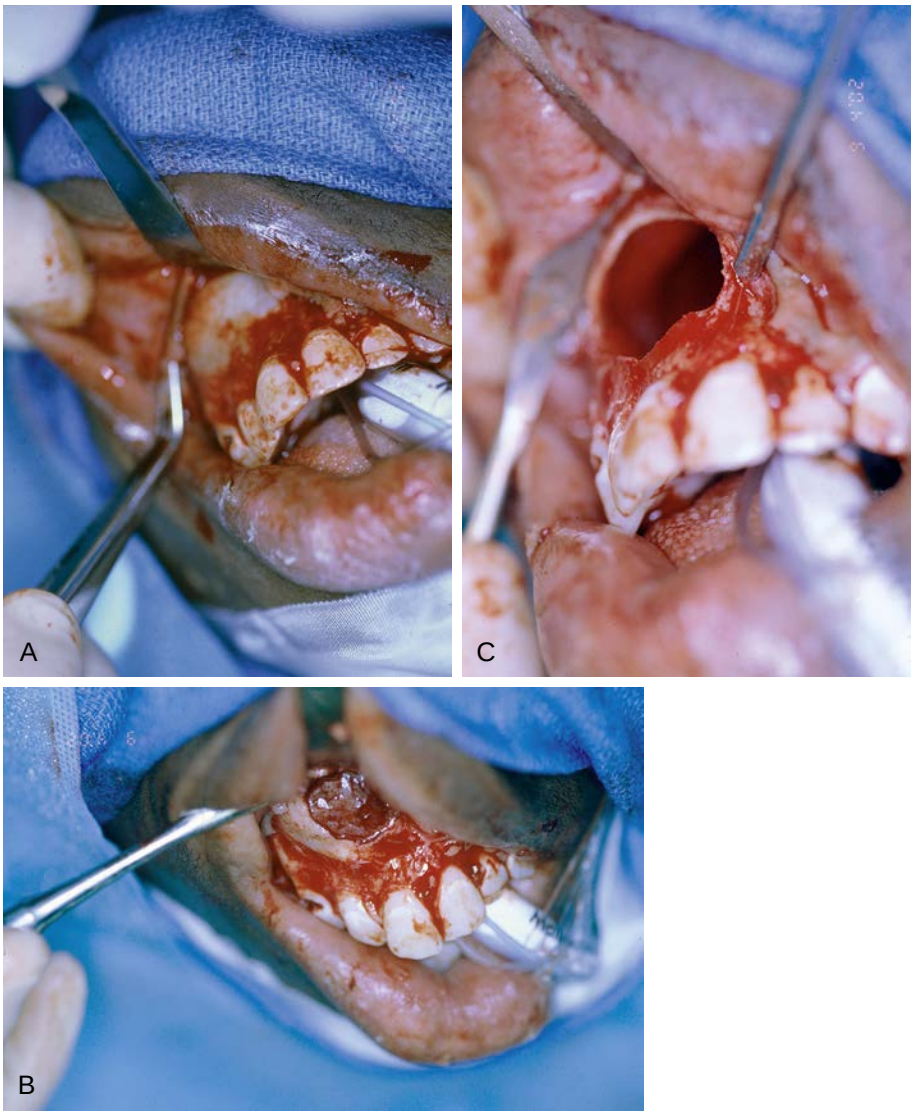
• **Figure 17-5** **A,** A residual right maxillary cyst with marked expansion in the buccal sulcus. **B,** Panogram from the same patient showing resorption of the roots of the adjacent teeth and a well-delineated radiolucency in the area of teeth #7 and #8. **C,** Cystectomy was performed by vestibular incision extending beyond the radiolucency, and cyst was enucleated. **D,** The cyst walls show significant inflammatory cell infiltrate. **E,** Focal presence of cholesterol clefts. **F,** An occlusal film from another patient shows a well-corticated radiolucency of a residual cyst in a 66-year-old woman.



• **Figure 17-6 A,** Radiographs of clinically diagnosed dentigerous cysts commonly associated with impacted third molars. **B,** Displacing associated molar high into the ascending ramus of mandible. **C,** Superiorly in the infra-orbital region. **D-E,** Impeding eruption of right mandibular premolars in a 7-year-old boy (extraction of the deciduous teeth in the same patient and enucleation of the cyst to allow eruption of the impacted teeth is in progression). **F,** Cyst causing facial cellulitis when infected.

Imaging Features

A panogram is usually the first indication of the presence of the dentigerous cyst. It is usually adequate for the diagnosis of the lesion with typical presentation of a well-corticated radiolucency associated with the crown of an incompletely formed tooth (see Figures 17-6, *A*, and 17-10, *A*). The availability of CT scans with or without contrast has almost conclusively replaced the need for plain facial films in the diagnosis of large dentigerous cysts that significantly displace associated teeth and encroach on important adjacent structures. Coronal and axial cuts with or without contrast are important not only to delineate the extent of the cyst but also for planning the surgical approach (see Figure 17-6, *B* and *C*). It is critical to recall that clinical and imaging features are not diagnostic of a dentigerous cyst, despite being very suggestive. Among important lesions to consider are



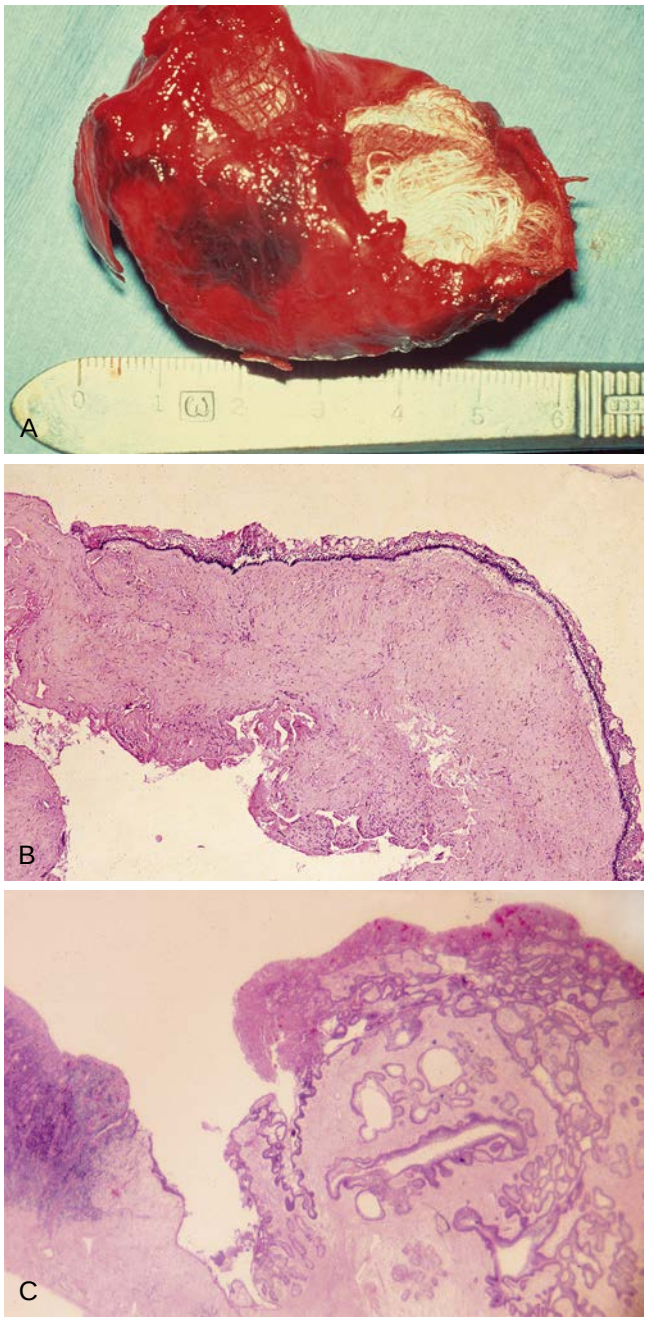
• **Figure 17-7** **A,** Photographs of a maxillary cyst causing significant buccal expansion and thinning of the bone cortex causing the clinical signs of "frog belly" and "eggshell crackling." **B,** Cyst wall apparent after removal of the residual thinned bone. **C,** Cyst bed after enucleation.

odontogenic keratocysts, unicystic ameloblastomas, and adenomatoid odontogenic tumors. The former two have a more aggressive biologic behavior. Dentigerous cysts lining epithelium retain some primordial odontogenic cells capable of ameloblastoma expression.[9] Therefore, dentigerous cysts are among the sources of ameloblastomas.[15] Odontogenic keratocyst, which is a histologic diagnosis, can present clinically and radiographically as dentigerous cyst. Therefore, in large cysts that radiographically appear to be dentigerous cysts, other differential diagnosis should be considered. A biopsy of the lesion is recommended either intraoperatively, by frozen section, or preoperatively, by incisional biopsy. The authors strongly believe in the value of intraoperative frozen section diagnosis and encourage its frequent use.

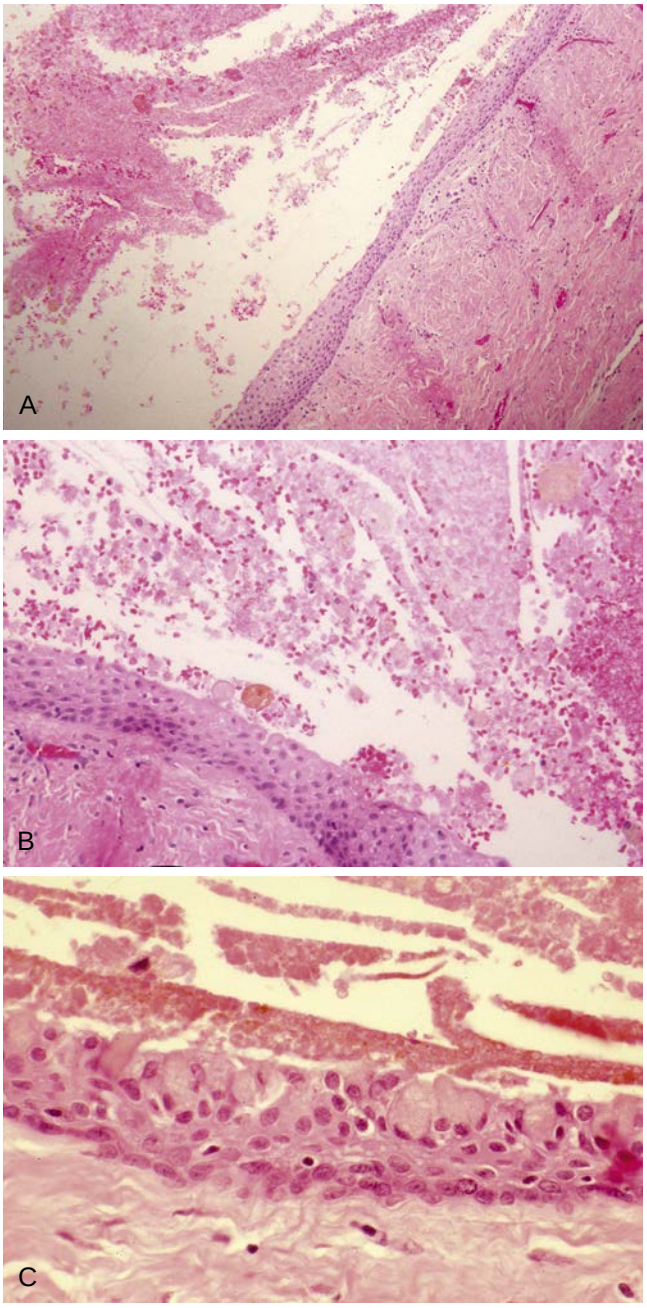
Pathologic Features

It is advisable to always aspirate a cystic lesion, particularly the expansible ones; examination of the aspirate is a good part of the diagnostic workup. We recommend critically evaluating the nature of the aspirate and, if needed, submitting it for cytopathologic examination. This simple step can be helpful in recognizing a vascular lesion, and cytopathology can strongly suggest the more aggressive odontogenic keratocyst.[1,2] Unless the dentigerous cyst is infected, the lesion contains straw-colored to brown fluid. When infected, the cyst contents would appear grossly suppurative. In noninfected lesions, the cyst wall is thin and attached to the cementoenamel junction of an associated tooth. Inflammation causes thickness of the cyst wall to varying degrees. The surgeon usually attempts to remove the cyst and the tooth from its bony bed in one piece (Figure 17-7, *A-C*). In large cysts in general, we have found that if intraoperatively the cyst is stuffed with gauze or other material after its enucleation and before it is placed in the fixative, this will help facilitate the selection of the part to be examined microscopically by the pathologist (Figure 17-8, *A*). Pathologists

favor sections from focally thickened wall or papillary projections into the lumen. This way a small early ameloblastoma or unicystic ameloblastoma arising from a dentigerous cyst would not be missed (see Figure 17-8, *B* and *C*). Usually the cyst consists of a thin connective tissue wall with minimal or no inflammatory cell infiltrate (Figure 17-9, *A* and *C*). The epithelial lining is stratified, non-keratinized epithelium, which is usually two to three cell layers thick with cuboidal basal cells (see Figure 17-9, *C*). If keratinization and other microscopic features of odontogenic keratocysts, as discussed previously, are present, the diagnosis is keratocyst rather than dentigerous cyst. It is important to remember that the dentigerous cyst epithelium is known to have the ability to differentiate into ciliated and mucus-secreting epithelium[16,17] (see Figure 17-9, *A-C*). Malignancies, including intraosseous mucoepidermoid carcinoma and carcinoma ex-dentigerous cyst, have been postulated to arise from the odontogenic epithelial cyst lining including dentigerous cyst.[18-22]



• **Figure 17-8** **A,** Photograph of an enucleated clinically diagnosed odontogenic cyst, intraoperatively filled with gauze to maintain its shape before fixation. **B,** Frozen section raised the issue of the possibility of early ameloblastoma because of this palisading basal cell layer and stellate-like epithelium. **C,** Permanent sections from the shape-maintained cyst facilitated sectioning of the focally thickened wall and the diagnosis of unicystic ameloblastoma.



• **Figure 17-9** **A,** Photomicrographs of epithelial lining of a dentigerous cyst showing non-keratinizing stratified epithelium with no inflammation of the cyst wall. **B,** Cell contents are proteinaceous debris. **C,** Mucous metaplasia with frequent presence of "goblet" cells.

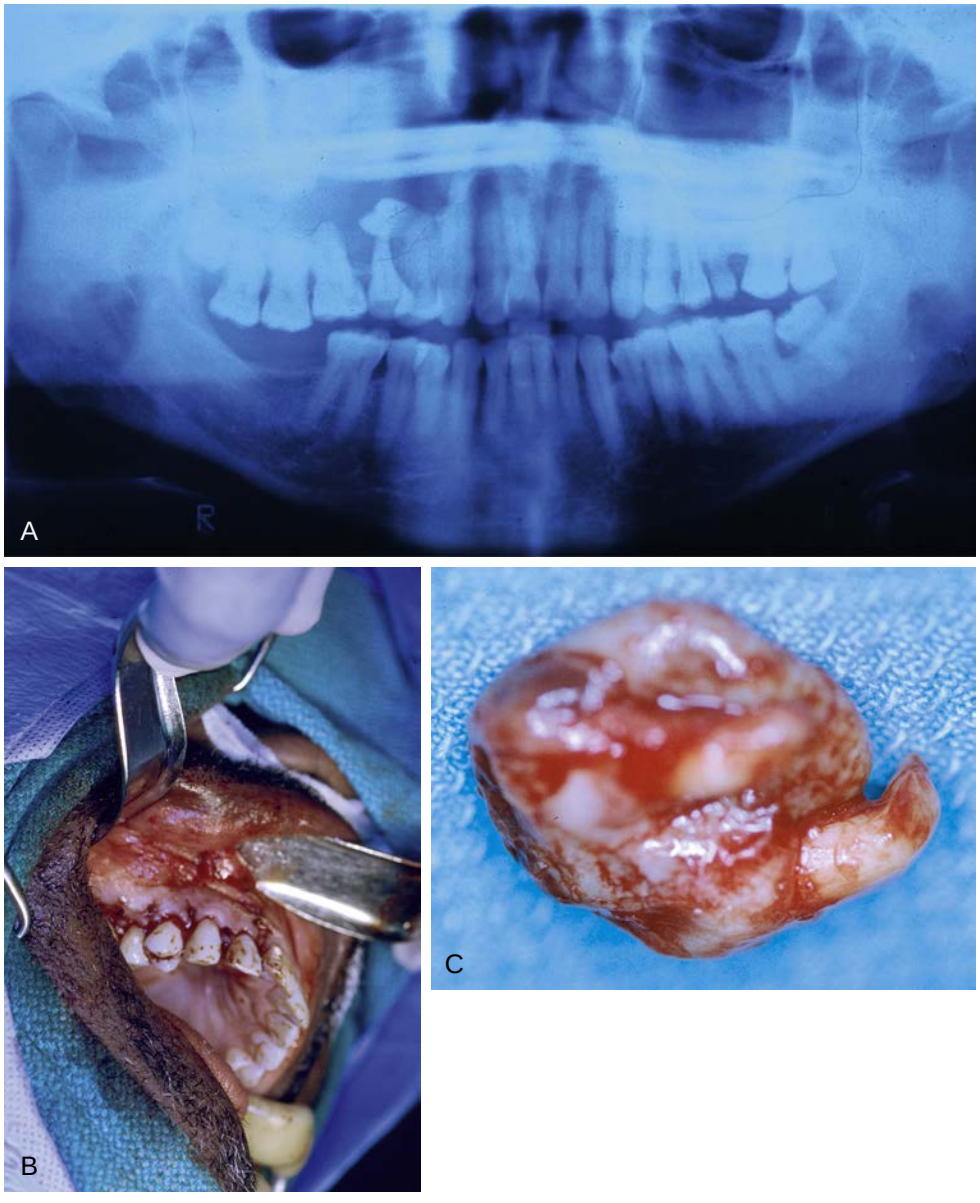
Surgical Management

Frequently, small dentigerous cysts associated with impacted teeth are totally enucleated during the surgical removal of these teeth (Figures 17-10, *A-C,* and 17-11). The majority of these cases are usually done in an outpatient setting, and it is critical that the cyst lining be submitted for histologic examination to rule out any unexpected metaplastic or proliferative changes. Although such changes may not necessarily change the performed surgical treatment, it should certainly change the follow-up protocol if the rendered diagnosis indicates a lesion with a history of significant recurrence rate such as an odontogenic keratocyst or ameloblastoma. On occasion, dentigerous cysts and their associated impacted teeth may require an extraoral approach and/or osteotomy in the mandible or a transantral maxillary approach in the maxilla (see Figure 17-6, *C*).

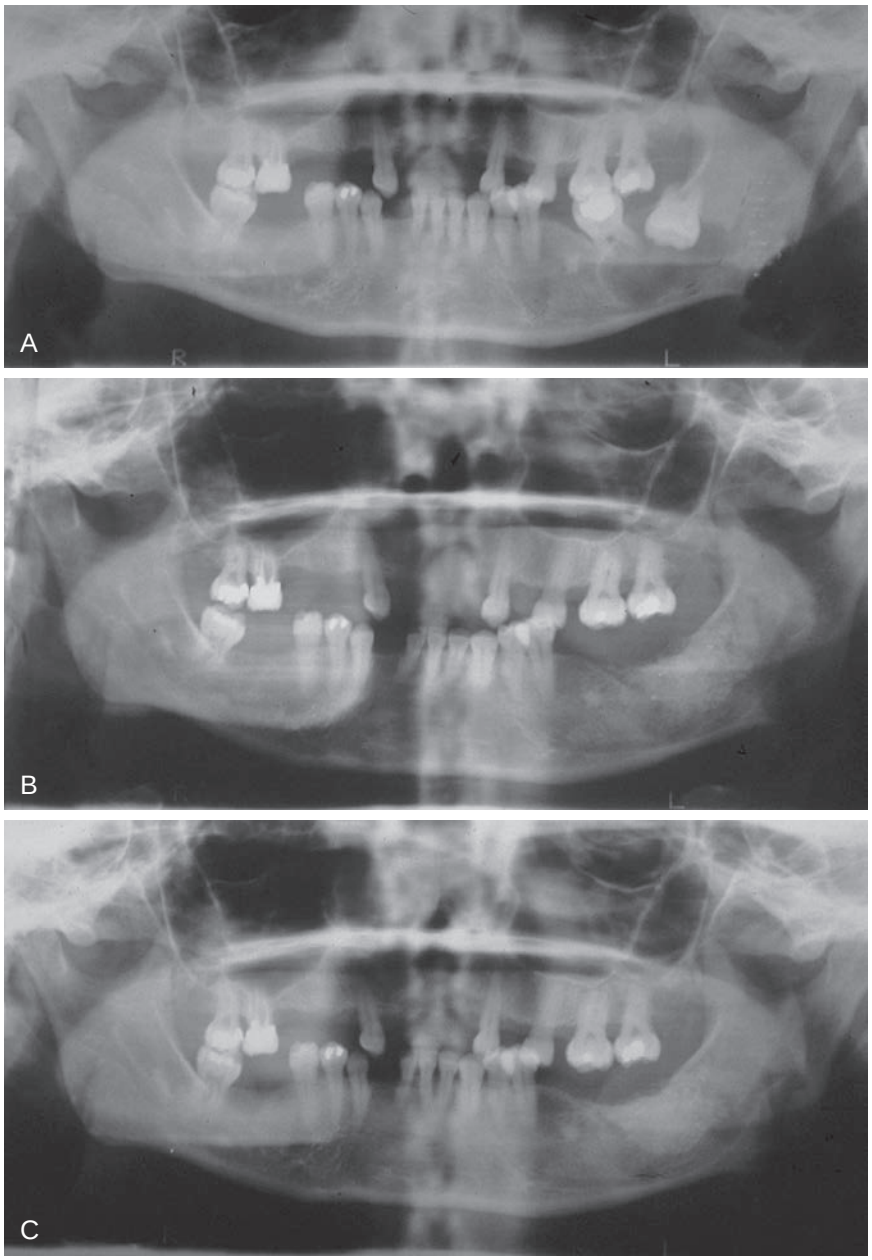
Keratocystic Odontogenic Tumor (Odontogenic Keratocyst)

Etiology

The keratocystic odontogenic tumor (KCOT) is a histologic diagnosis and can, therefore, clinically and radiographically present as any of several odontogenic cysts.[23] Because of its odontogenic keratocyst (OKC) to keratocystic odontogenic tumor. This change was based on several factors, including its high recurrence rate clinically, its histologic appearance, and the presence of tumor markers within the lesion. Specifically, the tumor markers associated with KCOTs include



• **Figure 17-10** **A,** Panogram of a dentigerous cyst associated with an impacted right maxillary first premolar. **B,** Intraoral buccal sulcus incision and exposure of the cyst. **C,** The enucleated specimen with the associated tooth.



• **Figure 17-11** A series of preoperative panograms of a dentigerous cyst of the left angle of the mandible **(A),** allogeneic bone grafting several months postoperatively **(B),** and good consolidation of the bone graft 2 years after enucleation **(C).**

proliferating cell nuclear antigen (PCNA), matrix metalloproteinase (MMP) 2 and 9, p53 protein, Ki-67, and BCE2 sequence of the enzyme dihydrolipoyl acetyltransferase. The KCOT may histologically be subdivided into parakeratotic and orthokeratotic types, which are discussed in more detail later in the chapter. This reclassification by the WHO refers

Keratocystic odontogenic tumors have characteristic features that are unique compared to other cysts of the maxillofacial region. However, the origins of these unique lesions have long been a topic of debate. Whereas the primordium of the tooth was originally thought by many authors to be the origin of these cysts, it is now the dental lamina that is thought to be the most likely origin.[26] The basal cell layer of the oral epithelium is also thought to possibly play a role in the etiology of these cysts. At approximately the sixth week of gestation, the future alveolar processes of the mandible and maxilla begin to form invaginations. These invaginations are the beginning of the dental lamina, consisting of epithelium that remains connected to the overlying epithelial tissue until the tooth buds of the deciduous dentition begin to form. When this connection "loosens," it supports the theory that remnants of the epithelium remain in the gingiva. This would mean that when teeth erupt, they

would have to do so through these remnants. However, as pointed out by Stoelinga,[26] this is where the theory proves to be flawed, as these small microcysts that are often seen in this epithelium do not show the characteristic features of the typical KCOT. The dental lamina that extends to the lingual surface of the mandibular tooth buds and the palatal surface of the maxillary tooth buds, and eventually forms the permanent dentition, does not have a connection with the overlying epithelium. Therefore it is possible for these islands to be enclosed in bony crypts. Some of these cysts (for instance, lateral periodontal cysts) do have characteristics of KCOTs. Other potential causes, though unlikely, include a genetic trigger. The fact that KCOTs are often present with nevoid basal cell carcinoma syndrome could indicate this. A responsible gene has been located for this syndrome, and although it is unlikely to be the same gene that would play a role in solitary KCOTs, it does have a presentation that is quite similar.[26] No matter what the true origin may be, the dental lamina and basal cell layer, offshoots from the mucosa, have been repeatedly documented to be the areas in which KCOTs are attached to the oral mucosa.[27-29]

Clinical Features

patients and accounted for 292 cysts (11%). Keratocystic odontogenic tumors occur over a very wide age range, starting from the first decade of life to as late as the ninth. There seems to be a peak in the frequency in the second and third decades. The peak seems to be roughly a decade younger for females.[31] Data, however, have shown that KCOTs are found much more frequently in men than in women. This finding is even more pronounced in the black community. One study found the male to female ratio in the black community to be as high as 5:1.[32]

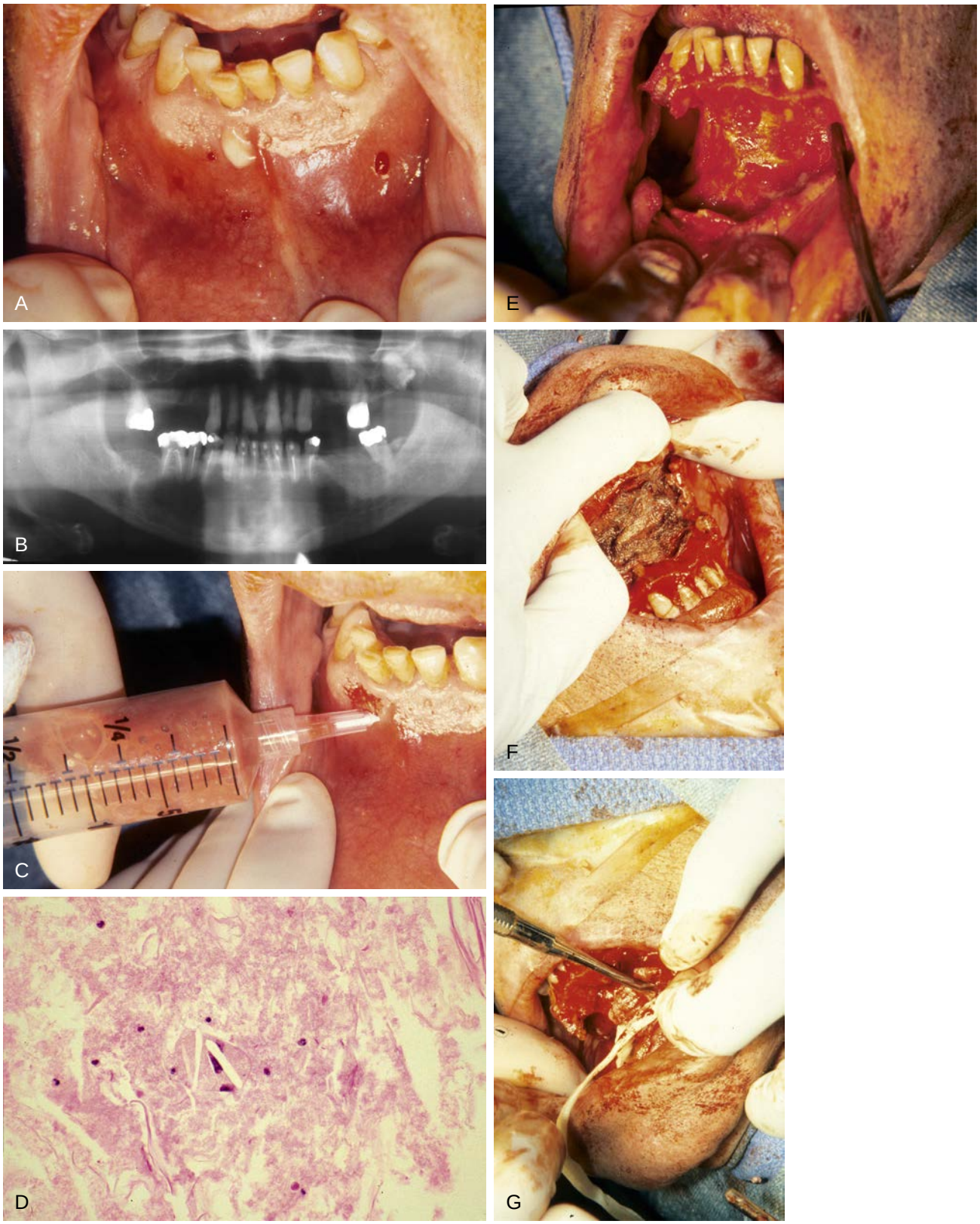
The most common site for keratocystic odontogenic tumors is by far the mandible. Findings ranging from 69% to 83% have been reported in the literature.[23,28,30,33-39] Approximately 50% of all KCOTs occur in the mandibular angle region. These can extend in any direction and become quite large and aggressive. There seems to be an increase in the number of KCOTs seen in the maxilla after the age of 50.[39] KCOTs that occur in regions other than the mandibular angle seem to be more related to systemic syndromes, especially those KCOTs that occur in the maxilla.[40,41] Common clinical findings associated with KCOTs are pain, swelling, and discharge (Figures 17-12, 17-13).

There also may occasionally be paresthesias of the lower lip if the inferior alveolar nerve has been impinged upon. Many patients are oblivious to the lesion until it is found on clinical and/or radiographic examination (see Figure 17-17, *A*). The cysts can vary greatly in size. Forssell[42] found that nearly half of all the KCOTs he studied were at least 40 mm in diameter, especially those that were in the ramus region of the mandible. Also, the larger these lesions become, the more likely they are to lead to displacement of teeth or other adjacent structures, such as the maxillary sinus (Figures 17-14, *A*, and 17-17, *C*). Some authors have reported very aggressive KCOTs that have penetrated into surrounding soft tissues.[43,44] Expansion has been reported to occur in up to 60% of cases.[36] Continuing investigation into their pathogenesis and optimal surgical management stems from the high recurrence rate. The incidence of recurrence for KCOTs has long been documented (see Figure 17-14). Recurrence rates ranging from less than 10% to more than 60% have been reported over the years.[30,36,37] As reported by several clinicians, there seems to be no definitive correlation between recurrence and patient age, location of the cyst, method of treatment, nature of cyst lining, or presence of cortical perforation, and whether or not the cyst was unilocular or multilocular.[33,35,45,46] However, others have found some correlation in recurrence rates with regard to location of the cyst.[32] Still others have also found there to be a correlation in regard to the type of procedure used to treat the original lesion as well as the type of cyst lining the original cyst.[47-49] Forssell and colleagues[50] found a significant recurrence rate in those patients whose KCOTs were found in conjunction with nevoid basal cell carcinoma syndrome. The reason for such a broad range of recurrences is yet unknown, but many theories have been suggested. Operative approach, improved clinical follow-up over 5 years, and improved intraoperative techniques are among the proposed factors related to the modulation of the recurrence rate (Figure 17-15).

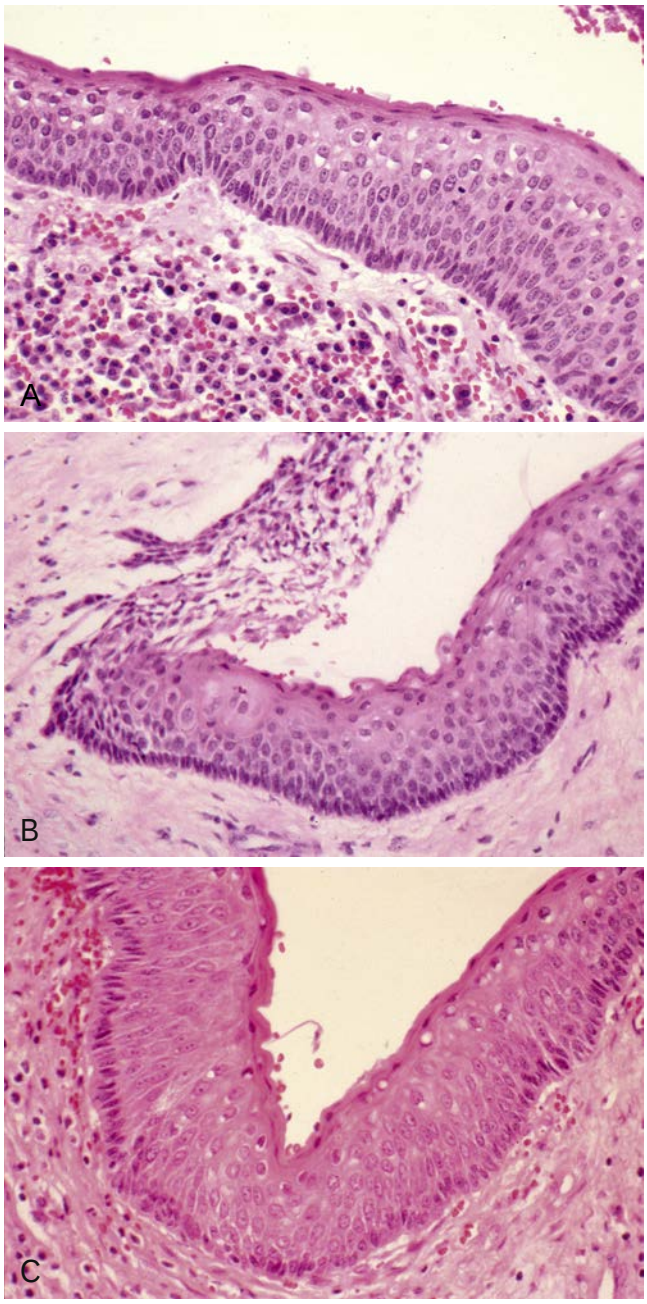
With such a high potential for recurrence, the following question must be asked: Why do KCOTs tend to recur so often? The most obvious reason is incomplete enucleation of the original cyst. KCOTs have a tendency to occur in multiples. This may be due to the occurrence of satellite cysts, which if not removed surgically can lead to recurrence[30] (Figure 17-16, *A* and *B*). Second, KCOT linings tend to be very thin and fragile, which makes them much more difficult to remove completely than cysts with thick wall linings. This increases the potential of leaving part of the cyst wall behind when enucleating these cysts. This has been demonstrated by several investigators.[34,49,50]

For some time now, investigators have examined KCOTs having intrinsic growth potential.[51] It is now believed that patients with a predisposition to form keratocysts, particularly those with nevoid basal cell carcinoma, will always have the potential to form keratocysts as long as a dental lamina or its remnant is present.[52-54] Stoelinga and colleagues[27,55] have theorized that cysts arise from proliferation of basal cells of the oral mucosa, or hamartomas. They particularly thought this to be the case in the mandibular ramus and angle regions. They felt that when KCOTs were removed this mucosa should also be excised to help prevent recurrence. In any event, the exact cause for recurrences is not yet known, and very well may be multifactorial. To that extent, it has been suggested that KCOTs may be designated as benign neoplasms. This is supported by histologic, immunochemical, and genetic studies.[35,46,52-54]

As previously stated, the keratocysts can be divided into two distinct variations, namely orthokeratotic and



• **Figure 17-12** **A,** An 83-year-old man complained of pain and discharge from the anterior mandible. **B,** Panogram showed a large cyst that was difficult to diagnose. **C,** Aspiration was done and submitted for cytopathologic examination. **D,** Cytopathology suggested parakeratotic odontogenic cyst because of the scattered keratin debris and few scattered parakeratotic cells. **E-F,** The patient underwent cystectomy without extraction of any teeth along with chemical cauterization of the cyst bed and **(G)** iodoform packing. (Surgery performed by Otto Tidwell, DDS, Philadelphia.)



• **Figure 17-13** Photomicrographs from the patient illustrated in Figure 17-12. The histopathology is the classic picture of an odontogenic keratocyst. **A,** There is marked inflammatory cell infiltrate in the wall of the cyst with multilayered stratifying and parakeratotic luminal surface. **B,** Partial ulceration of the epithelial lining does occur, especially in infected cysts. **C,** The higher magnification shows the classic palisading of the columnar basal cells and corrugated luminal surface.

parakeratotic. The orthokeratotic lesions were first reported in literature by Schultz in 1927.[56] He described these as multilocular cysts. Wright[57] studied 60 cysts diagnosed as KCOTs, and found 13% of those lesions to be of the orthokeratinized variety. Approximately half of these lesions showed separation of the epithelium from the connective tissue. There also was no recurrence after 1 year of follow-up. He concluded that the orthokeratinized variety of KCOTs was a distinct biologic entity from their parakeratinized counterparts and showed a much lower potential for recurrence.[57] Recently, more evidence has shown that there is a distinct difference in the expression of keratin proteins (specifically, 10, 13, and 14) as well as collagen (types 1 and 3) when comparing parakeratotic and orthokeratotic KCOTs.[58]

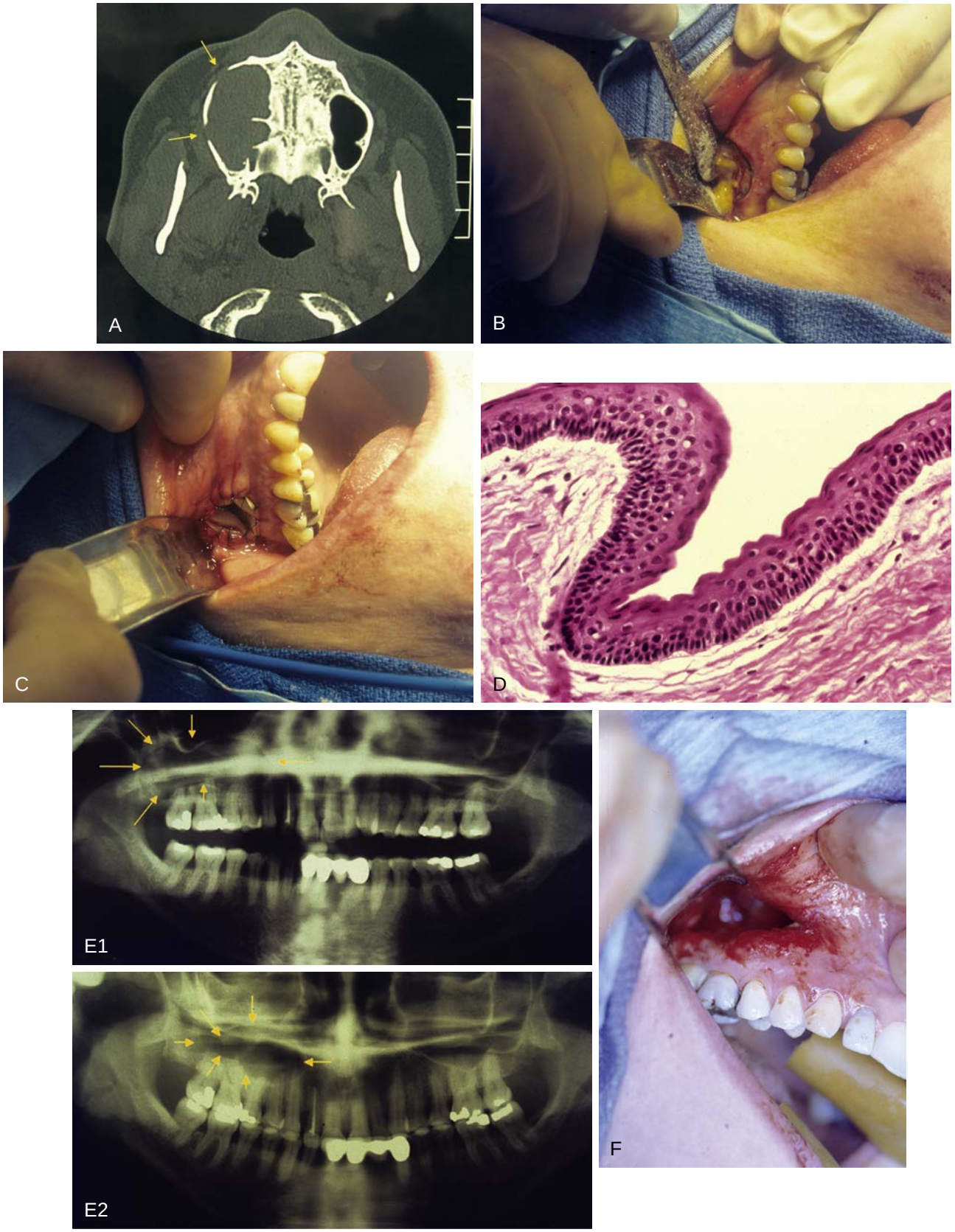
It has also been suggested that *orthokeratinizing keratocyst* is an outdated term and the lesion should not be called keratocyst at all, but instead referred to as a cyst that produces keratin, recognizing its low propensity for recurrence and the distinct histologic difference between the two lesions in question.[9]

Imaging Features

Radiologic findings seen with KCOTs include lesions that appear either unilocular or multilocular on either traditional radiographic film or CT scan (see Figures 17-12, *B*, and 17-14, *A*; Figure 17-17, *A-C*). Scalloping may be seen with these lesions as well. On CT scan, expansion of the cortical bone may be more readily apparent than on plain film (see Figure 17-14, *A*). Also, cortical perforation can be determined on CT scan or magnetic resonance imaging (MRI), which can be a determining factor in treatment plans, as discussed later. In addition, KCOTs are typically found with unerupted teeth. This is especially true with initial lesion presentation, although lesions that recur will not have association with unerupted teeth. Naturally these imaging features are not diagnostic, but corticated scalloped margins with moderate expansion of the jaw are highly suggestive of KCOT (see Figure 17-17, *A*).

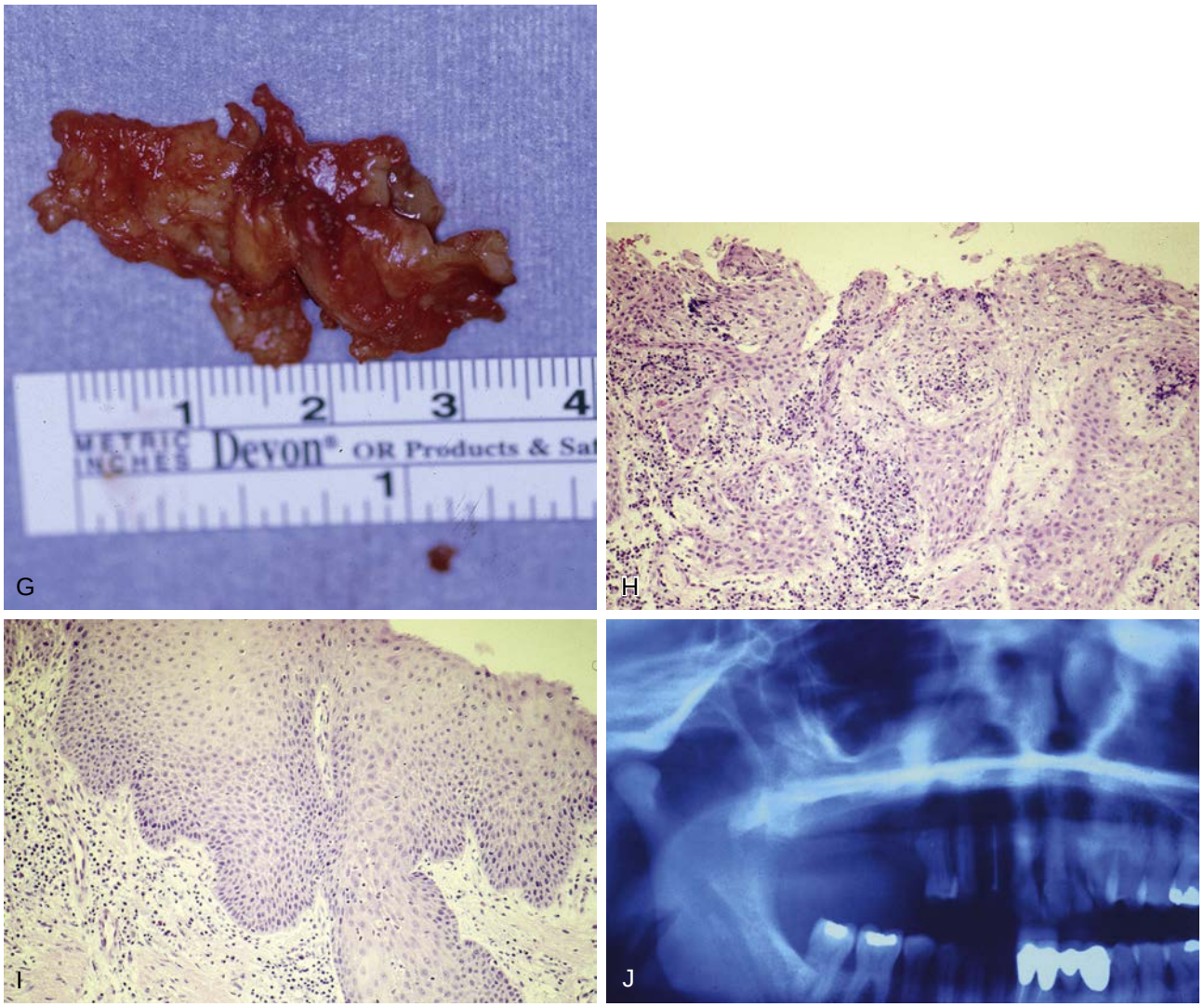
Pathologic Features

Undoubtedly, the most distinctive characteristic of the KCOT parakeratotic subtype is the presence of parakeratin (see Figures 17-13 and 17-16). It is so unusual that its presence along with other characteristic findings makes diagnosis usually obvious.[55] Histologic features include an epithelial lining of parakeratinized stratified squamous epithelium, ranging from 6 to 10 cell layers thick (see Figures 17-13 and 17-16). This epithelium also lacks rete pegs that create a flat interface between epithelium and connective tissue (see Figures 17-16, *B*, and 17-19, *D*). Small areas of orthokeratin may also be found, though this is rare. There is a well-delineated basal cell layer that is composed of columnar and cuboidal cells. Corrugation of the surface along with keratin in the lumen is also seen with parakeratinization (see Figure 17-16, *D*).[59] Although epithelial dysplasia has been described,[60] it is very rare; however, reports of squamous cell carcinoma have been published.[61-63] Mitoses are seen in both the basal and the parabasal regions of KCOTs. In 1970 Main[64] showed that the proliferation of cells in KCOTs was approximately four times that of non-odontogenic cysts and twice that of radicular cysts. In fact, it is more similar to that of ameloblastoma and the dental lamina. The wall of the KCOT is made up of a fibrous tissue that has mucopolysaccharides and normally has no evidence of inflammation (see Figure 17-14, *D*).



• **Figure 17-14** A 45-year-old woman with history of enucleated odontogenic keratocyst (OKC) in 1987 was seen with a recurring cyst initially seen in July 2003. **A,** Computed tomography scan of the recurring large cyst showed encroachment on the right maxillary sinus. **B,** A two-stage operation was done. Note the creamy contents of the cyst through the decompression site. **C,** A Penrose drain placed to maintain patency. **D,** The excised window showed classic OKC microscopic features. **E,** Original size of lesion shown by the *arrows* in *E1* panogram; 9 months later the cyst showed significant shrinkage (*arrows, E2* panogram).

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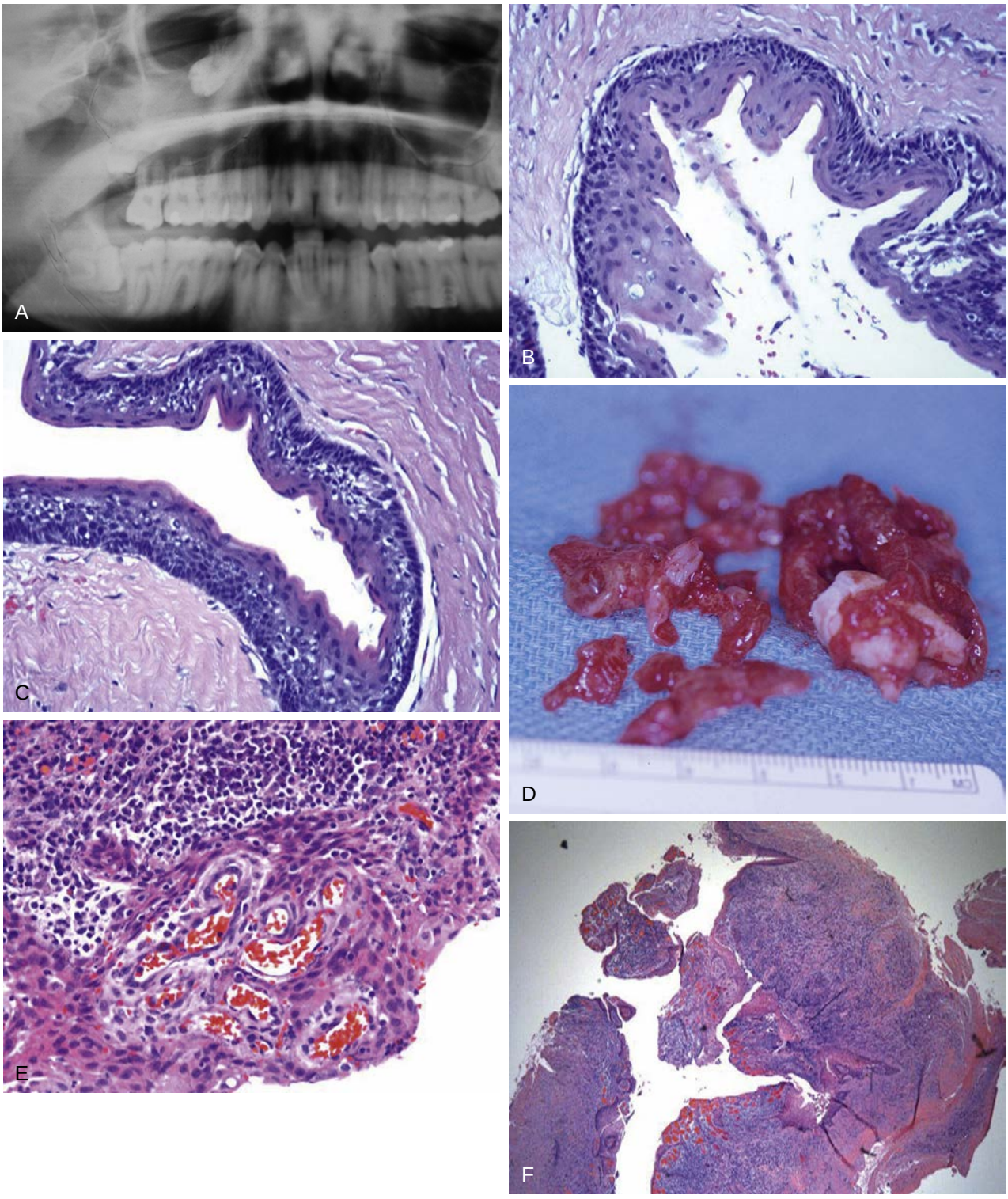


• **Figure 17-14, cont'd** **F-G,** The second stage was then performed with enucleation followed by cauterization by Carnoy solution and excision of the window margin. **H-I,** The resected specimen clearly showed the marked change of the epithelial lining to hyperplastic stratified squamous epithelium with intense inflammatory cell infiltrate of the cyst wall. **J,** Subsequent extraction of the maxillary molars was done, and the patient is currently free of recurrence as shown in the panogram taken in August 2005, revealing good bone healing.

There are instances in which KCOTs do in fact become infected and/or inflamed (see Figure 17-13, *A*). These lesions will have an even higher rate of proliferation than those that are not infected.[65] These lesions also show a tendency to change their epithelial lining to nonkeratinized[65,66] (see Figure 17-13, *B*). Satellite or "daughter" cysts may also be noted in the connective tissue wall of an OKC, but this is a more common finding when the KCOT occurs with nevoid basal cell carcinoma syndrome[67] (see Figure 17-16, *A* and *B*). Features unique to the orthokeratinized KCOT are an epithelium composed entirely of orthokeratinized stratified squamous epithelium two to three cell layers thick. There is obvious lack of palisading of the cuboidal basal cell layer, as characteristic of the parakeratotic variety. There are also no corrugations of the luminal surface, and there are abundant keratohyaline granules in superficial cells and pronounced orthokeratin in the lumen (Figure 17-18, *D* and *E*).[68]

Ultrastructure

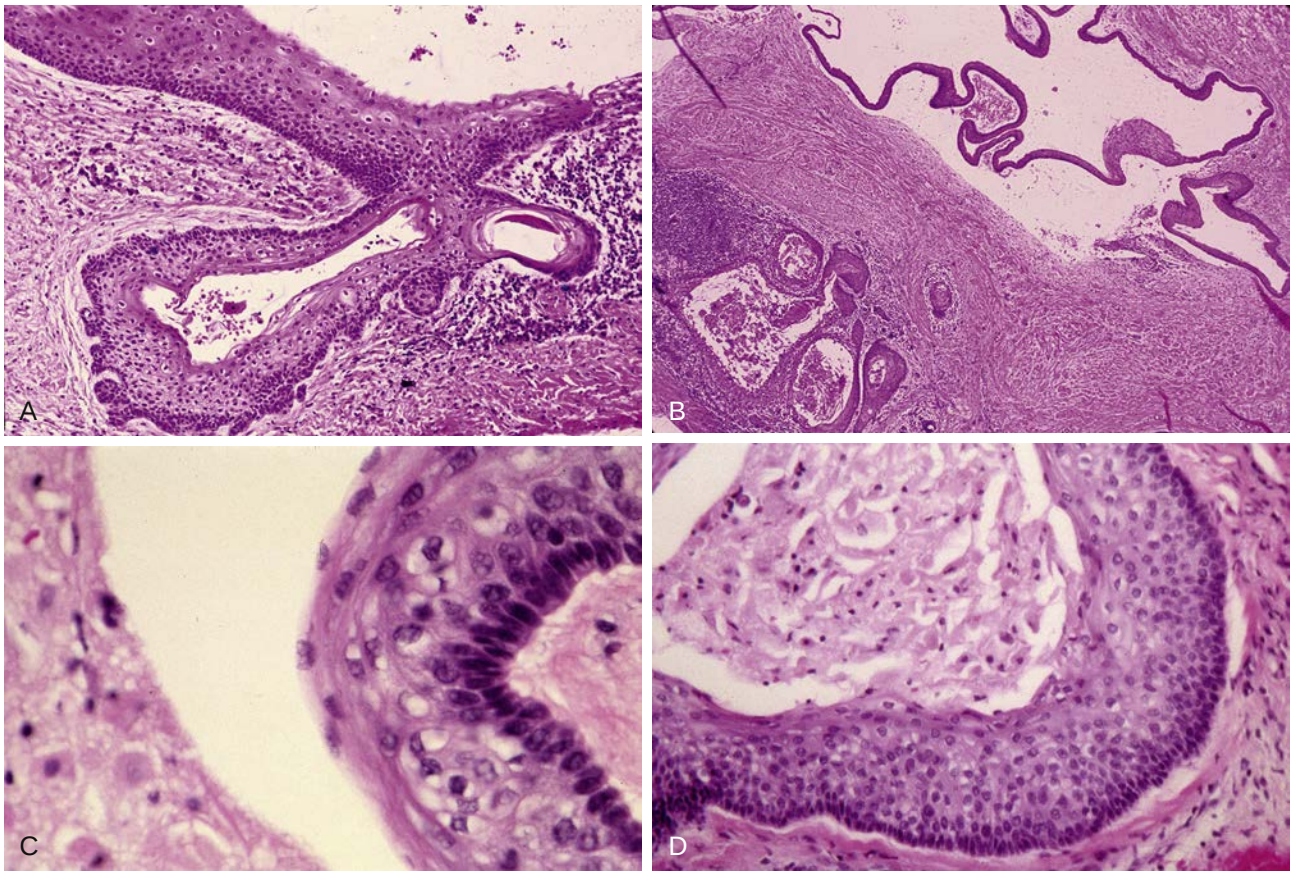
Features seen in KCOTs include deep epithelial folds, desmosomal junctions, and tall columnar basal cells, which can show some variation. Glycogen is a usual component of the cytoplasm in KCOTs (see Figure 17-16, *C*). It has been suggested that there is an increase in glycogen levels when KCOTs are associated with nevoid basal cell carcinoma syndrome.[69] Wysocki and Sapp[70] showed that there were definitive differences between the parakeratinized and orthokeratinized KCOTs. They found that the morphology of the orthokeratotic version is more uniform and entirely covered in a layer of keratin. There is also an increase in tonofilaments as the cells mature. The granular cell layer consists of compacted degenerated cells that contain keratohyaline granules, with the luminal surface consisting of shreds of orthokeratin[68] (see Figure 17-18, *D*).



• **Figure 17-15** **A,** A 19-year-old man presented with impacted teeth and clinical diagnosis of dentigerous cyst of the right maxilla. Panogram showed the large cyst with the associated impacted molar. The computed tomographic scan (see Figure 17-6, *C*) and aspiration of keratin debris raised the possibility of odontogenic keratocyst (OKC). A two-stage procedure was undertaken. **B-C,** The histopathology showed classic features of OKC. **D,** Eight months after decompression, enucleation was performed. **E-F,** The cyst lining shows the marked microscopic changes with intense inflammation and stratified non-keratinizing stratified epithelium with marked hyperplastic proliferation and no classic features of OKC.

Surgical Management

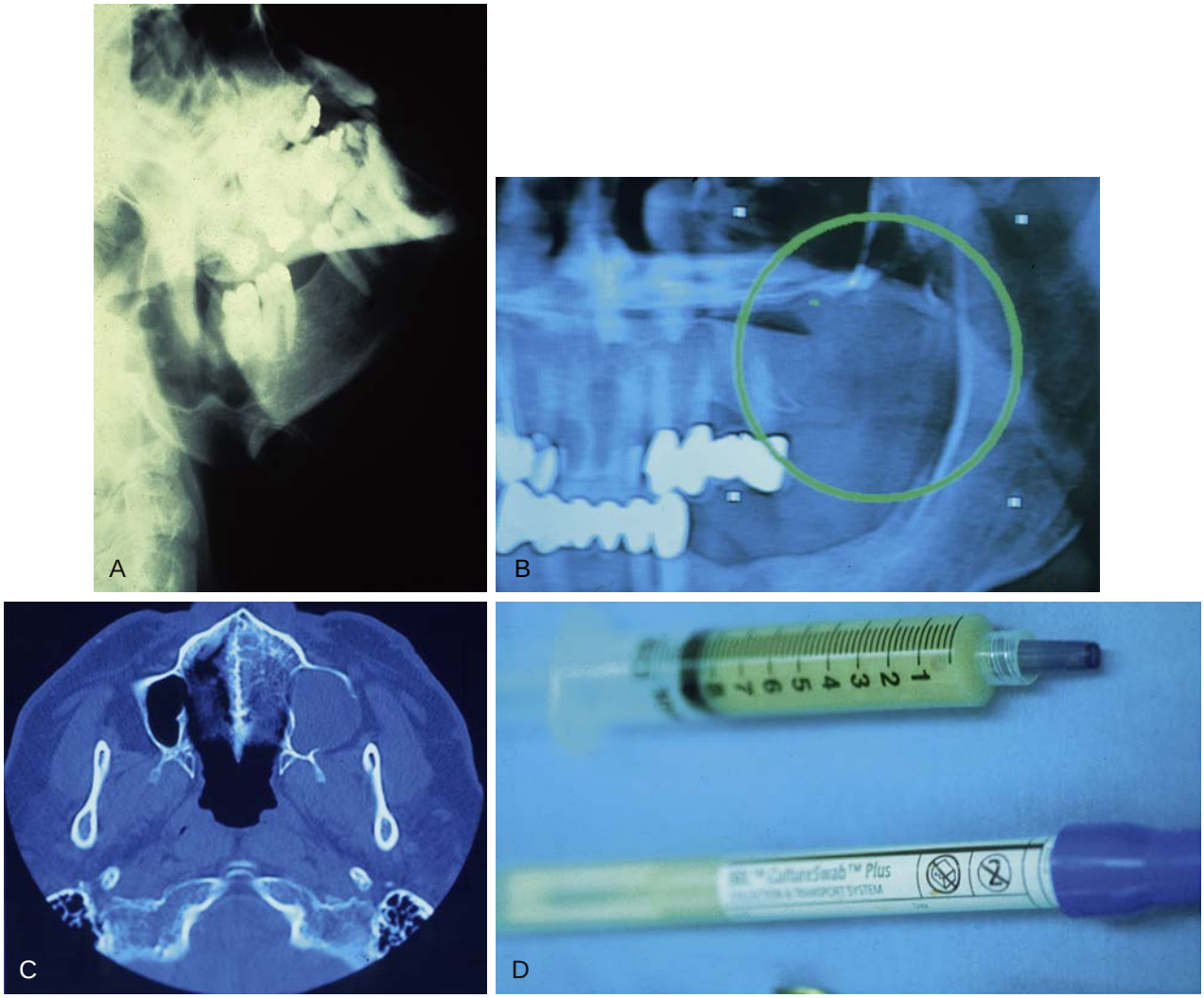
The management of KCOT, the parakeratotic subtype, has evoked considerable discussions and raises several questions in regard to the optimal approach for its management (see Figures 17-12, 17-14, 17-17, and 17-18). Unfortunately, the issue is yet to be settled, and long-term studies are needed. There are many options and opinions for the surgical management of KCOTs. In 2006 Herb[71] contributed a thorough review of the literature of the treatment modalities of these lesions. Ghali and Connor,[72] in 2003, reviewed the surgical management of the KCOT. They reviewed the available treatment and concluded that debate still exists as to the most effective treatment for this lesion. They included enucleation and curettage, enucleation with peripheral ostectomy, complete resection, enucleation with cryotherapy or chemical adjunct therapy, and decompression and marsupialization as treatment modalities. Enucleation and curettage is considered the most conservative treatment option for KCOTs. However, the highest frequency of recurrence is seen with this method of treatment, and therefore it is no longer recommended by most authors as an appropriate initial therapy.[72] However, several studies have shown that KCOTs delivered in one piece reduce this risk. As discussed previously, the friability of the cyst lining often makes this difficult. Peripheral ostectomy is thought to be an adjunctive treatment option when a total resection can be avoided.[72] The thought process behind this technique is that as cysts grow in size, usually their borders will also increase in irregularity, making it harder to remove them in one single piece. At the very least, the surgeon should ensure that all bony margins are clear of cyst lining; this requires the surgeon to use an instrument, usually a rotary round burr, and remove the bony periphery of the cystic cavity. As described by Ghali and Connor,[72] the problem associated with this technique is that there is no way to determine the amount of bony removal that is sufficient. Methylene blue dye has been used to stain the periphery of the cyst cavity, but the depth of staining from methylene blue is not known. Osseous resection is frequently considered the most extensive form of treatment for KCOTs (Figure 17-19). However, some clinicians feel that a benign cyst does not warrant such an approach, whereas others have shown that it is consistently the only form of treatment that approaches, or has, a zero recurrence rate.[38,43,73,74] The reason for this success seems to stem from the fact that the entire lesion is removed en bloc along with the surrounding margin of bone, usually 1 cm.



• **Figure 17-16** Other microscopic features of odontogenic keratocysts frequently present are **(A)** budding of the cyst lining into the connective tissue wall, flat epithelial and connective tissue interphase with fragmentation of the cyst lining, **(B)** formation of daughter cysts deep in the cyst wall, **(C)** subnuclear vacuolation of the columnar basal cells and clear cytoplasm (probably glycogen) of the suprabasal layers, and **(D)** exfoliation of parakeratotic cells in the lumen.

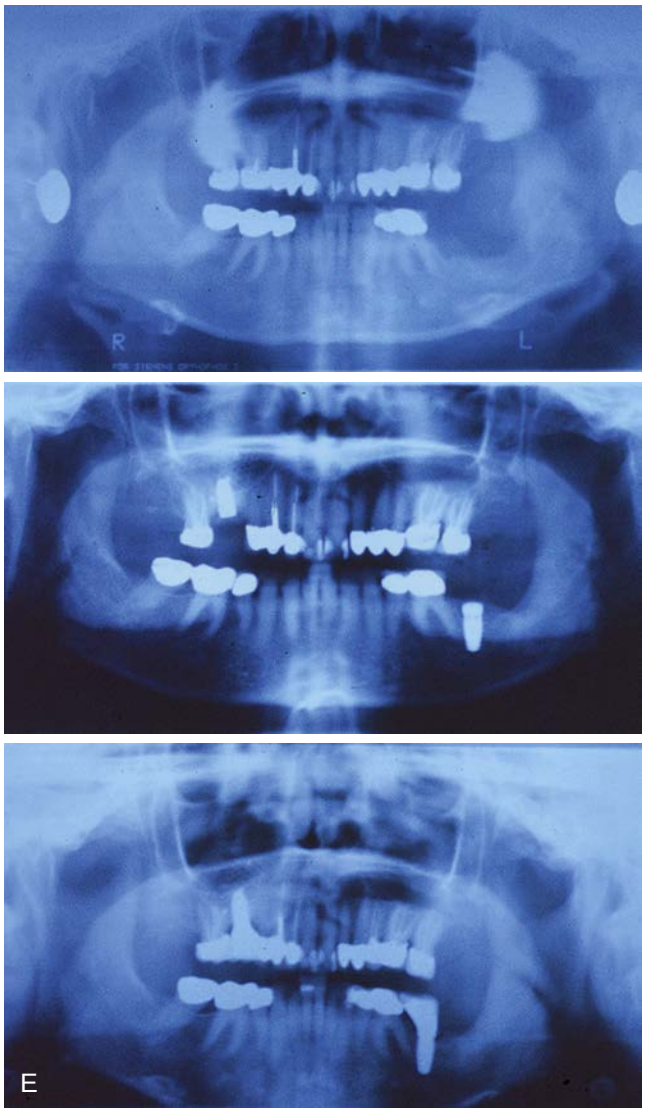
In cases with bony dehiscence, adjacent soft tissue can also be excised. For lesions occurring in the mandible superior to the inferior alveolar nerve canal, some authors have shown success with a marginal resection that spared the inferior border of the mandible.[75] Such large resections, however, do have drawbacks, including the need for future grafting, loss of nerve function, and cosmetic deformities. Use of cryotherapy is another form of treatment for managing odontogenic keratocysts.[76,77] The theory with this technique rests on the centuries-old belief that freezing can kill cells.[78] Freezing, however, does not destroy cells alone, as supercooling actually helps to preserve cells and, in fact, cooling will allow for survival of many tissues.[77,79,80] The technique of cryotherapy involves the formation of ice crystals, both intracellularly and extracellularly. This causes osmotic and electrolyte disturbances that ultimately lead to vascular stasis and then cell death by ischemic necrosis. The premise for using cryotherapy for the treatment of KCOTs rests in killing cells that cannot be seen by the naked eye. By freezing the bone that surrounds the cyst, the bone loses its vitality, presumably as would the cells within that bone. However, the bone does not lose its skeletal properties. After undergoing necrosis, the bone will then be re-formed by new cells in 2 to 3 weeks. Obviously this is a very appealing possibility in preventing the potential morbidity of resection. In addition to cryotherapy, Carnoy solution has been advocated for use in conjunction with surgical treatment.[81,82]

Other treatment options are decompression and marsupialization (see Figures 17-14 and 17-15). This is the process by which the overlying epithelium and bone are removed to essentially deroof the cyst; then, by keeping the hole open by various means, pressure within the cyst is relieved. It is important to realize, however, the difference between the two terms. Tucker and colleagues[83] clarify the



• **Figure 17-17** **A,** Characteristic but not pathognomonic radiographic features of odontogenic keratocyst (OKC) are well-corticated radiolucencies and minimal to moderate buccolingual expansion of common sites such as the angle and ascending ramus of the mandible. **B-C,** In large cases where extensive bone destruction occurred, there are no characteristic features as illustrated in the panogram and computed tomography scan of the same patient. **D,** However, aspiration of a significant amount of the creamy contents pointed toward OKC, which was proven microscopically.

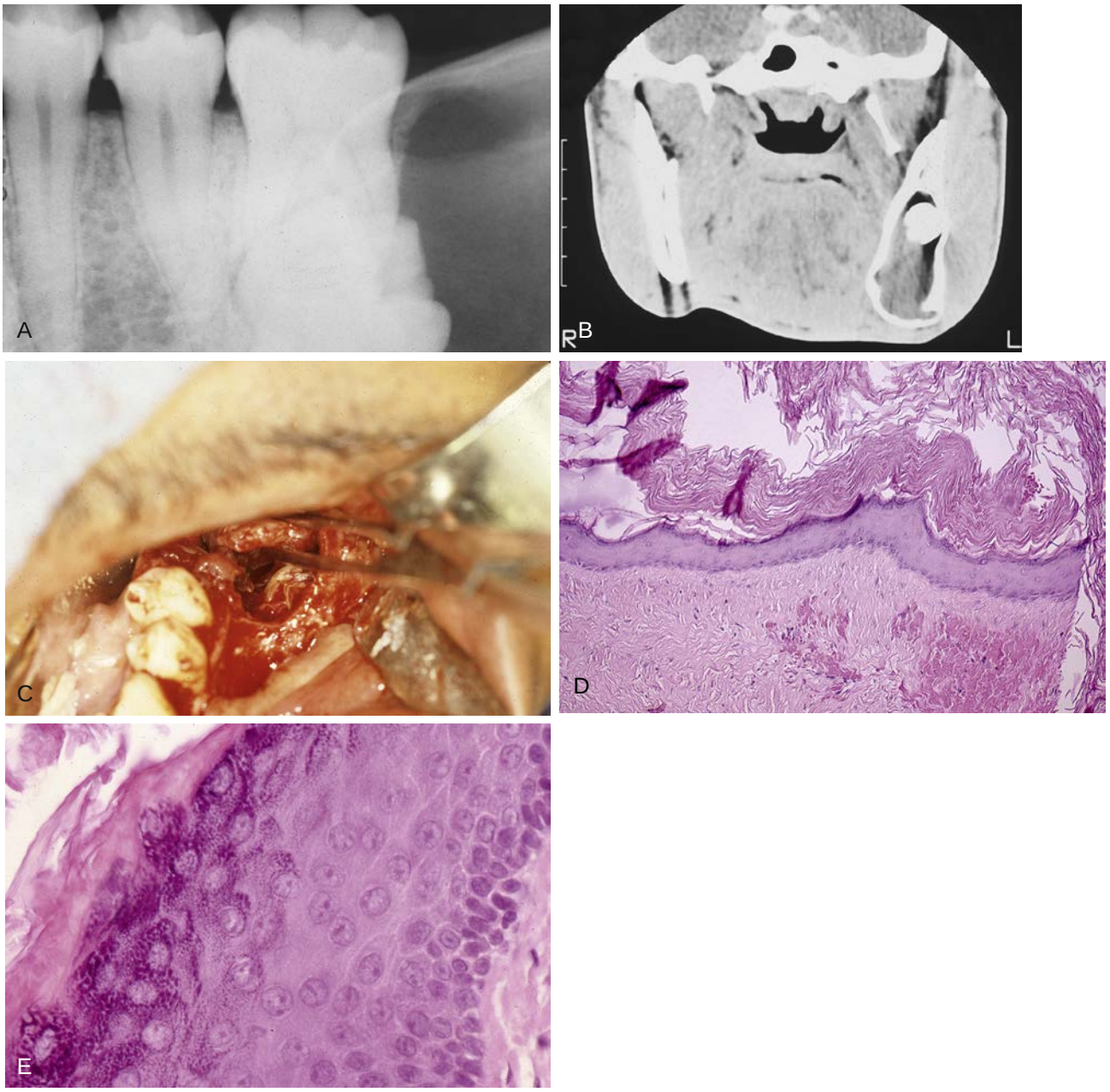
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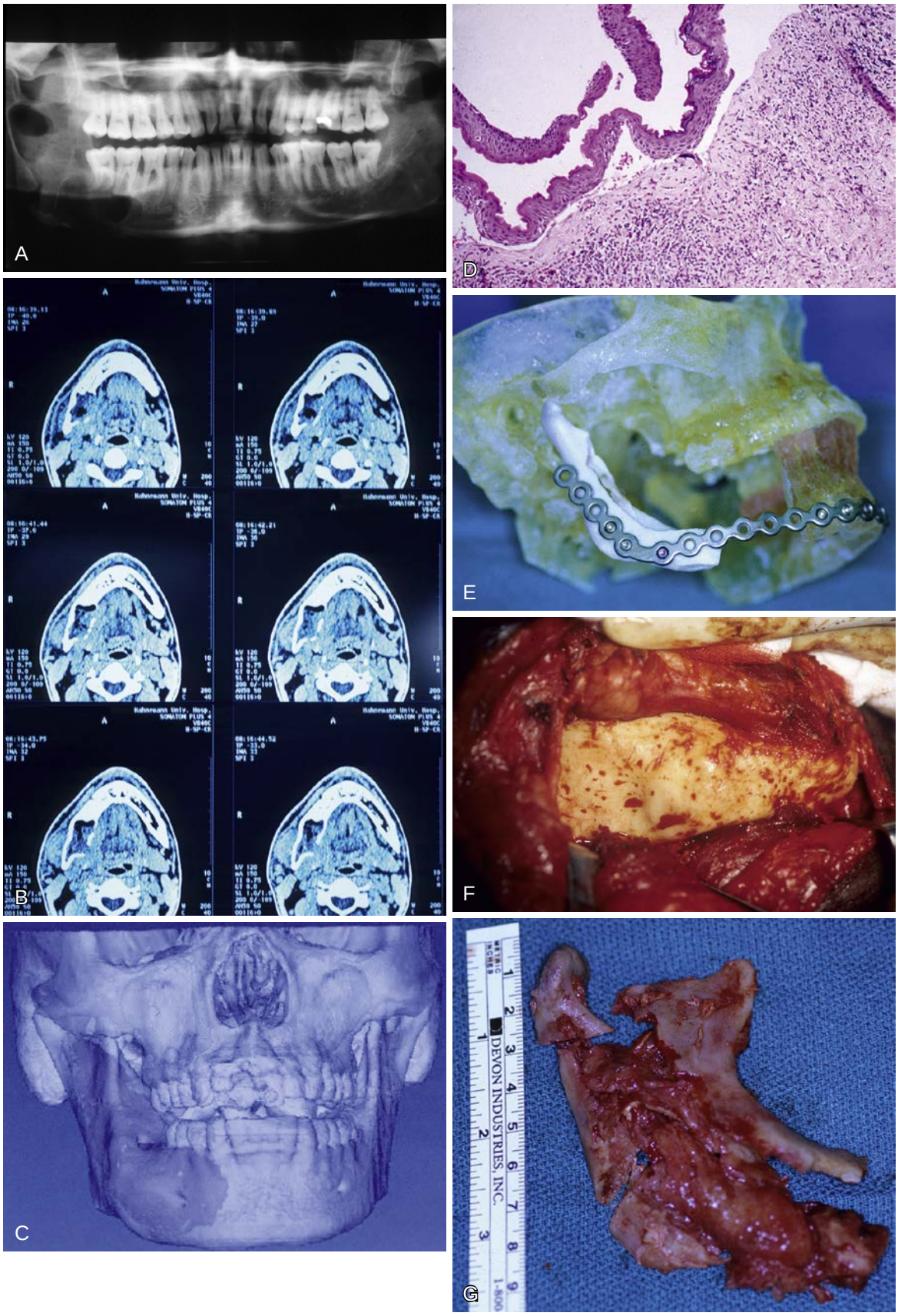
• **Figure 17-17, cont'd** **E-F,** A clinically diagnosed residual cyst proved to be OKC that had been enucleated. With subsequent bone grafting and implant placement, patient is free of recurrence 7 years after enucleation.

difference between the two procedures, despite the fact that both serve the same function and rely on the same principle of bone generation. Marsupialization is a one-stage definitive treatment, whereas decompression should be reserved for two-stage surgery of deroofing of the lesion followed several months later by cystectomy, with or without other adjunct therapy such as chemical cauterization or cryotherapy. There may be a role for marsupialization of large KCOTs; however, this modality of treatment has often resulted in mixed outcomes, especially in older patients.[84] The reported recurrence rate has ranged from 0%[84-87] to 100%.[85] Over the past few years, Pogrel and colleagues[84-88] have been advocating marsupialization and decompression as definitive treatment for KCOTs. However, in 2007 in a letter to the editor of the *Journal of Oral and Maxillofacial Surgery,* Pogrel issued a partial retraction to this concept.[89] He reported a recurrence rate of 12% in 42 of his cases with a maximum follow-up of 5 years. He stated that "in selected cases, decompression and marsupialization may be performed appropriately to decrease the size of the lesion, but once the lesion has been reduced in size sufficiently more definitive surgery is probably necessary"[89] (see Figures 17-14 and 17-15). Decompression has even been found to change the histologic makeup of the cysts themselves. Marker and colleagues[90] showed very good success in a large study of patients with KCOTs in which decompression was followed by cystectomy. They found that using a two-stage technique of decompression and then enucleation proved to be a very promising treatment option. The authors have had good results in the recent years with the two-stage decompression and enucleation technique and have applied it to multiple cases of KCOTs of various size. We have found the technique to be significant in reducing the size of cysts, which allows for easier enucleation and the ability to avoid

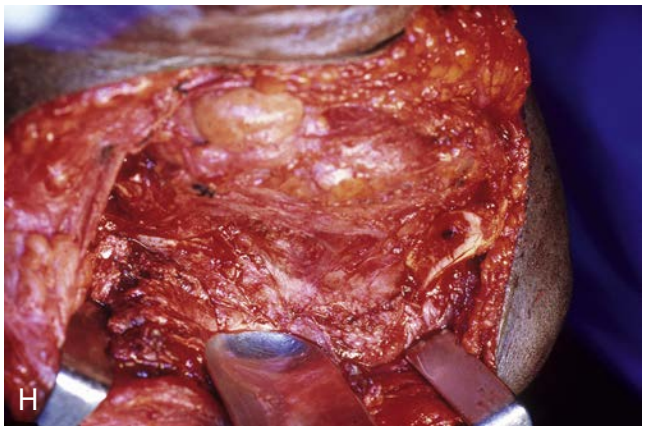


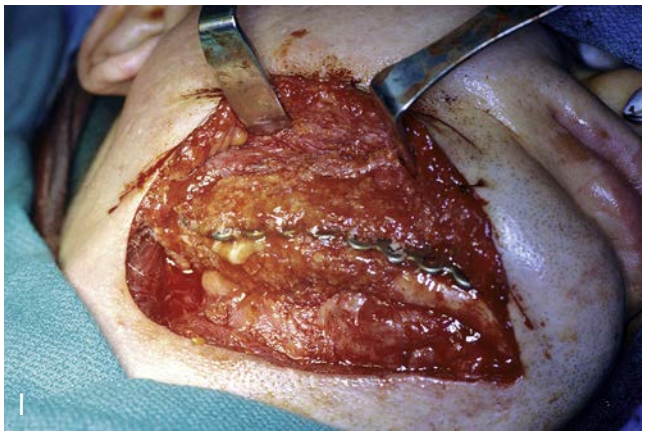
• **Figure 17-18** **A,** A routine periapical radiograph from a 26-year-old man shows a cyst with an associated second molar. **B,** A computed tomography scan revealed a well-corticated unicystic lesion with both impacted first and second molar. **C,** The cyst was enucleated. **D-E,** Histopathology shows stratified squamous epithelium with obvious lack of a columnar and palisading basal cells, marked keratohyaline granules in the superficial cells, and fibrillar keratin in the lumen. Diagnosis of orthokeratinized cyst was established.

large resections (see Figures 17-14 and 17-15). We have also had success when using this technique with recurrent KCOTs. For example, for a 45-year-old woman with recurrence of a maxillary KCOT, a decompression of approximately 9 months followed by enucleation and adjunct treatment with Carnoy solution was performed. The patient had no evidence of recurrence 3 years postoperatively (see Figure 17-14). As always, close and long-term follow-up is essential when treating the odontogenic keratocyst, regardless of the surgical modality used. The benefits of the use of the two-stage surgery approach far outweigh its drawbacks. Decreases in morbidity and fewer social consequences are the two most significant benefits. In summary, the available treatment modalities for KCOT are far from settled. There is no single approach that provides a cure with no or consistently low recurrence rates and simultaneously has limited morbidity. We therefore believe that all available surgical modalities, with the exception of marsupialization as the sole treatment, have a place in the armamentarium of the treating oral and maxillofacial surgeon. In small and bony



• **Figure 17-19** A 29-year-old man presented with chief complaint of recurrent pain and swelling for 2 years with no recommended management. A plain panogram **(A)** and 3D computed tomography scan **(B-C)** revealed a destructive lesion of left body and ascending ramus of mandible. **D,** An incisional biopsy led to a diagnosis of parakeratotic cyst. **E,** Preoperative planning was facilitated by stereolithographic model; the patient then underwent hemimandibulectomy with disarticulation. **F-G,** Intraoperatively, the resected specimen shows the expansion and destruction of bone.





• **Figure 17-19, cont'd H-I,** The resected mandible was immediately reconstructed with reconstruction plate with attached metal joint, bone grafting, and plasma-rich platelets. (Surgery performed by Dr. Nabil Abaza and Steven Kaltman, DDS, MD, Fort Lauderdale, FL.)

contained lesions, we believe that cystectomy followed by other adjunct therapies—including chemical cauterization by Carnoy solution or 5% phenol, cryotherapy, or peripheral ostectomy, if practical—offers the optimal chance for good initial management of these lesions (see Figure 17-12). In large cysts, a two-stage procedure (decompression followed by cystectomy and also adjunct therapy) offers a sound approach.

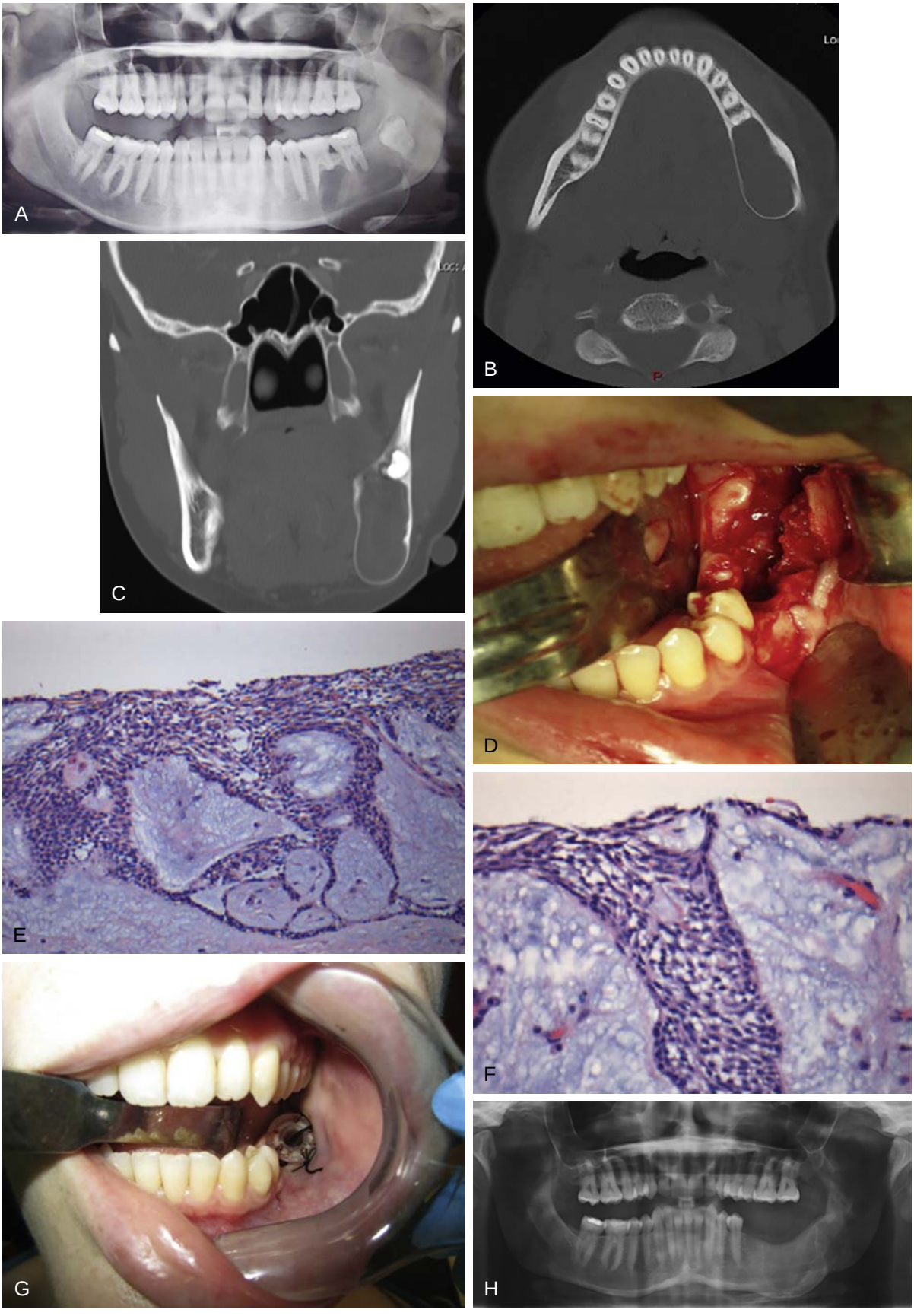
This is particularly the case if there is bony dehiscence in the cyst bed. The bone regeneration and thickening of the cyst wall secondary to inflammation usually facilitate the enucleation of the cyst in one piece. The excision of the gingival tissue around the decompression site is also recommended. In large, particularly multi-loculated KCOTs and those that involve the superior position of the ascending ramus or the posterior maxilla, resection of the lesion with discontinuity defect may be the only sound surgical approach. Therefore hemimandibulectomy, with or without disarticulation, and hemimaxillectomy or partial maxillectomy should also be included in the surgeons' choices. Immediate or delayed reconstruction of the mandible or maxilla is then indicated (see Figure 17-19).

In addition to treatment of keratocystic odontogenic tumors, this two-stage treatment modality has proven successful for unicystic ameloblastomas. Although the topic of ameloblastoma is discussed in much greater detail in other chapters of this book, we have had excellent results with conservative two-stage treatment of unicystic ameloblastoma variants and have incorporated two cases into this section (Figures 17-20 and 17-21). This decompression treatment approach is limited to the unicystic variant of ameloblastomas and cannot be used for multicystic or solid ameloblastoma variants. The solid and multicystic ameloblastoma variants will require marginal resection with 1-cm bony margins around the radiographic limits of the lesion and one anatomic barrier.[91] Thus, CT scan imaging is mandatory during the treatment workup to confirm that the lesion is, in fact, unicystic in nature. Unicystic ameloblastomas typically occur in the third decade of life compared to the fourth for their multicystic and solid counterparts, which makes this conservative treatment modality more appropriate for the younger population typically affected by these lesions. Treatment of unicystic ameloblastomas using a two-stage decompression mandates good patient compliance and close follow-up. These patients must follow up frequently during the decompression period, in addition, to perform daily irrigation of the surgical site. The second-stage enucleation should be performed after decompression stage when there is sufficient bone to prevent damage to adjacent structures.[92] For the cases presented, a decompression stage of 9 months was successfully used.

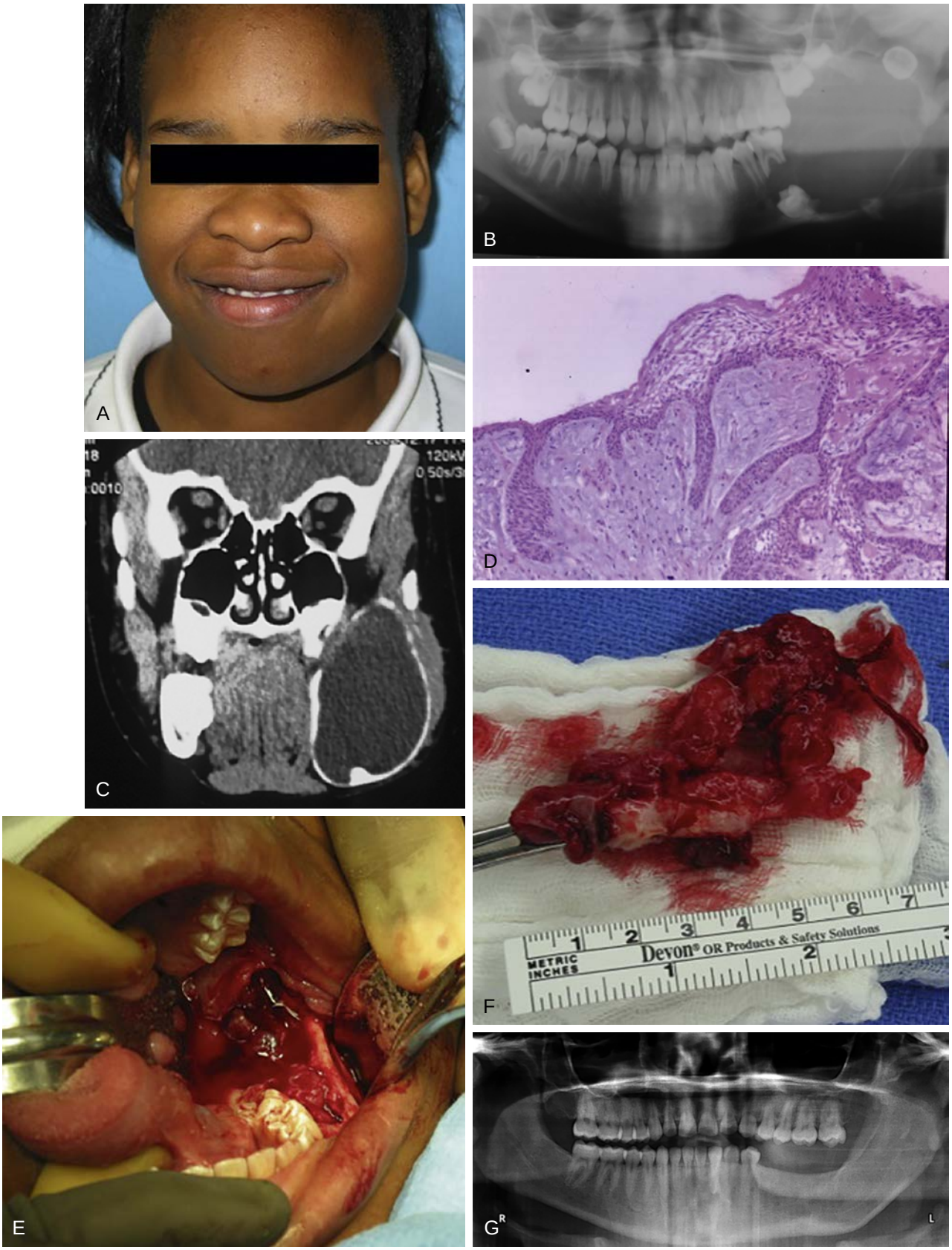
Nevoid Basal Cell Carcinoma Syndrome

Overview

This syndrome is a genetic disorder with autosomal dominant inheritance, high penetrance, and variable expression.[93,94] In 1987 Gorlin[94] reviewed the syndrome history, tabulated the disease findings and their frequency, and commented on the naming of the syndrome. Historically, the syndrome was documented in two ancient Egyptian skeletons where multiple cysts, bifid ribs, relative shortening of the fourth metacarpal, and other skeletal findings were present.[95] In 1951 Binkley and Johnson[96] reported on a 30-year-old woman who had manifestations of the syndrome including numerous basal cell nevi, multiple jaw cysts with associated impacted teeth, and bifid ribs. The patient died from widespread metastases of an osteosarcoma of the jaw, apparently secondary to the irradiation therapy she received. Autopsy showed partial agenesis of the corpus callosum. The patient had a daughter who had many skin lesions as well, and these authors, therefore, speculated that the disease was genetic in origin. It was not until 1960, however, when Gorlin and Goltz[93] established the relationship of multiple basal cell epitheliomas, multiple jaw cysts, and bifid ribs, that the term *nevoid basal cell carcinoma syndrome* was coined. The syndrome also is frequently referred to as Gorlin-Goltz syndrome, Gorlin syndrome, and



• **Figure 17-20** **A,** Radiograph of a 31-year-old woman with progressive left facial swelling. **B,** Axial and coronal computed tomography scan images **(C)** demonstrating the unilocular nature of the left mandibular cystic lesion. **D,** First-stage decompression surgery was completed. **E,** Low-power and **(F)** high-power photomicrographs of the ameloblastic epithelium show evidence of stellate reticulum and reverse polarization of the peripheral column cells. **G,** An acrylic button was placed during the 9-month decompression period, prior to second-stage enucleation. **H,** 1 year postoperative panogram shows good bone healing after second-stage enucleation. (Surgery performed by Dr. Nabil Abaza and Fizza Jaffery DMD, MD, Woodbury Heights, NJ.)



• **Figure 17-21** **A,** An 11-year-old girl presenting with left facial asymmetry. **B,** Panogram obtained at initial consultation and coronal computed tomography image **(C)** confirming unilocular nature of left mandibular lesion. **D,** Photomicrograph of the lesion showing ameloblastic epithelium with stellate reticulum, consistent with the diagnosis of unicystic ameloblastoma. **E-F,** Intraoperative images of the second-stage enucleation of the unicystic ameloblastoma after a 9-month period of decompression. **G,** 6-year postoperative panogram demonstrates successful treatment of the unicystic ameloblastoma without recurrence.

nevoid basal cell carcinoma syndrome (NBCCS) or the syndrome; dermatologists prefer the term *nevoid basal cell carcinoma syndrome*.[6,96,97] Gorlin[94] has expressed his opposition to eponyms because they say nothing about the syndrome.

Genetic studies have found the NBCCS gene to be mapped to chromosome 9, 9.622.3. It is proposed to function as a tumor suppressor by deletion of this region in many of the neoplasms related to the syndrome.[30,31] Tod and August[98] discussed molecular approaches to the diagnosis of sporadic and syndrome-associated KCOTs. The most studied marker is the *PTCH* gene, the human homolog of the *Drosophila* segment polarity gene, which is a tumor suppressor gene located on chromosome 9. These authors stated that the *PTCH* gene is a key regulator of the pluripotent hedgehog signaling network that is believed to have widespread consequences. Several congenital and neoplastic disorders are associated with gene mutations within this network.[98,99] Classic genetic and molecular studies have shown that the *PTCH* gene is mutated in patients with NBCC.[98]

• BOX 17-2 Features of Nevoid Basal Cell Carcinoma Syndrome

Cutaneous

Basal-cell epitheliomas
Milia
Palmar pits
Plantar pits
Epidermal cysts of skin
Subcutaneous calcifications
Cleft lip or palate
Polydactyly

Skeletal

Odontogenic keratocysts
Bifid ribs
Scoliosis
Mandibular prognathism
Increased calvarial diameter
Well-developed supraorbital rims
Spina bifida of cervical or thoracic spine
Hyperpneumatization of paranasal sinuses
Short fourth metacarpals
Marfanoid build

Ocular

Glaucoma
Cataracts
Coloboma of the iris
Hypertelorism
Strabismus
Nystagmus

Neurologic

Calcified falx cerebri
Mental retardation
Cerebral tumors
Agenesis of corpus callosum
Calcified tentorium cerebelli

Sexual

Undescended testes
Ovarian tumors
Hypogonadism

From Rogerson KC: Gorlin's syndrome: an update on diagnosis and management, *Oral Maxillofac Surg Clin North Am* 3:155, 1991.

Clinical Features

neurologic, and sexual[100] (Box 17-2). The components of the syndrome are numerous with varying frequency (Table 17-2). The multiple odontogenic cysts and the basal cell nevi

TABLE 17-2 Components of Nevoid Basal Cell Carcinoma Syndrome and Their Frequency

I. Jaw and Skull	
1. Odontogenic keratocysts	>85%
2. Calcified falx cerebri	> 85%
3. Large calvaria	>60%
4. Large paranasal sinuses	>60%
5. Hypertelorism	>50%
6. Bridging of the sella turcica	>70%
7. Cleft lip and palate	<15%
1. Basal cell carcinomas	>70%
2. Milia/epidermoid cysts	>50%
3. Palmar-plantar pits	>50%
4. Calcified ovarian fibromas	>50%
5. Subcutaneous calcifications	<15%
6. Fetal rhabdomyomas	<15%
7. Ovarian fibrosarcomas	<15%
III. Axial Skeletal Abnormalities	
1. Rib abnormalities	>60%
2. Spina bifida	>50%
3. Kyphoscoliosis	>40%
4. Short fourth metacarpal	>25%
5. Lumbarization of sacrum	>40%
6. Pseudocysts of phalanges	>30%
IV. Central Nervous System	
1. Medulloblastomas	<2%
2. Congenital hydrocephalus	<3%
3. Mental deficiency	<3%
4. Craniopharyngiomas	<1%
5. Meningioma	<1%

From Marx RE, Stern D: Odontogenic and nonodontogenic cysts. In *Oral and maxillofacial pathology: a rationale for diagnosis and treatment*. Quintessence, 2003, Chicago, p 603.

constitute frequent and clinically significant expressions of the syndrome. The oral and maxillofacial pathologist and surgeon may be the first health care providers who diagnose or suspect the syndrome. They not only provide treatment for these patients, but also are obligated to consult other specialty providers because of the systemic nature of the syndrome. Genetic counseling of the patients and their families is strongly recommended. Some guidelines for the diagnosis are a family history, oral and complete skin examinations, radiographs of the jaw and chest, MRI of the brain, and also ultrasound of the pelvis in women. Keratocystic odontogenic tumors, usually multiple, occur with high frequency in the syndrome.[94] It is well established, however, that sporadic non–syndrome-associated cysts also occur.[23,94] The syndrome KCOTs are frequently multiple, and the patient is younger when the first lesion is diagnosed[9] (Figure 17-22). Shear[30] emphasizes that multiple cysts are not necessarily present at the time of the initial diagnosis, because cysts may develop afterward (see Figure 17-22, *C*). Basal cell carcinoma is a significant lesion in these patients[8,9] (Figure 17-23). Lesions begin during puberty or the second or third decade of life. They vary from flesh-colored papules to ulcerating plaques (see Figure 17-23, *A*). They are located most commonly in the midface area but also occur in non–sun-exposed sites. Among the skeletal abnormalities detailed in Boxes 17-1 and 17-2 and Table 17-2, the bifid ribs and calcification of the falx cerebri are most frequent (see Figure 17-22, B). The patient often has a characteristic face with frontal bossing, hypertelorism, and mild prognathism present.

Imaging and Pathologic Features

There are no special features to distinguish syndrome-associated from non–syndrome-associated KCOTs. The size varies depending on the time of diagnosis. The lesions can assume large size and can be unilocular or multilocular with significant displacement of associated teeth (see Figure 17-22, *A* and *B*).

The microscopic features are not pathognomonic for syndrome-associated cysts. The epithelial lining can be orthokeratinized or parakeratinized. The degree of inflammatory cell infiltrate depends on whether the lesion communicated with the oral cavity and became secondarily infected. Neville and colleagues[8] summarized the histopathologic characteristics of the syndrome cysts. These lesions tend to have more satellite cysts, solid islands of epithelial proliferations, and odontogenic epithelial rests within the fibrous capsule than do isolated keratocysts. The skin lesions in the syndrome exhibit a wide spectrum of histopathologic findings that range from benign adnexal basal cell lesions to aggressive, ulcerating basal cell carcinomas (see Figure 17-23; Figure 17-24).

Surgical Management

It is important to recognize that these patients must undergo multiple surgeries to excise current, recurring, or newly developing cysts. We treat these lesions like other KCOTs—by enucleation followed by adjunctive therapy if the size is small with no evidence of bony dehiscence. In large lesions we have been using the two-stage approach, with primary decompression followed by cystectomy and adjunct chemical cauterization, within a few months (see Figure 17-22).

Other Odontogenic Cysts

For the sake of completeness, the less frequently encountered odontogenic cysts are briefly discussed.

Gingival Cyst of Infants

This cyst occurs in infants a few hours to a few months old (Figure 17-25). Cysts appear as multiple, firm, white gingival nodules on the edentulous maxillary or mandibular ridges. They arise from proliferation of the dental lamina.[6,8] They usually involute, and no treatment is required except parent reassurance.[9]

Other inclusion cysts such as Epstein pearls and Bohn nodules are found in the midline of the palate or laterally on the hard and soft palate.[6,8,9]

Gingival Cyst of Adults

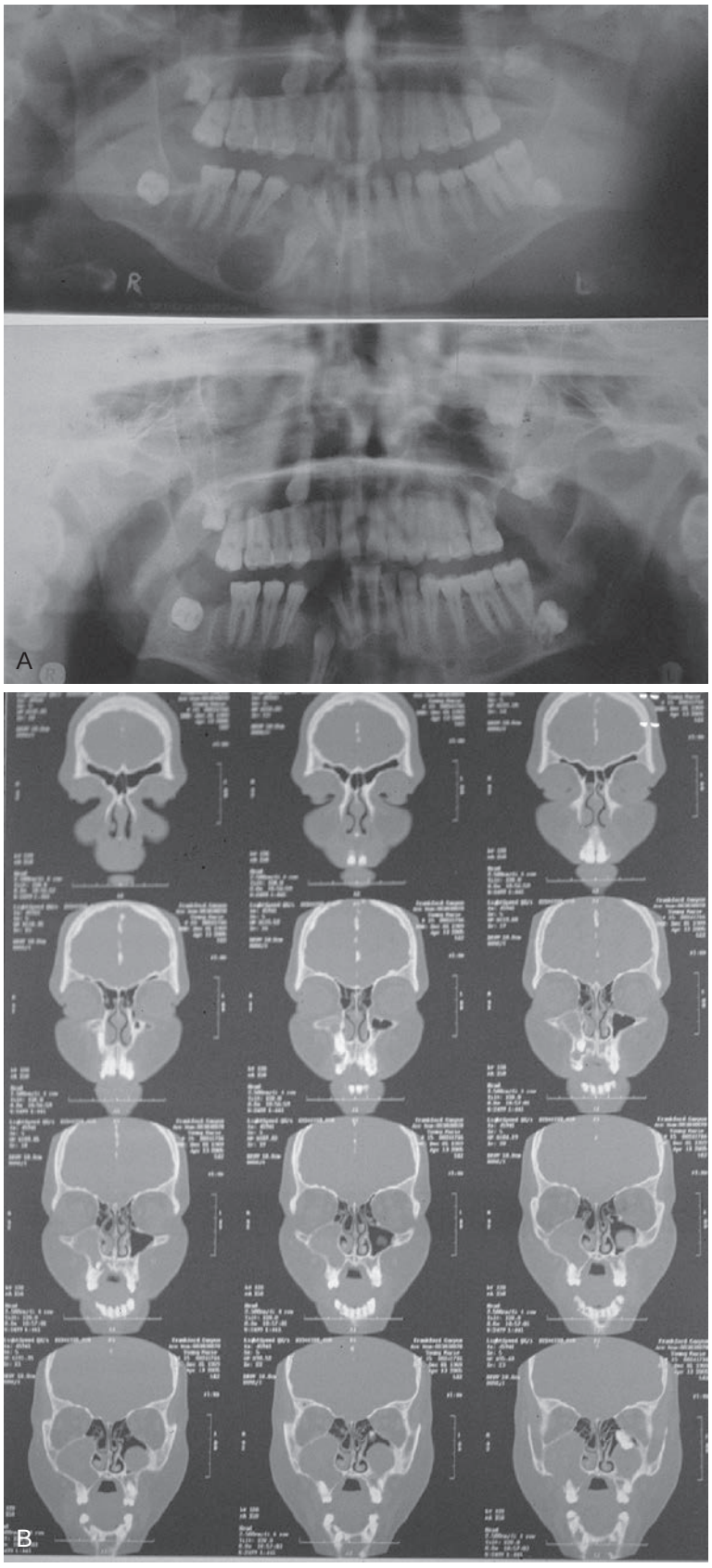
This is an uncommon lesion considered to be the soft tissue counterpart of the lateral periodontal cyst.[6,8,9] It is derived from the rests of Serres (the dental lamina) and has microscopic features similar to those of the lateral periodontal cyst.

Lateral Periodontal Cyst: Botryoid Odontogenic Cyst (BOC)

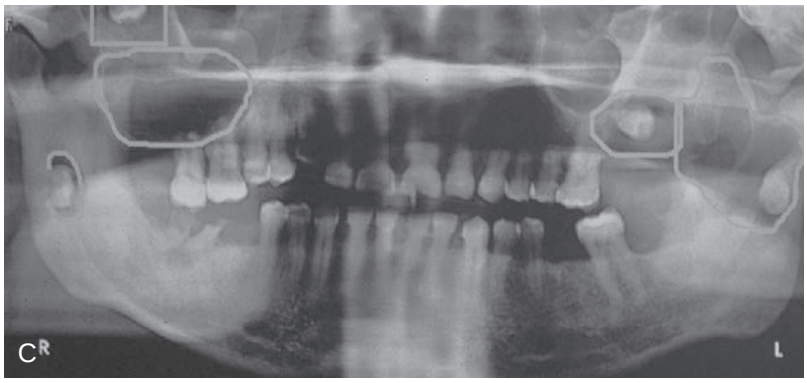
This is a rare odontogenic lesion that is derived from proliferation remnants of the dental lamina. It occurs generally in the mandible between premolar and cuspid teeth. Histologically it is lined with a thin band of stratified squamous non-keratinized epithelium that has clear focal plaques, because of their high glycogen content. It may be multiloculated, but its lining epithelium rarely shows keratinization.[101] A variant of the lateral periodontal cyst is the botryoid odontogenic cyst. The latter differs from the former in being radiographically and microscopically multilocular with numerous lobulations and thickened epithelial tufts resembling a grape cluster or botryoid.[9] It has a higher recurrence rate, probably because of the difficulty of its excision. Neville and colleagues[8] indicate that the term *lateral periodontal cyst* was used to describe any cyst developing along the lateral root surface, such as lateral radicular and odontogenic keratocysts. The lesion does have distinctive clinical and histopathologic features that differentiate it from other lesions that develop in the same location.[8,9]

Glandular Odontogenic Cyst

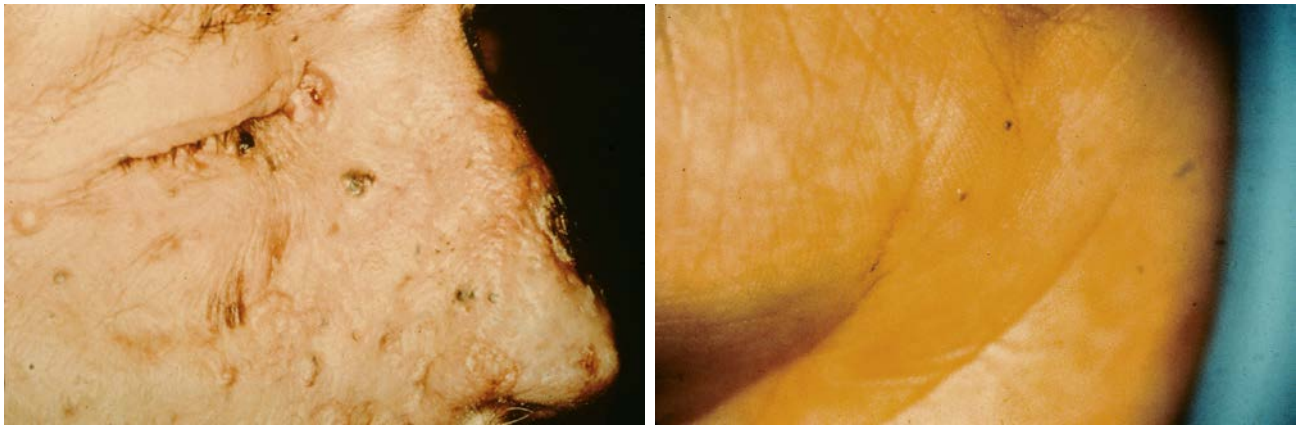
This is a relatively new entity and was initially referred to as a sialo-odontogenic cyst.[6,8,9] Most of these cysts occur in the anterior mandible, as seen in the panogram in Figure 17-26, *A*, of a 54 year-old man who was diagnosed with a glandular odontogenic cyst after incisional biopsy.



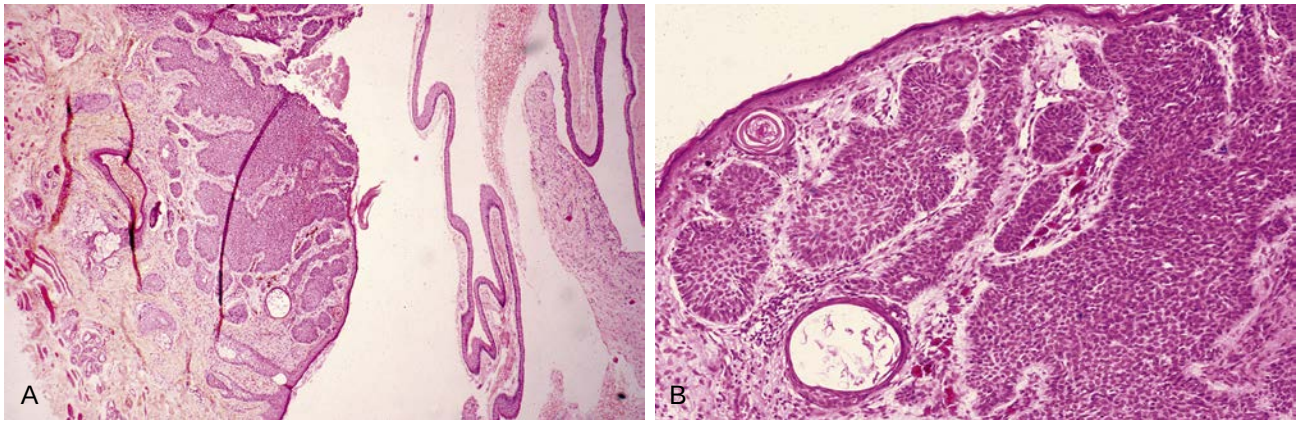
• **Figure 17-22** Frequent features of nevoid basal cell carcinoma syndrome includes multiple odontogenic keratocysts (OKCs) as illustrated in **(A)** a panogram and **(B)** computed tomography scan imaging **(B)** in a 16-year-old girl who has two siblings with jaw cysts. **A,** The patient initially seen with infection of anterior mandible; after clearing of the infection the cysts in this site were connected, decompression initiated to allow for the eruption of the lower right canine. The patient has had other procedures and continues to be under our care. **B,** Note the calcification of the falx cerebri.



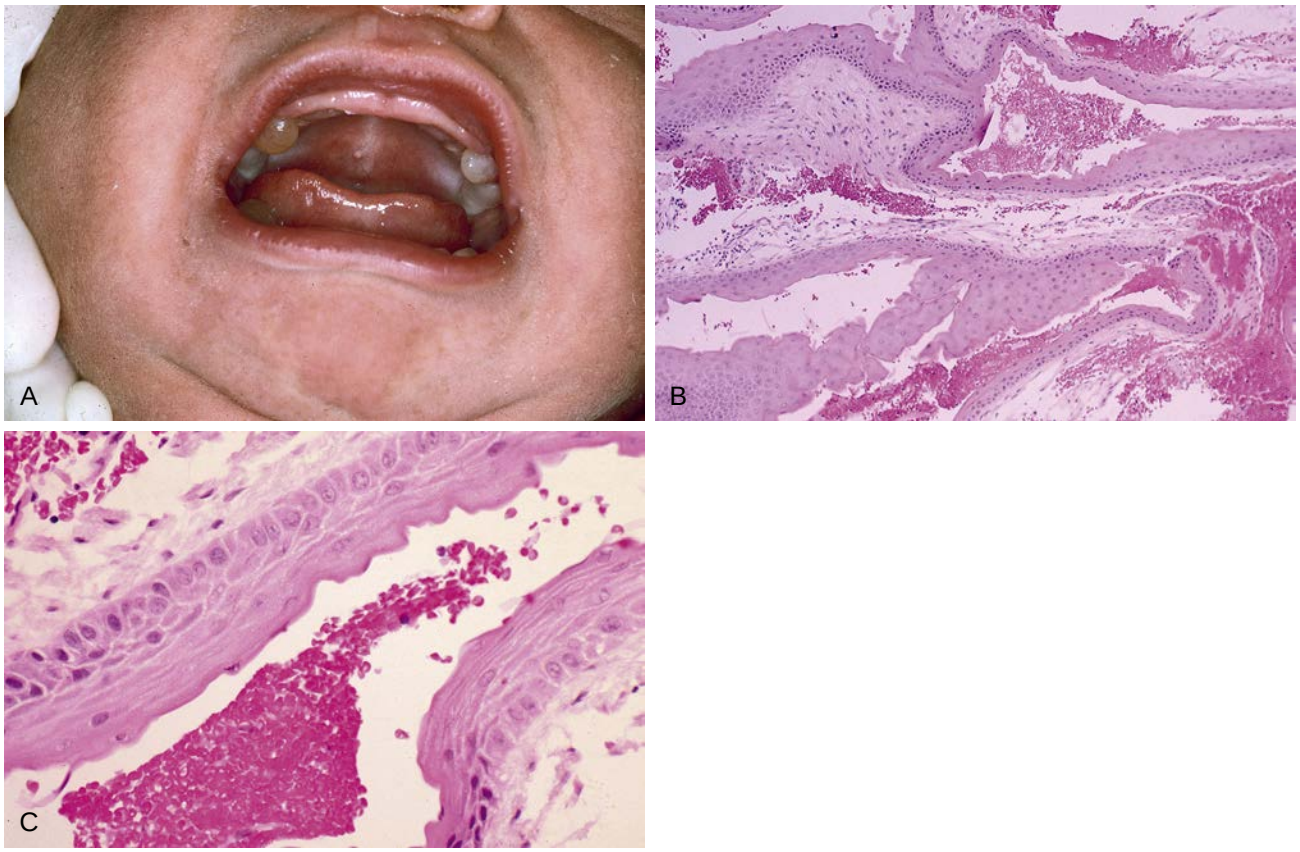
• **Figure 17-22, cont'd C,** Not all patients with multiple OKCs have the syndrome, as illustrated in a panogram of a 45-year-old man who has been recently seen with no apparent signs and symptoms of the syndrome.



• **Figure 17-23** Basal cell carcinomas and palmar pitting are common and significant features of the syndrome.



• **Figure 17-24 A,** A lower-power photomicrograph of odontogenic keratocyst and basal cell carcinoma from the same patient with nevoid basal cell carcinoma syndrome. **B,** Higher magnifications of multifocal basal cell carcinoma.



• **Figure 17-25** **A,** A 2-day-old baby boy with multiple cysts in the mandible and maxilla. Because of difficulty in nursing and the concern of the parents, the cysts were evacuated. **B-C,** Low and high magnification photomicrographs show a cyst lined with stratified parakeratotic squamous epithelium with surgical hemorrhage.

Radiographically, these lesions are multiloculated. Histologically, they are lined by nonkeratinized epithelium consisting of cuboidal cells, often with cilia at the luminal surface. The cyst has features that suggest a mucus-producing lesion. Gardner and Morency[102] and Kramer and colleagues[6] detailed the microscopic features of the cyst. The lining epithelium is cuboidal or columnar with crypts or cystlike spaces within the thickness of the epithelium. Histologic features of the cyst, such as mucous metaplasia, may overlap with other lesions (e.g., mucoepidermoid carcinoma and botryoid cyst). These lesions can also be quite aggressive and recur in up to 25% of cases.[102-104] In 2005 Kaplan and colleagues[103] reviewed 49 cases from the literature and added 7 new cases. These authors reasserted the aggressiveness of these lesions and reviewed the frequency of recurrences associated with the various available surgical modalities of treatment.[103] They recommended enucleation of small lesions and enucleation with peripheral ostectomy and resection for larger unilocular and multilocular lesions, respectively. Figure 17-26 shows treatment of a large, multilocular lesion with mandibular resection and immediate reconstruction. A two-stage surgery—decompression followed by a second-stage surgical therapy—is suggested for large lesions approaching vital structures. This approach to the lesion surgical management is similar to that for the odontogenic keratocyst and unicystic ameloblastoma, as presented in this chapter.

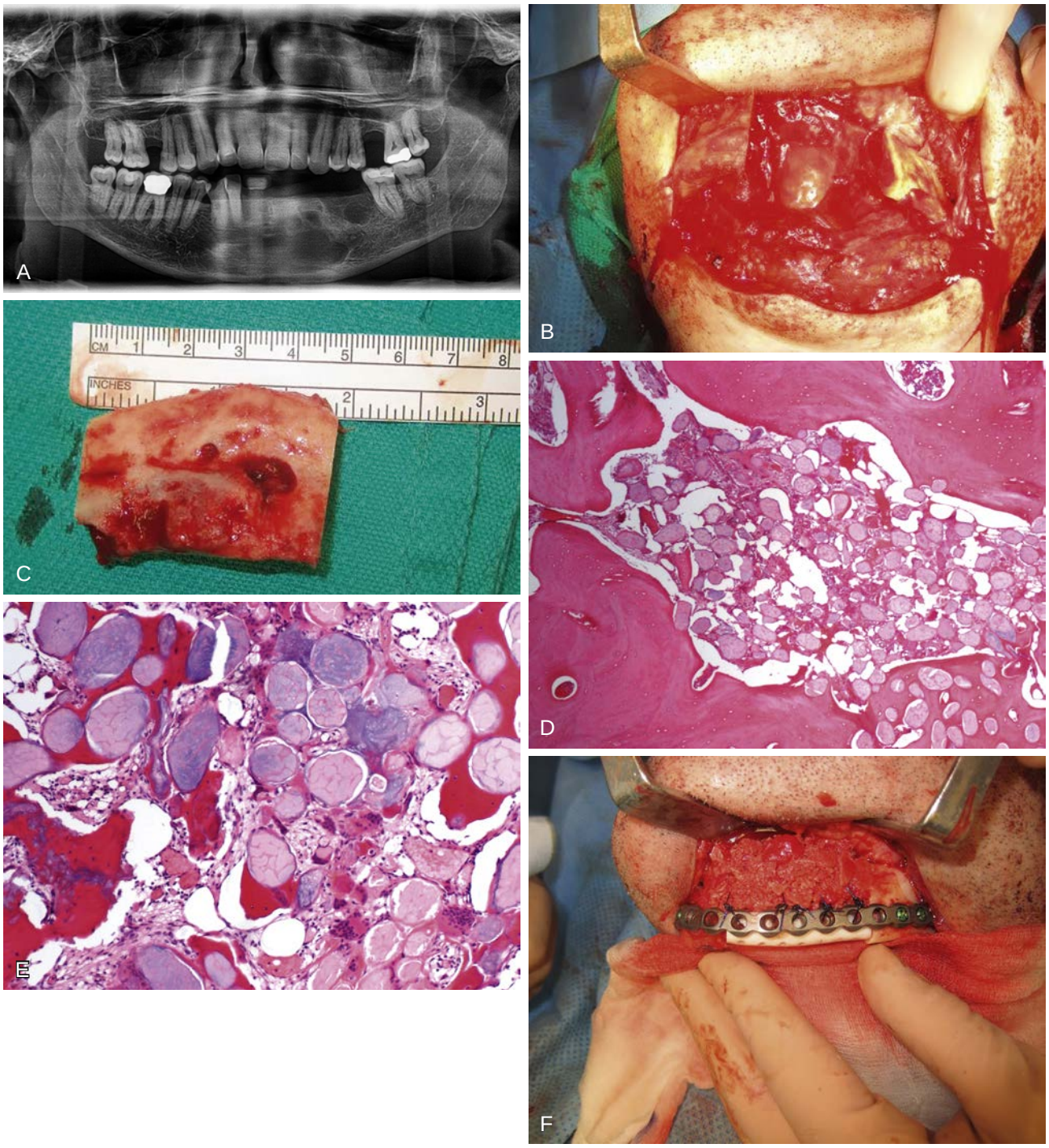
Calcifying Odontogenic Cyst/Tumor

Overview

In the oral and maxillofacial region, as in other anatomic sites, there are lesions that are cystic and defy a widespread acceptance in one classification or another. The calcifying odontogenic cyst (COC) and the adenomatoid odontogenic tumor (AOT) are among such lesions of interest to the is not widely accepted. We discuss in detail the COC and tumor-related lesions. The AOT is presented elsewhere in this volume.

Clinical Features

The COC is an uncommon odontogenic lesion. In 1962 Gorlin and colleagues[105] identified the lesion as odontogenic and suggested it to be the counterpart of the cutaneous calcifying epithelioma of Malherbe, or pilomatricoma. In 1963 Gold[106] independently described three other cases. Pilomatricoma is a benign lesion that is hard and fixed to the skin but



• **Figure 17-26** **A,** Panogram of a 54-year-old man presenting with buccal cortical expansion of the left mandibular parasymphyseal area. Incisional biopsy of the mandibular lesion revealed diagnosis of glandular odontogenic cyst. **B-C,** Surgical resection performed and specimen sent to pathology. **D,** Low-power photomicrograph of the glandular odontogenic cyst demonstrates the glandular structure of the lesion invading the bone. **E,** Higher-power magnification shows significant mucus production within the lesion, along with scattered giant cells. **F**, Immediate mandibular reconstruction performed with autogenous bone harvest using the posterior iliac crest. (Surgery performed by Joseph Kern, DDS, MD, Plymouth Meeting, PA; Fizza Jaffery, DMD, MD, Woodbury Heights, NJ; and Dr. Nabil Abaza. Photomicrographs were provided by Beth Mapow, DO, Drexel University Department of Pathology, Philadelphia.)

not the underlying tissue, and it occurs in the maxillofacial region in children, adolescents, and young adults. In analysis of a large series of the oral counterpart of pilomatricoma, the COC occurs, in descending order of frequency, as a central cystic lesion, which may be unilocular, multilocular, or associated with an odontoma; a peripheral cystic lesion on the gingiva or alveolar mucosa; or a peripheral or central solid growth or neoplasm.[107,108] Hong and colleagues[107] reviewed the published terms used to designate the lesion, and among the more frequently cited names are calcifying odontogenic cyst, keratinizing and calcifying odontogenic cyst, keratinizing ameloblastoma, calcifying ghost cell tumor, and cystic calcifying odontogenic tumor. These authors concluded that "the existence of numerous terms reflects a diverse histopathology and confusion about their nature as cysts, neoplasms, or hamartomas."[107] The second edition of the WHO classification of odontogenic lesions in 1992 includes the COC as an odontogenic tumor but indicates that most lesions appear non-neoplastic.[6] Praetorius and colleagues,[109] however, concluded that the spectrum of lesions designated as COC conders suggested more names such as dentino-ameloblastoma, epithelial odontogenic ghost cell tumor, calcifying ghost cell odontogenic tumor, and dentinogenic ghost cell odontogenic tumor as reviewed by Moleri and colleagues[108] in their reporting on the lesion in 2002. Gold's[106] original designation of the lesion as a keratinizing and calcifying odontogenic cyst accurately describes the lesion.[9,110] The tumor designation of this lesion arose from the solid pattern of growth. Furthermore, the tumor entity has been subcategorized into benign and malignant, based on the presence of malignant cytologic features; no metastasis has been reported.[6,111] The incidence of such malignant transformation is rare, but it has been documented.[111,112] It is of interest to recall that the skin pilomatricoma has malignant transformation to pilomatrix carcinoma in up to 9% of benign lesions.[113] Johnson and colleagues[110] suggested that in indisputably neoplastic cases, the lesion may be called ameloblastoma with COC or a ghost cell component. Hong and colleagues[107] have used the term *ameloblastoma ex-COC*. However, the following question remains: If the ghost cell component was absent, how would the lesion be diagnosed?

In summary, the COC is predominantly an intraosseous lesion, but it also appears extraosseously in around 12% to 20% of cases.[107] Maxillary and mandibular lesions have similar frequency and are diagnosed in patients in the second and third decade of life, younger if associated with an odontoma.[107,114] The extraosseous COC usually presents as a localized sessile or pedunculated mass on the gingiva.

Imaging Features

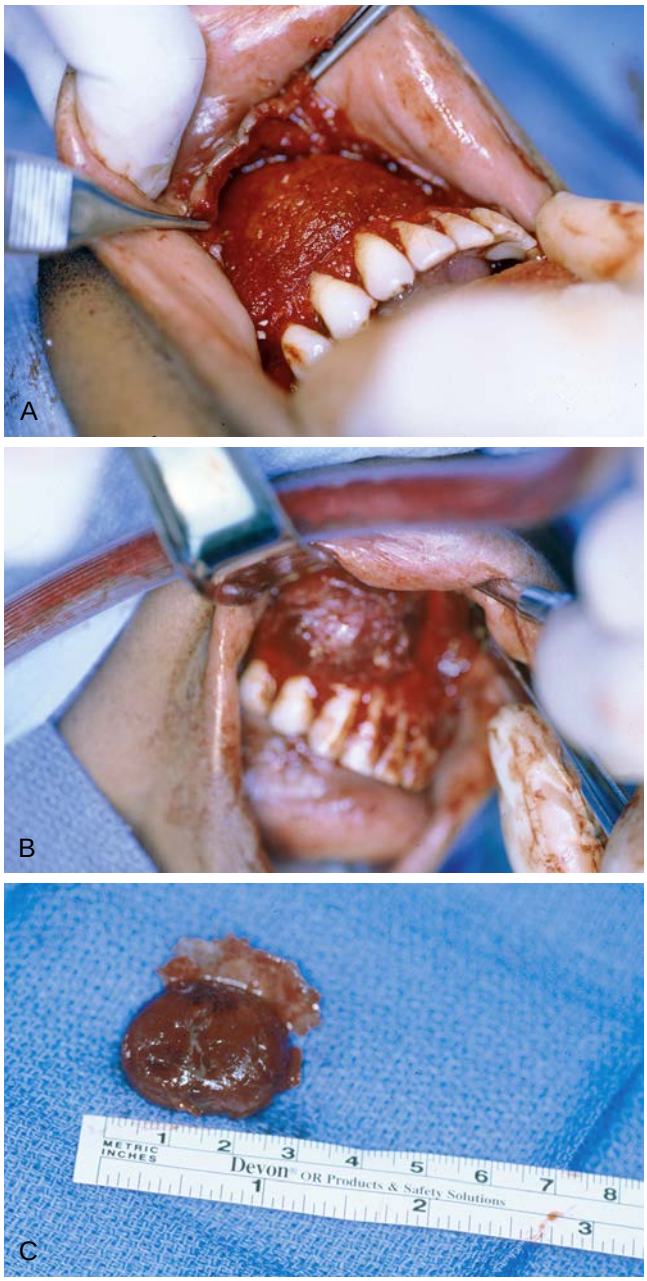
COCs are usually small lesions ranging from 2 to 4 cm in diameter, but they can attain large size with displacement of teeth and root resorption.[109,115] Most lesions are unilocular and cause saucerization of the bone, but some are multilocular. Irregular calcifications ranging from tiny flecks to large masses are usually scattered throughout the radiolucency.[68,108] The association with odontomas is well established.[107,115] With large lesions, thinning of the bone and encroachment on adjacent soft tissue can occur. In such cases and in suspected solid growth, a CT scan is advisable. The imaging features are nonspecific except perhaps the presence of scattered radiopacities that may shorten the differential diagnosis list.

Pathologic Features

The well-defined cystic lesion has a relatively thick connective tissue wall with an epithelial lining of variable thickness and morphology.[68,106,110,115] The basal cell layer is tall columnar or cuboidal, similar to ameloblasts, with the nuclei palisading away from the basement membrane (Figures 17-27, 17-28, *A-C*). Superficial to the basal cell layer is a multilayered epithelium resembling stellate reticulum. The hallmark of the lesion is the presence of "ghost cells" (see Figure 17-28, *A-C*). These cells display a progressively eosinophilic and granular cytoplasm and pyknotic nuclei and become swollen. The cells attain "ghostly" outlines, with only shadows of the cells and nuclear membranes faintly recognizable. These cells usually fuse and form extensive sheets that may fill the cyst lumen or herniate through the basement membrane into the connective tissue cyst wall. In the latter situation, foreign body–type granulomas are usually seen. The presence of these ghost cells is diagnostically helpful but is certainly not pathognomonic for the diagnosis of COC. Ghost cells are also present in odontomas, ameloblastomas, craniopharyngiomas, and pilomatricomas[107,116] (see Figure 17-28, *D*). The ghost cells usually fuse and form extensive sheets, and they may fill the cystic lumen.[108] Individually these cysts may undergo calcification or lose their cell outline and form sheetlike areas of calcification[106,110] (see Figure 17-28, *A*). The calcification has been reported to be dystrophic.[101,103,105] When the epithelium is in direct contact with the connective tissue, the calcification has been reported to contain dentinal tubules and, therefore, is occasionally referred to as dentinoid-like. COCs have been studied immunochemically and ultrastructurally.[68,111,117,118] Johnson and colleagues[110] found that the lining epithelial cells were strongly positive for cytokeratin, whereas full-blown and disintegrating ghost cells were unreactive.

Ultrastructure Features

Ultrastructurally, COCs in paraffin-embedded blocks have been examined previously by several authors.[68,117,118] The nature of the mature ghost cell remains unsettled. It has been claimed that they represent the product of normal or abnormal keratinization,[105,106] squamous metaplasia of odontogenic epithelium,[119] or abortive enamel or pre-enamel matrix formation.[120] The COC basal cells are cuboidal or low columnar in shape and are attached to neighboring cells by desmosomes and a lamina densa, which separates them from adjacent connective tissue by hemidesmosomes. Intracellular individual or small bundles of tonofilaments and a moderate number of regular organelles are present. The nucleus is



• **Figure 17-27** **A,** The calcifying odontogenic cyst (COC) is a well-delineated lesion that can cause cortical expansion and **(B-C)** is easily enucleated.

irregularly ovoid, with irregularly clumped chromatin. The stellate reticulum type cells are polygonal, with more desmosomal attachments to the neighboring cells. Their villus-like cytoplasmic projections into prominently expanded intercellular spaces are more frequent than those of the basal cells. The ghost cells are mostly anuclear and contain pyknotic nuclei or residues of chromatin in the negative nuclear zone.[68,117,118] The only organelles in their cytoplasm are very thick electron-dense fibrils of uniform size sharply defined against large empty spaces previously occupied by the nucleus (Figure 17-29, *A* and *B*). Small needlelike crystalloid structures are present in these cells. Fejerskov and Krogh[117] concluded from these observations that the COC keratinization pattern is not identical to that of the normal epidermis and oral mucosa. Chen and Miller[118] found similar ultrastructural features of ghost cells, in which the plasma membrane was thickened and irregularly disrupted, with disappearance of desmosomes and the villus-like projections seen in other cells. In addition, these two authors described another cell, packed and evenly distributed tonofilaments oriented in different directions with occasional residue of organelles (see Figure 17-29, *C*). Mineral crystals were deposited on bundles of tonofilaments of the ghost cells and the surrounding collagen fibers (see Figure 17-29, *D*). They concluded that mineralization of ghost or hornified cell residues is explained in ghost cells are definitely not keratin, and the calcification must be considered a dystrophic process.[119]

Surgical Management

For the more frequently encountered intraosseous calcifying odontogenic cysts, enucleation is adequate (see Figure 17-27). Few recurrences have been reported.[8,9,108,109] The peripheral lesions are cured by excision. In the rare large lesions, the COC is eradicated by enucleation or conservative excision.[8,9] If the COC is associated with microscopic features, besides the ghost cells, the diagnosis and treatment should naturally be geared toward the predominant histopathology.

Non-odontogenic Cysts

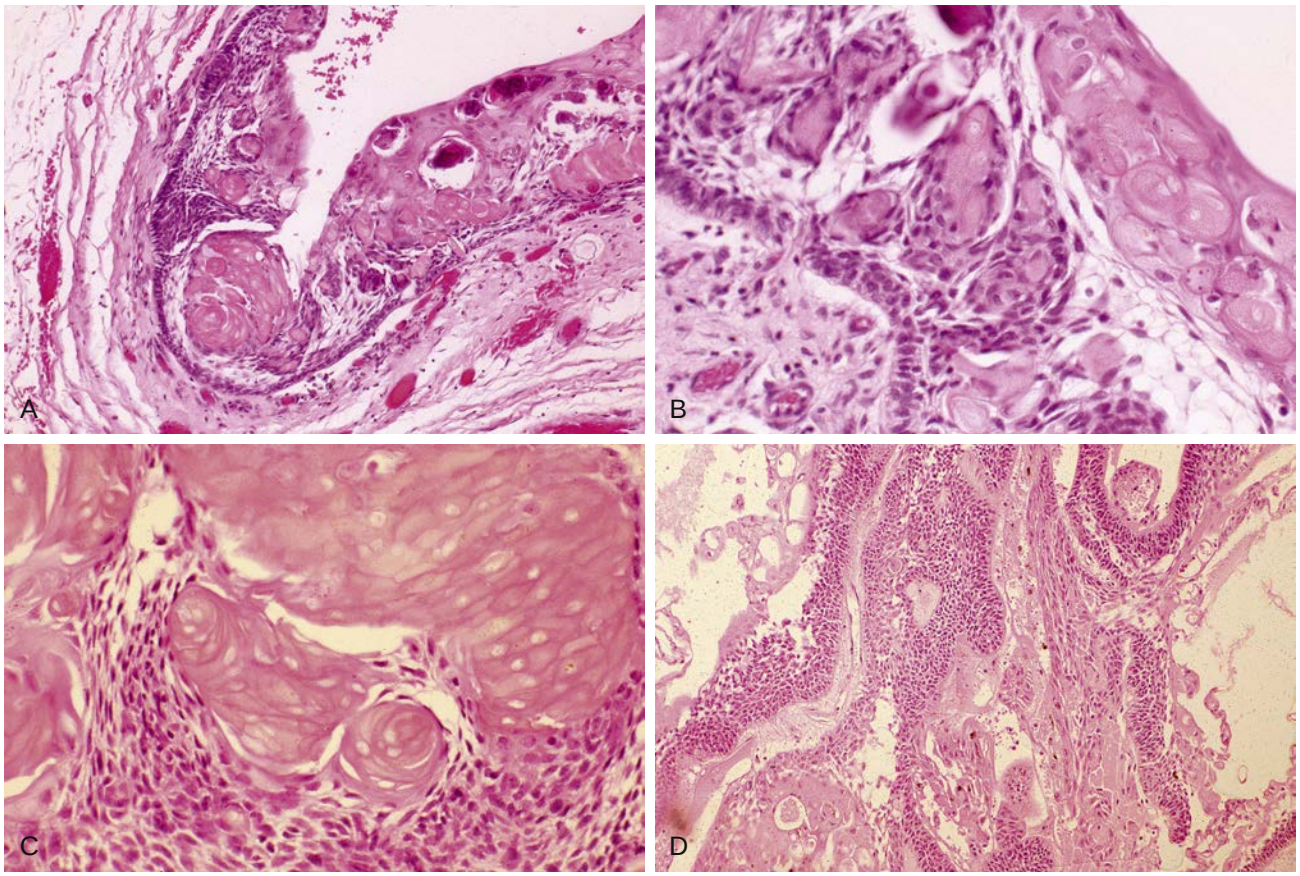
In the oral and maxillofacial region, several cysts do occur in line of fusion of the several zones of the jaw bone, the soft tissue associated with the maxillomandibular complex, and the neck. The stimulus for proliferation of the embryogenic remnants is still unclear. The more common lesions are discussed in some detail. For completeness, a summary of the less common cysts is also presented.

Non-odontogenic Developmental Cyst of the Jaw and the Associated Soft Tissue Complex

Nasolabial Cyst

Clinical Features

The nasolabial cyst was first described by Zuckerkandl in 1892[121] and was known as the nasoalveolar cyst.[122] The term *nasolabial* was coined by Rao[123] and is a more accurate description of the lesion than nasoalveolar.[122] In a review of 8000 cystic lesions of the oral cavity over a 10-year period, Allard[124] identified only 17 cases of these lesions. A report by Yuen and colleagues[122] in 2007 detailed the clinical features, diagnosis, and treatment of the lesions. The nasolabial cyst is, therefore, a rare entity; however, it has been suggested that its occurrence may be more common than previously



• **Figure 17-28** **A-C,** The cyst lining characteristically shows columnar basal cells, stellate reticulum-like supra-basal cells, microcalcification, and, above all, the "ghost" cells. **D,** These ghost cells are not pathognomonic for the calcifying odontogenic cyst, as they can be present in other lesions such as ameloblastoma.

thought.[122,125,126] Two theories have been proposed for the pathogenesis of nasolabial cysts.[122,124,127] The first suggests that the lesions are inclusion cysts arising from the epithelium that is retained in the mesenchyme after the fusion of the medial and lateral nasal processes. The second theory suggests that these cysts arise from proliferation of epithelial remnants from the nasolacrimal duct that extend between the lateral nasal process and the maxillary process.[124] These lesions may present as a nasal obstruction and deformity. They are smooth, fluctuant soft tissue masses between the upper lip and nasal aperture with obliteration of the nasolabial fold and elevation of the nasal ala.[122] Nasolabial cysts may grow in three possible directions: toward the nasolabial fold, toward the vestibule of the mouth, or toward the vestibule of the nose.[122,127] The lesion is best palpated bimanually intraorally or internasally.[122,127] Acute painful symptoms may develop secondary to infection. These symptoms should be differentiated from those caused by an odontogenic source. Rarely is the lesion bilateral (Figure 17-30, *A* and *B*).

Imaging Features

The nasolabial cyst is a soft tissue mass that is completely extraosseous. The radiographs may show bony rarefaction and deformity of the lateral and anterior edges of the nasal floor. There is rarely erosion of the maxilla.[126,127] MRI may show the cyst hypertense relative to cerebrospinal fluid (CSF) on T_1-weighted images, and isointense with CSF on T_2-weighted images.[128] Elaborate imaging is usually not necessary for proper diagnosis.

Pathologic Features

This soft tissue lesion usually contains mucoid and serous fluid, and if infected the contents are suppurative and hemorrhagic. The cyst capsule is a thick connective tissue capsule. The epithelial lining is pseudostratified epithelium, stratified squamous, and/or cuboidal epithelium with goblet cells.[93,122,127]

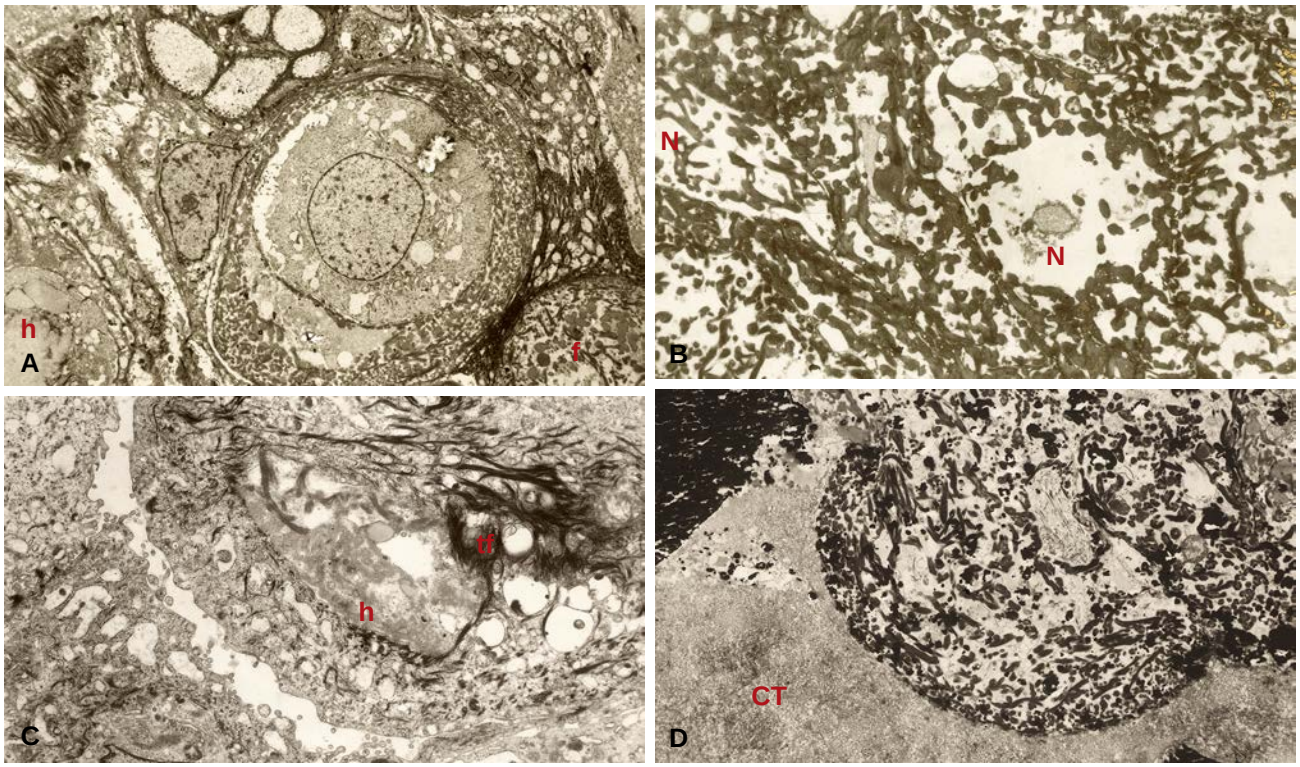
Surgical Management

Total excision of the cyst is curative, and care should be taken not to rupture the cyst. The surgical removal is accomplished by a sublabial incision in the buccal sulcus. If the nasal mucosa is breached, repair is not necessary.[122] Reepithelialization occurs with gentle packing of the vestibule (Figure 17-31, *A* and *B*).

Nasopalatine Duct Cyst

Clinical Features

This is a rare lesion but is the most common non-odontogenic cyst of the maxilla.[129,130] Swanson and colleagues[129] analyzed 334 cases that were diagnosed as incisive canal cyst, nasopalatine duct cyst, median palatine cyst, or cyst of the incisive papilla.



• **Figure 17-29** **A,** Ultrastructure examination shows degenerating cells *(center)* surrounded by ghost like cells that are mostly anuclear, with very thick electron-dense fibrils in their cytoplasm *(f)*. A part of a hornified cell *(h)* is seen (3750×). **B,** High magnification of ghostlike cells, showing the very thick electron-dense fibrils sharply defined against a large space previously occupied by the nucleus *(N)*. There is a disruption of the plasma membranes and disappearance of desmosomes (7500×). **C,** Hornified cell residue *(h)* densely packed with tonofilaments *(tf)* oriented in different directions and residue of organelles (7500×). **D,** Dense osmophilic calcification of denucleated ghost cell and the adjacent connective tissue *(CT)* (3750×). (From Abaza NA: Ultrastructural features and biologic aspects of odontogenic cysts and tumors: implications for surgical management. *Oral Maxillofac Surg Clin North Am* 6:523-577, 1994.)

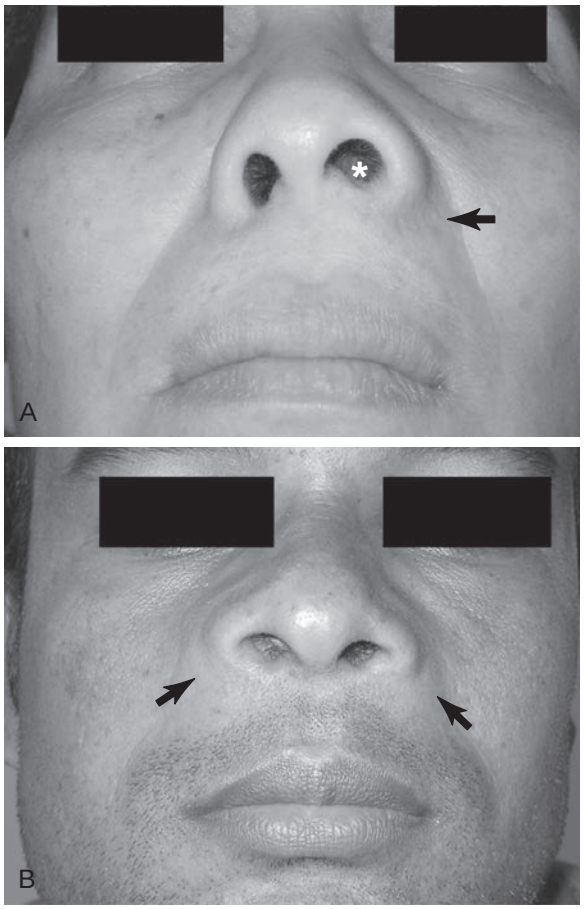
These authors found the lesion to occur in the fourth and sixth decades of life, with slight male predilection. The lesions in this study had a 17-mm mean radiographic diameter with 75% of the lesions 20 mm or less in diameter; 70% of the cases studied were symptomatic. The cyst is thought to originate from epithelial remnants of the nasopalatine duct.[131,132] The stimulation of the epithelium to proliferate has been claimed to result from trauma, infection, or mucus retention.[9,129,131] Spontaneous cystic degeneration is also speculated because the lesions have been found in the human fetal incisive canal.[129,133] The entrapped epithelial remnants may be located at any site of the fusion of the two embryonic nasopalatine ducts from the median posterior palate to the soft tissue of the incisive papilla.[6] Therefore, cysts may occur in the posterior palatal midline, the incisive canal nasopalatine duct, or the soft tissue of the incisive papilla (palatine papilla). Because the incisive canal is several millimeters in vertical height, the cyst can present as either a labial or a palatal expansion, usually labial. When the cyst is large, both labial and palatal expansion is evident with fluid fluctuation present (Figures 17-32, 17-33, *A*, and 17-34, *A*). Diversion of the maxillary incisors is commonly present (Figure 17-34, *B* and *C*). Most of the lesions are small and asymptomatic (Figure 17-32, *A* and *B*).

Imaging Features

Imaging reveals a well-corticated lesion either round or heart shaped. A significant finding is that the radiolucency of the cyst is superimposed on the shadow of the periodontal membrane of the maxillary teeth. A feature that helps to clinically differentiate between this cyst and a periapical lesion (see Figure 17-34, *C* and *D*) is vitality testing of the associated teeth. Despite the availability of high-resolution imaging technology, a simple occlusal film may be very useful in the lesion diagnosis and in planning the surgical approach (see Figure 17-34, *D*). Small cysts should be differentiated from the normal radiographic diameter of the incisive canal, which has been stated to be 6 mm[131] (see Figure 17-32, *B*). With large cysts, perforation of overlying mucosa may occur, resulting in infection and pain. Large radicular cysts associated with infected maxillary incisors may be difficult to clinically differentiate from nasopalatine duct cysts.

Pathologic Features

The epithelial lining of the cyst may be squamous, pseudostratified ciliated, or a mixture of the two.[129,133] It has been reported the majority of the lining is mostly squamous epithelium.[129,134] This probably depends on the location

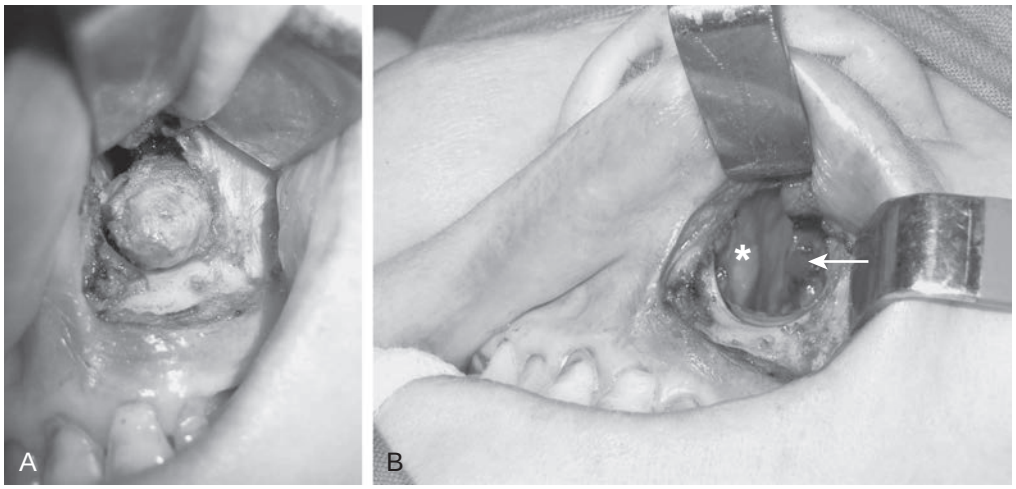


• **Figure 17-30 A,** Uncomplicated nasolabial cyst *(asterisk)* showing characteristic facial deformity with blunting of the nasolabial fold, elevation of the ala nasi, and protrusion of the upper lip *(arrow)*. **B,** A rare case of bilateral nasolabial cysts *(arrows)*. (From Yuen H-W et al: Nasolabial cysts: clinical features, diagnosis and treatment, *Br J Oral Maxillofac Surg* 45:293-297, 2007.)

of the initial epithelial proliferation either superiorly or inferiorly in the vertical height of the incisive canal (Figure 17-35). Frequently, mucus-secreting glands are seen (see Figure 17-35, *B*). Varying degrees of inflammatory cell infiltrate are present on the cyst wall (see Figure 17-35, *B*).

Surgical Management

Complete enucleation of the cyst is curative; recurrences are rare if completely excised. Recurrence rate has been reported to range from none to 11%.[129,135,136] The design of the surgical approach varies according to the location, labially or palatally, and the size of the lesion (see Figures 17-33 and 17-34). If the cyst is localized on the incisive papilla, a palatal mucoperiosteal flap around the crown of the maxillary teeth is used for excision of the lesion. In general, most nasopalatine duct cysts can be adequately approached by a labial incision around the cervices of the maxillary anterior teeth with an approximately 1-cm margin beyond the bony defect (see Figure 17-33). Once the flap is reflected, thinned bone is removed and the enucleation is accomplished. On occasion a second palatal flap may be necessary to free the cyst from both the labial and the palatal tissues, respectively. In large cysts that are markedly expanded palatally, a wide palatal approach may be required. A cervical incision from one maxillary first molar to the other is made (see Figure 17-34). Reflection of palatal mucosa is carefully undertaken, with care not to compromise the greater palatine blood vessels that are critical to the survival of the palatal tissue after cyst enucleation. Again it is important to recognize that the cyst may be adherent to the palatal mucosa. Therefore reflection of the palatal mucoperiosteum and enucleation of the cyst may need to be simultaneously performed. Plan of dissection should always favor removal of the cyst wall with care to maintain the integrity of the palatal mucosa. It is



• **Figure 17-31 A,** Intraoperative view of left nasolabial cyst exposed through a sublabial incision. **B,** The buccal mucosa has been incised, elevated, and retracted. Intraoperative view of the resulting defect in the floor of the nasal vestibule when the nasal mucosa has been breached. The nasal septum *(asterisk)* and partially resected inferior turbinate *(arrow)* can be seen clearly. The defect is packed gently and allowed to granulate. (From Yuen HW et al: Nasolabial cysts: clinical features, diagnosis and treatment, *Br J Oral Maxillofac Surg* 45:293-297, 2007.)

always necessary to preoperatively fabricate a stent to support the palatal tissue and help prevent sagging of the palatal mucosa (see Figure 17-34, *F*). In large cases in which there is extensive bony destruction of the hard palate and the greater palatine vessels are compromised, sloughing of palatal mucosa may occur even if a complete palatal stent is used (see Figure 17-34, *H*). A secondary repair procedure will be required. Before reconstruction, it is advised to use the stent to avoid nasal phonation until the extent of the defect is stabilized. Depending on the size of the defect, rotating a palatal flap works well. In cases of extensive defects, palatal reconstruction by temporalis muscle[137] or tongue[138] flaps may be considered.

Other Non-odontogenic Cysts

Median Palatal (Palatine) Cyst

Classically the lesion was described as a fissural cyst from entrapped epithelium between the fused lateral shelves of the maxilla. The question arises whether such a lesion exists or whether it is a nasopalatine duct cyst arising from the posterior end of the migration tract of the two embryonic nasopalatine ducts.[8,9] The lesion is rare and usually present in young adults as a firm or fluctuant swelling of the palatal midline. The lesion may be symptomatic or asymptomatic and appears as a well-circumscribed radiolucency on an occlusal film. The cyst may be lined by squamous or respiratory epithelium. Complete excision is curative.



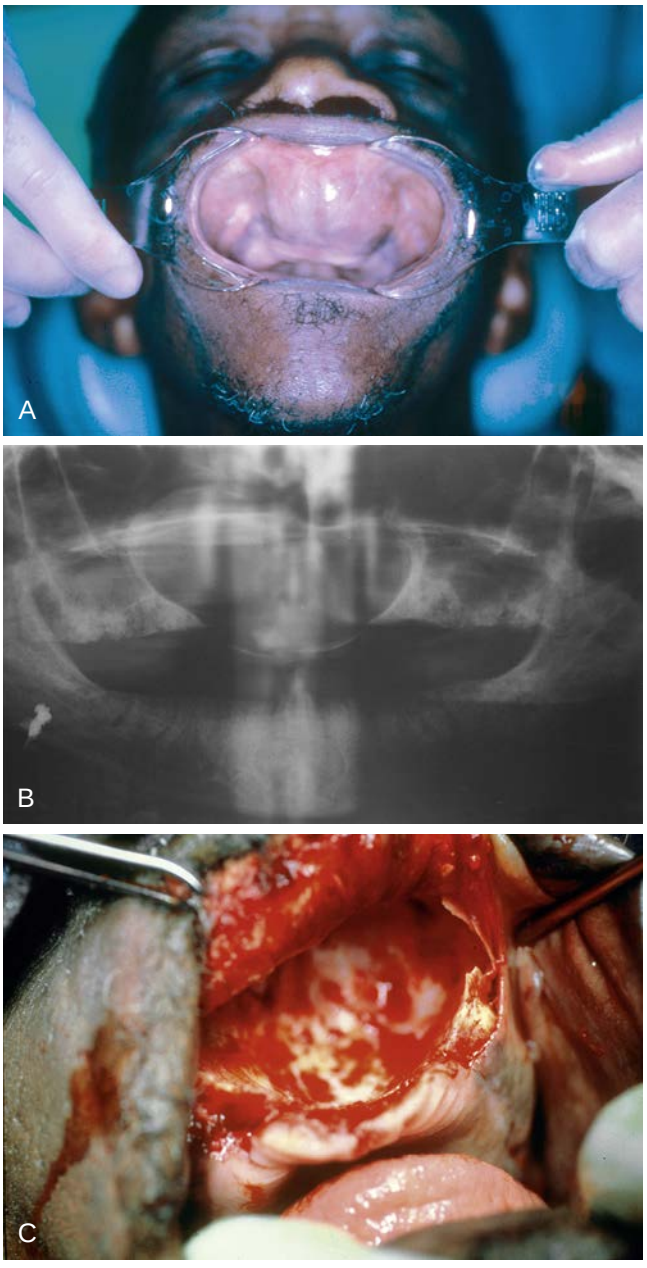
• **Figure 17-32 A,** An edentulous anterior maxilla of a patient with complaint of enlarged palatine papilla. **B,** Computed tomography scan revealed a small incisive canal cyst with evidence of palatine bone resorption.

Median Mandibular Cyst

Neville and colleagues[8] briefly discussed the questionable existence of this lesion and concluded that the lesion is probably odontogenic in origin.

Globulomaxillary Cyst

Embedded in the literature for years, this lesion was included in the 1971 WHO classification of histologic typing of odontogenic tumors[4] but removed in the second edition in 1992.[6] It was included as a fissural cyst secondary to proliferation of entrapped epithelium between the

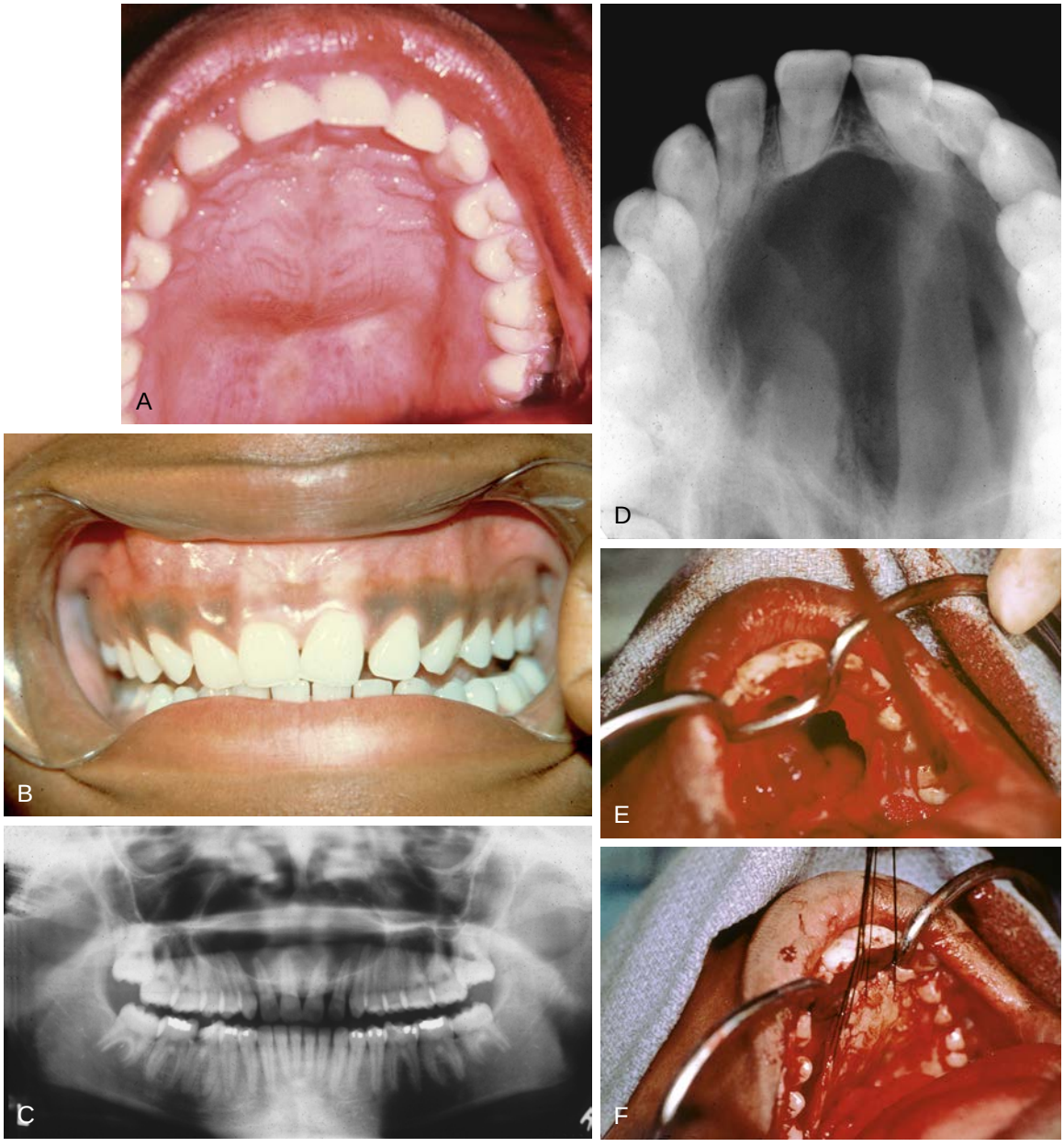


• **Figure 17-33 A,** A patient with large nasopalatine duct cyst that caused complete resorption of the buccal cortex. **B,** Panogram. **C,** The cyst was enucleated through a buccal approach.

globular portion of the medial nasal and maxillary processes. Because of lack of evidence to support the theory of embryogenic epithelial entrapment in the site, most authors dispute the presence of the lesion despite attempts to reclassify it as a fissural cyst.[8,9,139-141] The cyst most commonly appears as a radiolucency between the maxillary lateral and cuspid teeth, occasionally between central and lateral incisors. It is believed that it may represent an odontogenic keratocyst, a lateral periodontal cyst, a calcifying odontogenic cyst, or a periapical cyst that happens to occur in this region.[9,139,140,142] The histopathology reflects these diagnoses. Surgical enucleation is curative.

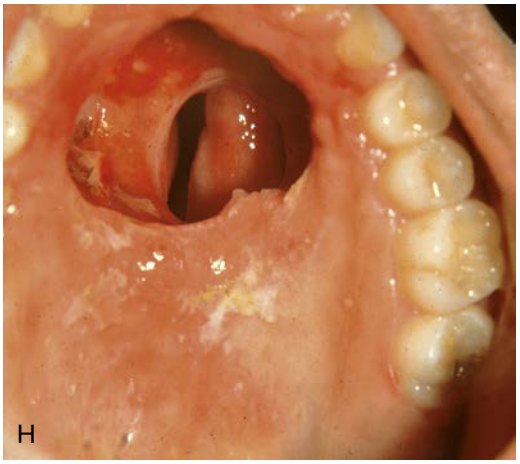
Non-odontogenic Developmental Cyst of the Neck

Developmental cysts are rare cystic malformations that commonly develop along embryonic fusion lines or from other embryonic remnants. In the neck the cysts may occur in the midline, such as in the cases of dermoid, epidermoid, and thyroglossal duct cysts; or they may present on the lateral aspect of the neck, as in the case of the branchial cleft cyst.[143-145]



• **Figure 17-34** **A,** A 16-year-old girl seeking treatment for palatal swelling. **B,** The maxillary central incisors showed crown diversion. **C,** Panogram and upper occlusal films **(D)** show a large nasopalatine duct cyst. **E-F,** The cyst was enucleated palatally.





• **Figure 17-34, cont'd** **G,** The palatal mucosa was supported by a palatal splint. **H,** The mucosa partially dehisced, which was subsequently repaired. (Surgery performed by Barry Hendler, DDS, MD, Philadelphia, and Dr. Nabil Abaza.)

Dermoid and Epidermoid Cysts

Overview

The term *dermoid cyst* has been used to describe three histologically related, developmental keratinizing squamous epithelium lined cysts, namely, dermoid cyst, epidermoid cyst, and teratoid cyst.[145,146] An essential difference between dermoid cyst and epidermoid cyst is the presence of dermal appendages such as sebaceous glands and hair follicles within the wall of the former and the absence of these features in the latter. Teratoid cysts contain in their cyst walls structures derived from all three germinal layers, such as nervous, gastrointestinal, and respiratory tissues.[145,147,148] The teratoid cysts are extremely rare in the head and neck and are not discussed further.

Developmental epidermoid cysts should be distinguished from the more common keratinous cysts of the skin that are acquired and may arise as a result of cystic changes in hair follicles, as in the case of infundibular cysts.[147,149]

In reviews of a large number of dermoid cysts, only 7% occurred in the head and neck, with the periorbital lateral eyebrow area being the most common location.[150,151] The floor of the mouth is the second most common site; it accounts for 12% of all head and neck dermoid cysts,[150,152] followed by the tongue. In a review of 49 cases of pediatric dermoid cysts of the head and neck, Prayor and colleagues at the Mayo Clinic[153] found that 60% occurred periorbitally, 18% in the neck, 10% in the head (mainly scalp and forehead), 6% in the nose, and 4% in the ear.

Epidermoid cysts are rare and much less commonly encountered in the head and neck than dermoid cysts; most occur during infancy.[154]

Clinical Features

The cysts develop most commonly in children and young adults (Figure 17-36). They are frequently present at birth and are identified when large enough.[155,156] The most common clinical appearance of dermoid and epidermoid cysts of the neck is a midline suprahyoid-growing mass.[154] The mass is soft, mobile, and unattached to the overlying skin. Unlike thyroglossal duct cysts, the dermoids are not intimately associated with the hyoid bone and thus do not move on protrusion of the tongue.[157] The size of the cysts ranges from a few millimeters to 12 cm. Rapid increase in size may occur occasionally as a result of sinus formation, increased keratin desquamation, and sebum secretion during puberty and pregnancy.[154,158]

Dermoids of the neck usually arise from the floor of the mouth. Those arising inferior to the mylohyoid muscle cause a prominent submental swelling (Figure 17-37), whereas cysts developing between the geniohyoid and mylohyoid muscles in the sublingual space result in only a small external swelling.[159,160] Occasionally the cysts are displaced laterally into the submandibular space.[145,161]

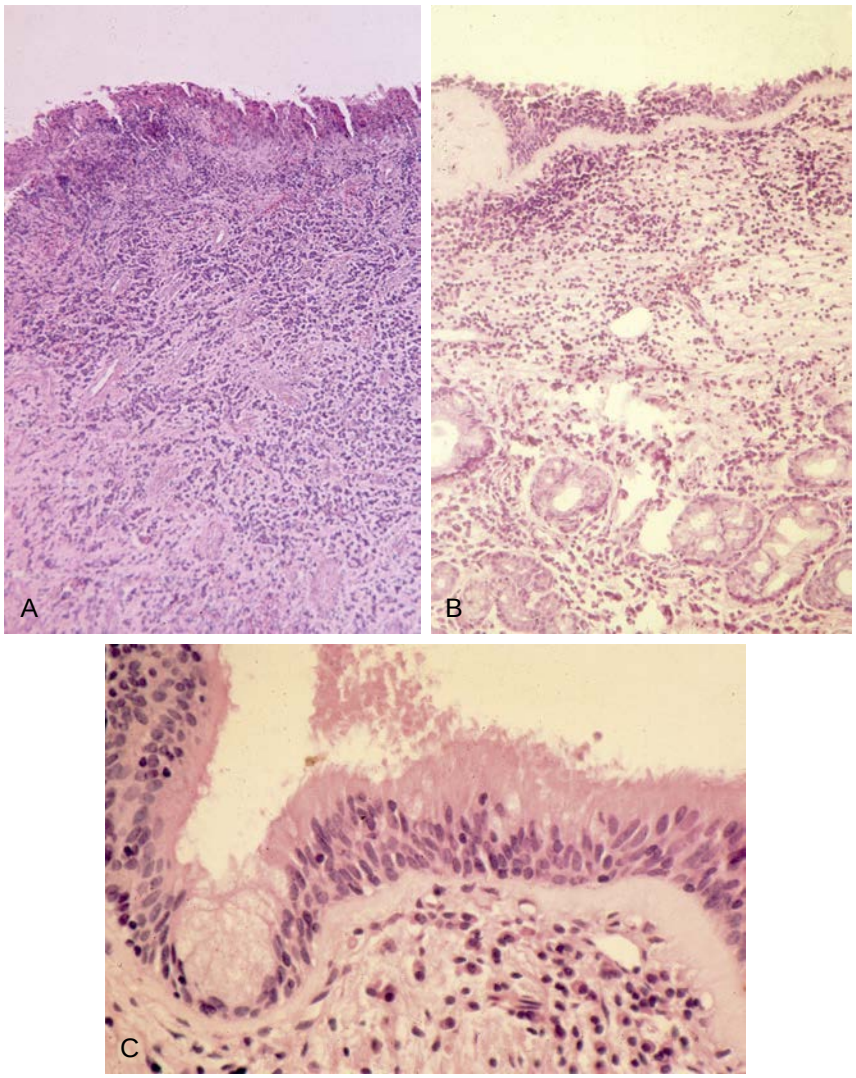
Radiographically, dermoid cysts appear as a moderately thin-walled, unilocular mass. On CT scan the central cavity is usually filled with homogeneous, hypoattenuated fluid material. Discrete intracystic foci "marbles," with moderate hyperintensity, may be present. These structures result from coalescence of fat into small nodules within a fluid matrix.[162] This appearance is virtually pathognomonic of dermoid cysts in this location. Epidermoid cysts have fluid attenuation on CT scan and are hypointense on T_1-weighted images and hyperintense on T_2-weighted images, following the signal intensity of fluid.

Pathologic Features

Both dermoid and epidermoid cysts are lined with stratified squamous epithelium with keratin and/or a sebaceous material–filled cavity. However, in a true dermoid cyst the connective tissue wall shows variable dermal appendages, including sebaceous glands, hair follicles, and sweat glands[146,147,155] (Figure 17-38). The epithelial lining in either of the cysts may on occasion contain respiratory epithelium.[158]

Surgical Management

Complete surgical excision is the treatment of choice. Cysts occurring above the geniohyoid muscle can be removed through an intraoral approach. Cysts below that muscle and those below the mylohyoid muscle require an extraoral



• **Figure 17-35** **A,** Photomicrographs of nasopalatine duct cyst lined by pseudostratified ciliated epithelium and inflammatory cell infiltrate of the wall. **B,** The wall focally contained mucous glands. **C,** Higher magnification clearly shows the ciliated epithelium.

approach.[150,163] According to Prayor and colleagues, among 49 pediatric patients only 1 patient had recurrence on follow-up.[153] Malignant transformation to squamous cell carcinoma has rarely been reported.[150]

Thyroglossal Duct Cyst

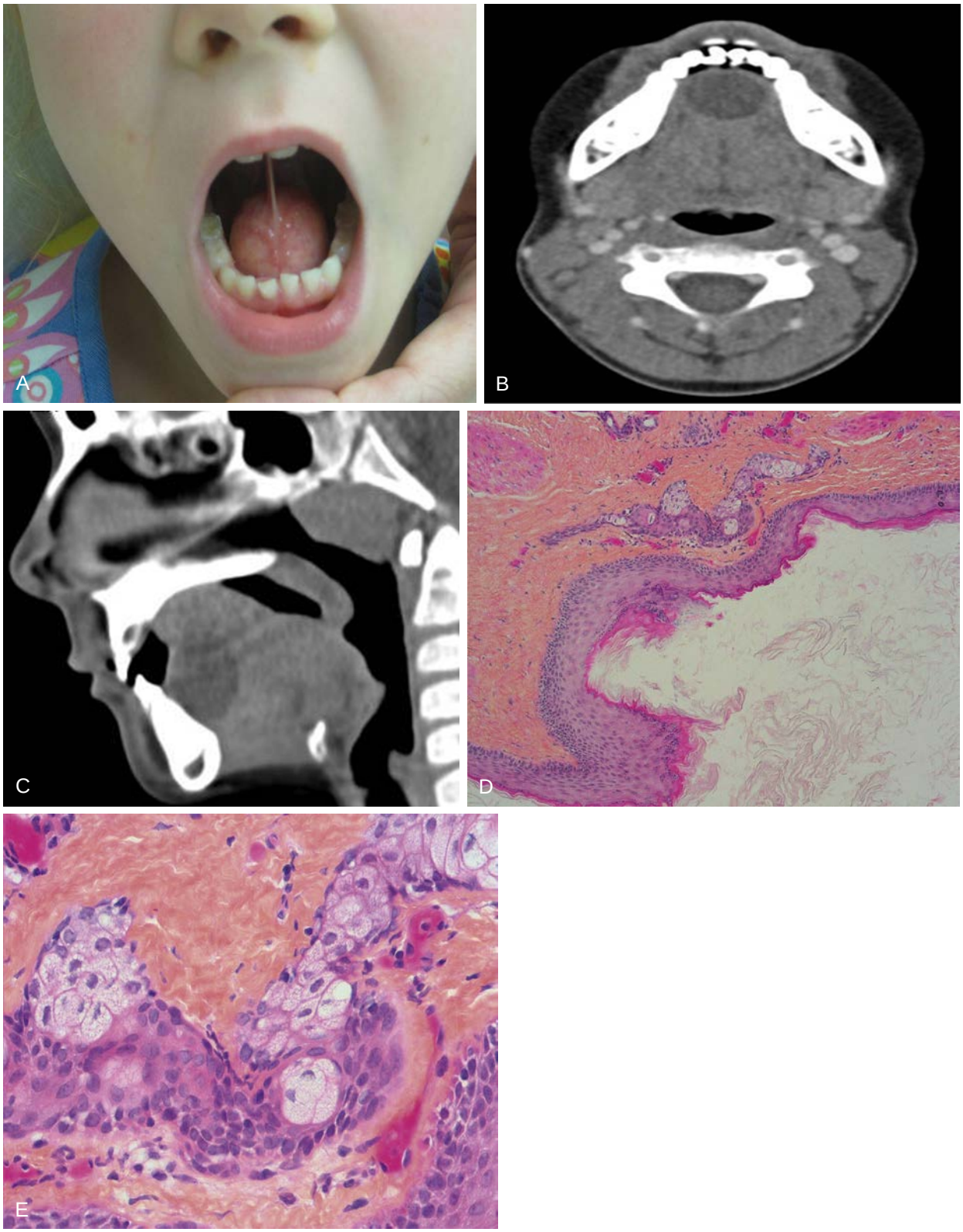
Overview

The thyroid gland develops as a median outgrowth from the floor of the primitive pharynx during the third week of fetal life. The thyroid primordium originates at the level of the foramen cecum, which in adults lies at the junction of the anterior two thirds and posterior one third of the tongue. The primitive thyroid descends through the mesoderm of the tongue and floor of the mouth and eventually passes anterior to the developing hyoid bone and laryngeal cartilage (Figure 17-39). The primitive gland reaches its final position in the anterior part of the neck by the seventh week of gestation.[143]

During migration, the anlage of the thyroid gland is connected to the tongue by a narrow tubular structure, the thyroglossal duct. This duct normally involutes by the eighth to tenth gestational week. The superior end of the canal persists as the foramen cecum of the tongue while the inferior end becomes the pyramidal lobe of the thyroid gland.[143,144] If any portion of the thyroglossal duct persists, cystic changes may occur as a result of secretion from the epithelial lining. Recurrent infections and inflammation may contribute to such events.[164]

Clinical Features

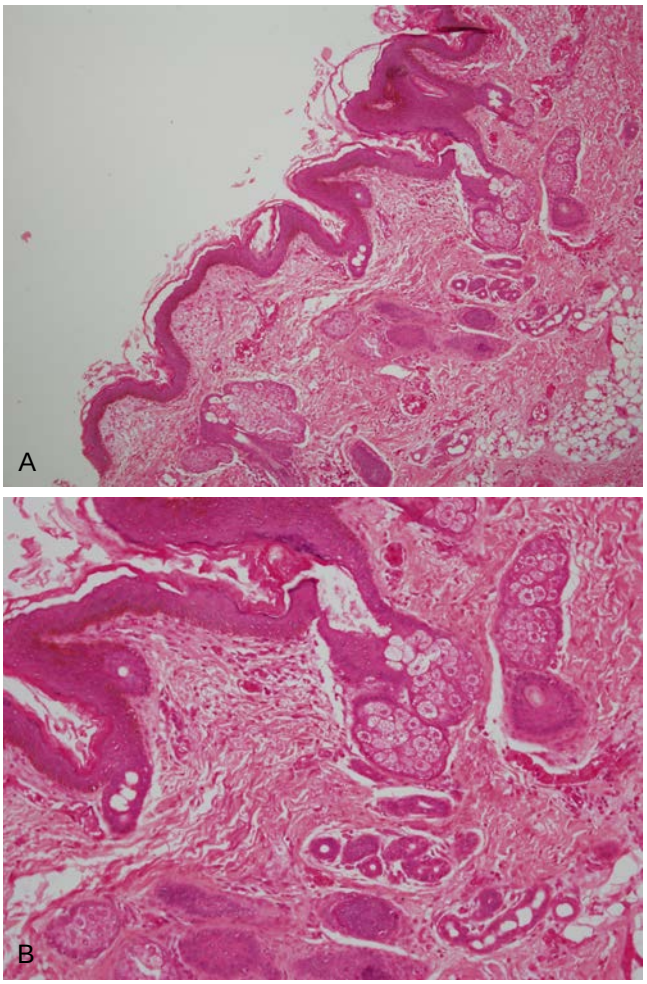
The thyroglossal duct cyst (TGDC) can develop at any age, but they are most commonly diagnosed in the first 2 decades of life. About 50% of cases occur before the age of 20 years.[165,166] In a review of 70 cases of TGDCs, the average age of presentation was 21.5 years.[165] There is no gender predilection.[164,166] However, a slight female bias with a



• **Figure 17-36** **A,** A 5-year-old girl presents with a midline floor of the mouth lesion. **B,** Axial, and sagittal computed tomography scan images **(C)** showing a well-circumscribed, hypodense lesion. **D,** Low-power photomicrograph showing stratified squamous epithelial lining of the dermoid cyst. **E,** High-power photomicrograph revealing sebaceous foci within the lesion. (Surgery performed by Joseph Kern DDS, MD, Plymouth Meeting, PA.)



• **Figure 17-37** Dermoid cyst of the floor of the mouth in an adult causing a prominent submental swelling.



• **Figure 17-38** **A,** Dermoid cyst lined with stratified squamous epithelium. Dermal appendages are seen in the cyst wall, including hair follicles, sebaceous glands, and sweat glands. **B,** Higher magnification.

female-to-male ratio of 3:2 has been reported.[165] Rare cases of hereditary TGDC have been diagnosed. Typically, these cysts have an autosomal dominant pattern of transmission and occur in prepubertal girls.[167]

The majority of TGDCs are located in the midline or slightly off the midline. They are always within 2 cm of the midline.[168] Of those in a paramedian location, most will occur on the left, for reasons that are not well understood.[169] The cysts usually manifest as an enlarging painless fluctuant mass in a pediatric or young adult patient. The size of the cyst ranges from 0.5 to 6 cm in diameter, but most are between 1.5 and 3 cm.[170] Some cases may present with infection-related symptoms. These may improve by antibiotic treatment, but they frequently recur after completion of the antibiotic course.[170]

Approximately 80% of the cysts occur either at or below the level of the hyoid bone. The remaining 20% are located above that bone (Figure 17-40). In either case the cyst usually involves the hyoid bone (Figure 17-41). Rarely a TGDC may manifest as a mass in the floor of the mouth or tongue.[171-174] Characteristically the lesion moves upward on tongue protrusion, a reflection of the origin of the duct at the foramen cecum.[168,175]

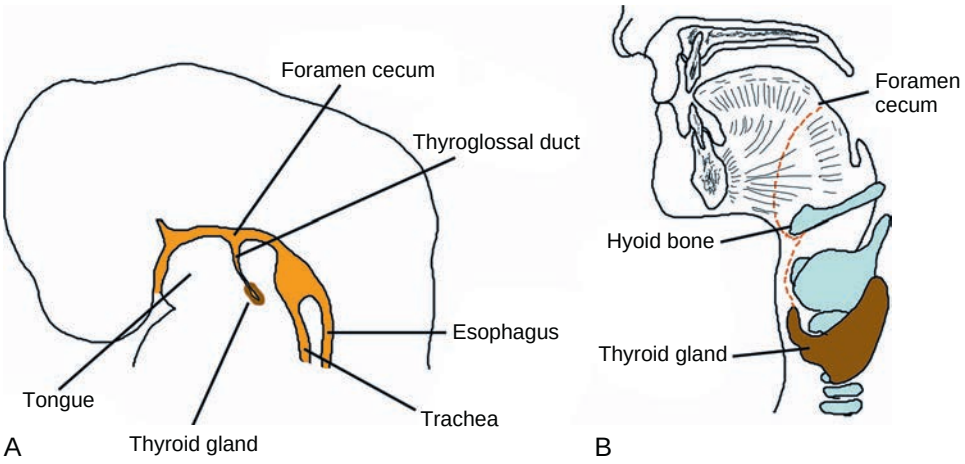
Radiographically a TGDC appears in CT scans as a smooth, well-circumscribed mass anywhere along the vertical course of the vestigial thyroglossal duct; the mass has a thin wall and homogeneous attenuation[171] (Figure 17-42). With MRI the cyst has low signal intensity on T_1-weighted images and is hyperintense on T_2-weighted images, which reflects its fluid contents. The rim of the cyst is unenhancing unless inflammation is present.[159]

Pathologic Features

A TGDC contains colorless, viscous secretions. Microscopically the cyst is lined with pseudostratified columnar ciliated respiratory-type epithelium, or squamous epithelium[176-180] mucous glands may be present.[178] However, in our experience the latter finding is not common. Thyroid tissue is variably found in the wall of the cyst (Figure 17-43). The frequency of detection of glandular tissue depends on the diligence with which it is sought. It is variably reported for up to 62% of cases.[175,178,180-182] Using isotope scanning, Dische and Berg[182] found functioning thyroid tissue in one third of their patients with TGDC.

Surgical Management

Total surgical excision is the treatment of choice. Partial resection of the TGDC virtually always leads to recurrence. The recommended surgery is called the Sistrunk procedure. This operation involves en bloc excision of the entire thyroglossal



• **Figure 17-39** **A,** The primitive thyroid arises as an epithelial diverticulum at the level of the foramen cecum, in the midline of the pharynx. **B,** The *dashed red line* indicates the path of migration of the thyroid gland to its final position. (From August M, Faquin WC, Traulis M, Kaplan LB: Differentiation of odontogenic keratocysts from nonkeratinizing cysts by use of fine aspiration biopsy and cytokeratin-10 staining, *J Oral Maxillofac Surg* 58:935-940, 2000.)



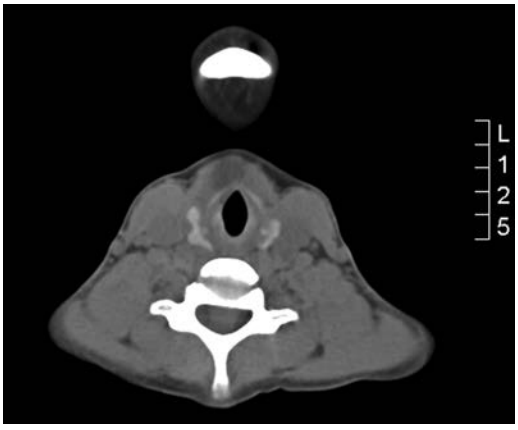
• **Figure 17-40** **A,** Thyroglossal duct cyst located below the hyoid bone and **(B)** above the hyoid bone.

duct tract to the foramen cecum, as well as the central 1 to 2 cm of the hyoid bone. When this procedure is used, the rate of recurrence rarely exceeds 4% to 6%.[176,177,183,184] When the central part of the hyoid bone is not removed, a recurrence rate of 25% or more may be expected.[176] Incision and drainage of TGDC is not recommended.

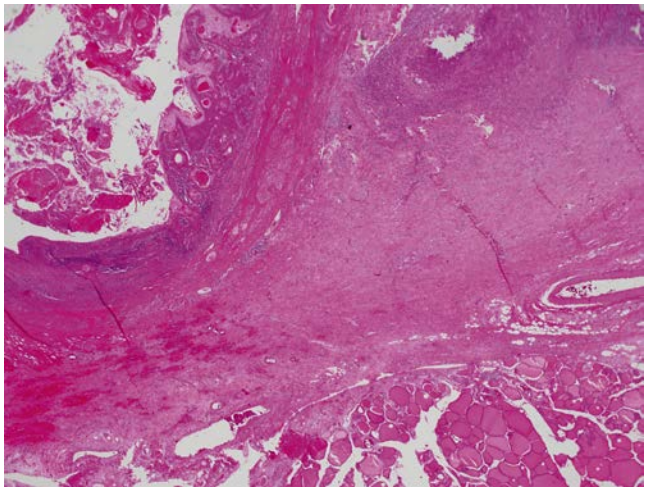
Malignant changes in a TGDC are very rare, developing in less than 1% of patients.[185] They are more common in women by a margin of up to 2:1 and have been described in individuals from 6 to 84 years of age with an average of 39 years.[179,186,187] The most common carcinoma arising from TGDC is papillary thyroid carcinoma, developing in the ectopic thyroid tissue present in the cyst wall (Figure 17-44). It accounts for 80% to 90% of TGDC carcinoma, followed in frequency by squamous cell carcinoma at 5% (Figure 17-45) and follicular carcinoma at 3%.[179,181,186-189] Only two cases of concurrent papillary and squamous carcinomas in thyroglossal duct cysts have been reported.[190] One such case, but unreported, was diagnosed at our institution. Anaplastic thyroid carcinomas are extremely rare, and medullary carcinoma of the thyroid has never been seen in TGDC.[181,191] A majority of carcinomas arising in TGDCs are asymptomatic and are diagnosed only on microscopic examination of an excised, long-standing benign-appearing



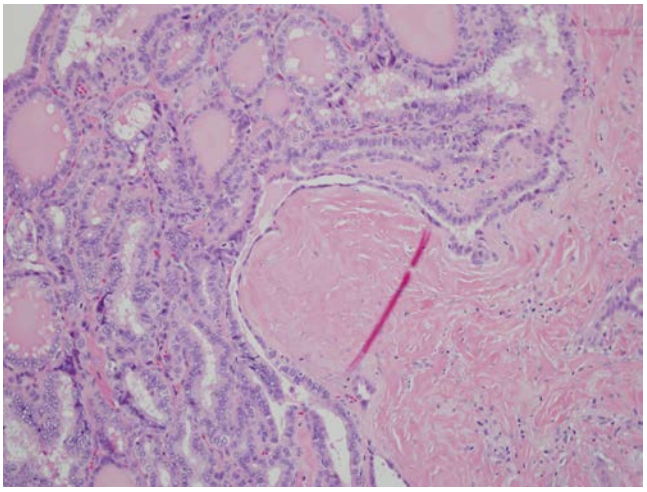
• **Figure 17-41** Sagittal section in a cadaver showing thyroglossal duct cyst intimately associated with the hyoid bone.



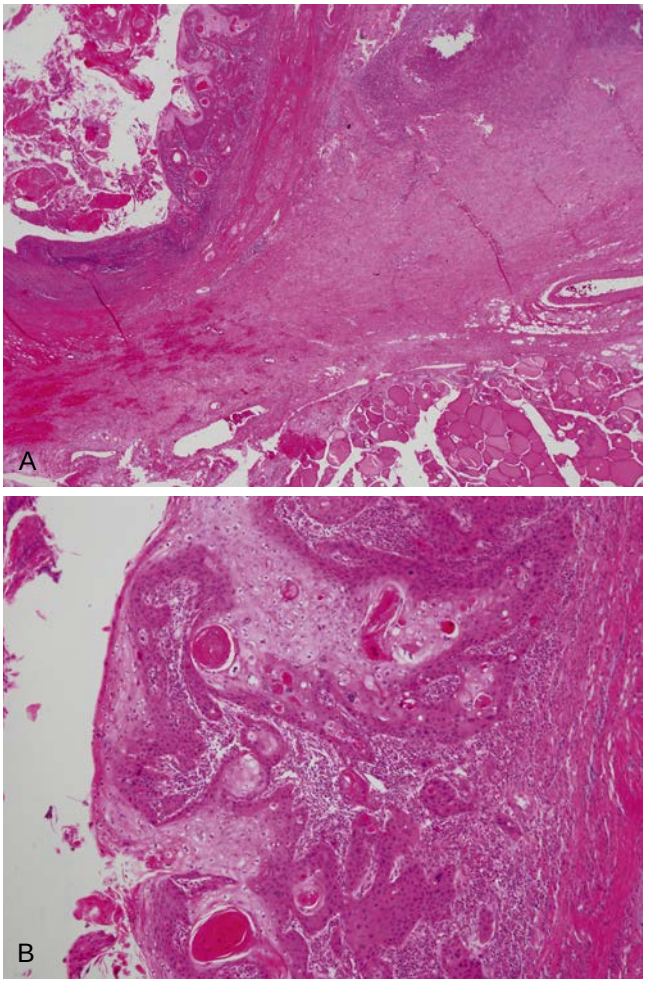
• **Figure 17-42** Axial computed tomography scan showing a thyroglossal duct cyst present anterior to the thyroid cartilage, at the midline and extending slightly to the right side.



• **Figure 17-43** Thyroglossal duct cyst showing ciliated columnar epithelial lining. Thyroid follicles are present in the cyst wall.



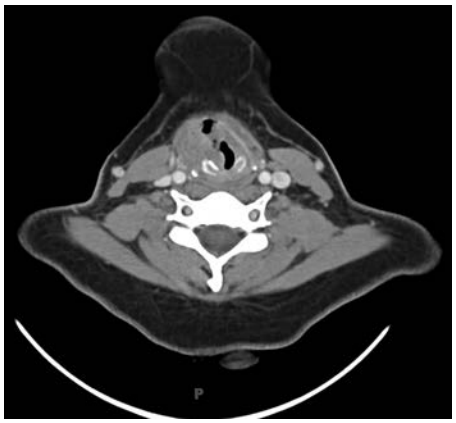
• **Figure 17-44** Papillary thyroid carcinoma arising in thyroglossal duct cyst. The epithelial cyst lining is seen at the upper left corner. The carcinoma in the cyst wall shows papillary and follicular growth patterns as well as characteristic nuclear features of papillary thyroid carcinoma.



• **Figure 17-45** **A,** Invasive squamous cell carcinoma arising in thyroglossal duct cyst. **B,** Higher magnification.

cyst. Rarely, pain, sudden enlargement, hoarseness, airway compromise, or cervical lymphadenopathy may suggest malignant change.[192]

Radiographic examination may be useful in identifying malignancy. CT scans typically show dense, enhancing mural nodules (Figure 17-46). Additionally, in cases of papillary carcinomas, foci of calcification may be present.[193,194] FNA biopsy may confirm the diagnosis of malignancy. Microscopic examination reveals classical papillary thyroid carcinoma within the walls of the cyst. The tumor shows papillary and follicular features as a result of a combination of both growth patterns (see Figure 17-44). The tumor cells exhibit the classical cytologic features of papillary carcinoma of the thyroid, including large crowded nuclei, nuclear clearing, nuclear grooves, and pseudoinclusions. Psammoma bodies are seen in some of the cases.[192,194]



• **Figure 17-46** Axial computed tomography scan of squamous cell carcinoma arising in thyroglossal duct cyst. Enhancing soft tissue mass is seen in the wall of the cyst that involves the thyroid cartilage and extends into the endolaryngeal space.

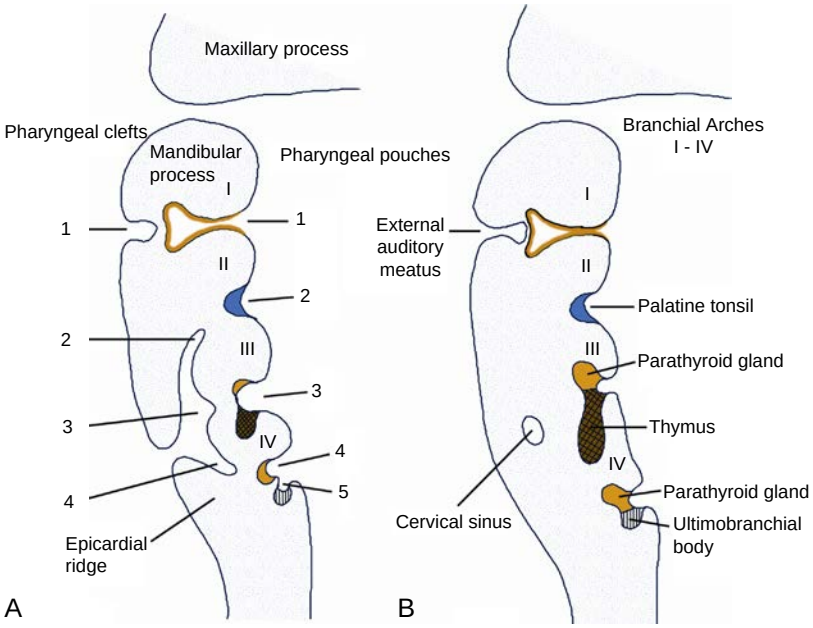
Because carcinomas arising in TGDC are frequently coincidental, most are treated by the Sistrunk procedure described previously. In the absence of positive surgical margins or lymph node metastasis, no additional treatment is warranted. In the event of positive margins or lymph node involvement, wider resection of the lesion and neck dissection is indicated. Any associated thyroid gland disease should be evaluated and managed accordingly.[192,194]

It is generally agreed that the prognosis in the case of papillary carcinoma arising in TGDC is favorable and parallels that of primary papillary thyroid carcinoma. Local recurrence, metastasis, and death have rarely been reported.[186,189] However, squamous cell carcinoma arising in TGDC behaves more aggressively and may warrant more extensive surgery and possibly postoperative radiotherapy.[186,190,195]

Branchial Cleft Cyst

Overview

Four pharyngeal clefts separating the branchial arches are recognizable in the 5-week-old embryo (Figure 17-47). The dorsal part of the first cleft penetrates the underlying mesoderm and gives rise to the external auditory meatus. Active proliferation of the mesodermal tissue of the second arch causes it to overlap the third and fourth arches. Finally, it fuses with the epicardial ridge. The second, third, and fourth clefts lose contact with the outside and temporarily form an ectoderm-lined sinus, the cervical sinus (see Figure 17-47). With further development this sinus disappears entirely.[143,144]



• **Figure 17-47** **A,** Schematic representation of the development of the pharyngeal clefts and pouches. The second arch grows over the third and fourth arches. **B,** Remnants of the second, third, and fourth pharyngeal clefts form the cervical sinus. (From Langman J: *Medical embryology,* Baltimore, 1984, Williams & Wilkins.)

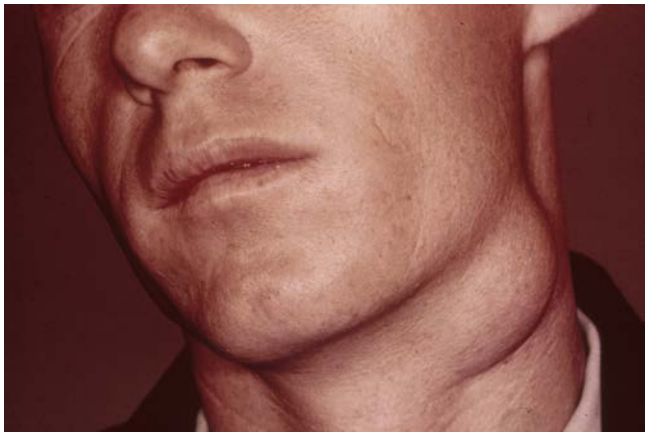
Branchial cleft anomalies are believed to develop as a result of incomplete obliteration of the cervical sinus or from epithelial rests of the branchial clefts.[196] Abnormalities of the branchial clefts are usually cysts, sinuses, and fistulae. They occur primarily on the lateral side of the neck along the anterior border of the sternocleidomastoid (SCM) muscle, but may also be found in or around the parotid gland and external ear. The abnormalities are rarely bilateral and on occasion may be familial.[197-200] The lesions usually exist as an isolated phenomenon but on occasion may be associated with other defects such as patent ductus arteriosus, tear duct atresia, hearing abnormalities, and malformed auricles.[193-196]

In a review of 274 patients with branchial cleft anomalies, at the Mayo Clinic, the majority (75%) were cysts; 25% were fistulae.[201] Patients with branchial cleft cysts are usually older children or young adults, in contrast to patients with fistulae, who are usually infants or young children.[201,202]

The first branchial cleft cysts occur in the parotid gland as lymphoepithelial cysts. Those account for 5% of all branchial cleft defects and are most commonly seen in middle-age women.[203,204] Cysts arising from the third and fourth branchial clefts are extremely rare, with only a few cases reported. They occur in the posterior cervical space, usually in children and young adults.[196,205] The vast majority (95%) of branchial cleft anomalies arise from the second cleft, predominantly as cysts.[169] The following discussion addresses this entity, which will be referred to as branchial cleft cyst.

Clinical Features

The cysts are most commonly located in the submandibular space. However, because of the anatomic relationship of the second branchial cleft and the cervical sinus, they can occur anywhere along a line from the oropharyngeal tonsillar fossa to the supraclavicular region of the neck.[203] These cysts usually present as painless fluctuant masses in the lateral portion of the neck adjacent to the anteromedial border of the SCM muscle, at the mandibular angle[155,173,206] (Figure 17-48).



• **Figure 17-48** Branchial cleft cyst presenting as a mass in the submandibular area, adjacent to the anterior and medial borders of the sternocleidomastoid muscle.

The mass enlarges slowly over time and may become tender and painful if secondarily infected.[206] In a young patient, a history of recurrent inflammation in the region of the mandibular angle is highly suggestive of a branchial cleft cyst.

In CT scans these cysts are typically well-circumscribed, homogeneous, hypoattenuated masses surrounded by a uniformly thin wall[155] (Figure 17-49). Mural thickness may increase after infection. The typical location of the cysts from either CT scan or MRI imaging is at the anterior medial border of the SCM muscle lateral to the carotid space and at the posterior margin of the submandibular gland. The cyst typically displaces the SCM muscle posteriorly or posterolaterally, pushes the vessels of the carotid space medially or posteromedially, and displaces the submandibular gland anteriorly[173-203] (see Figure 17-49).

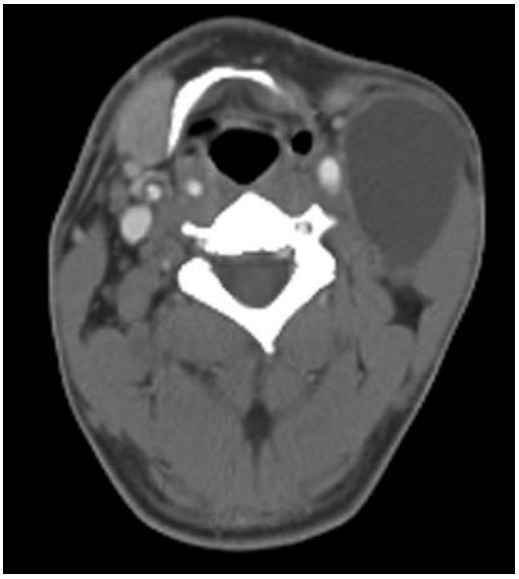
Pathologic Features

The cysts are usually unilocular and vary in size from 1 to 10 cm. They are usually filled with turbid yellowish fluid that may contain cholesterol crystals. Their walls are thin and lined with stratified squamous epithelium, in the majority of cases. Occasionally cysts may be lined with respiratory epithelium or combinations of both types of epithelium.[154,168,169,206] In almost all cases the epithelial lining overlays lymphoid tissues that may be diffuse or nodular with germinal centers and mantle zones[207] (Figure 17-50).

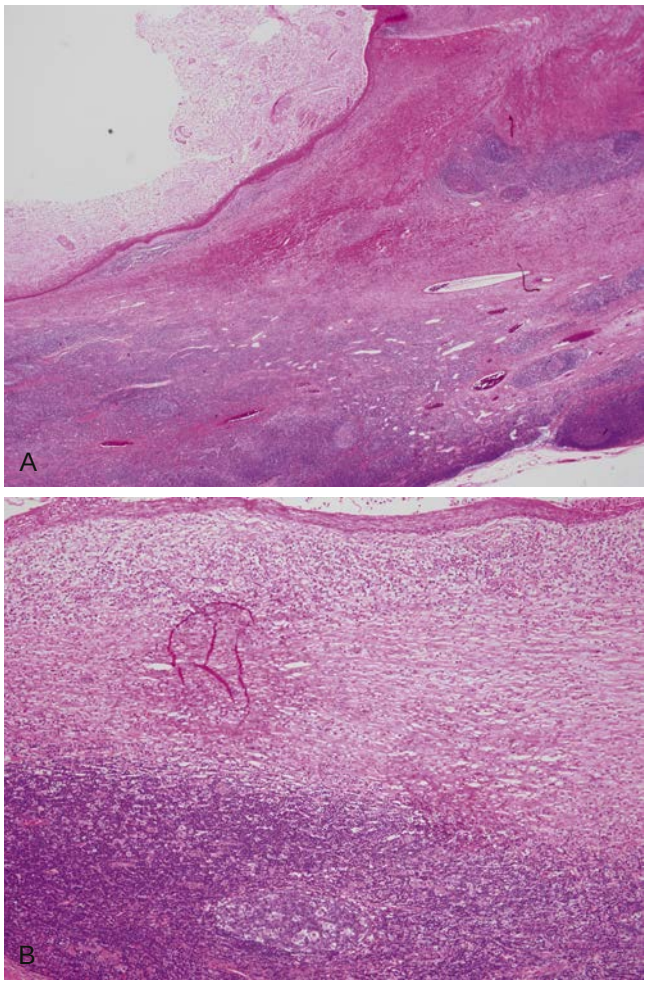
With repeated infection the wall may become fibrotic and the epithelium may then be partially replaced by granulation tissue or fibrous tissue.

Surgical Management

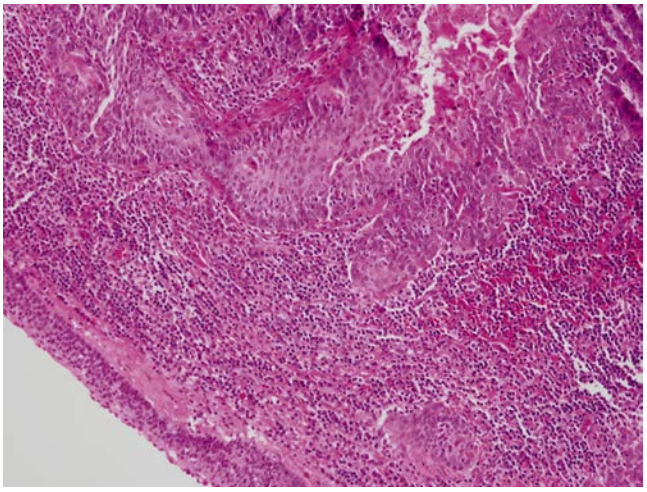
Complete surgical excision is indicated because of the frequency of secondary infections. In cases in which there is



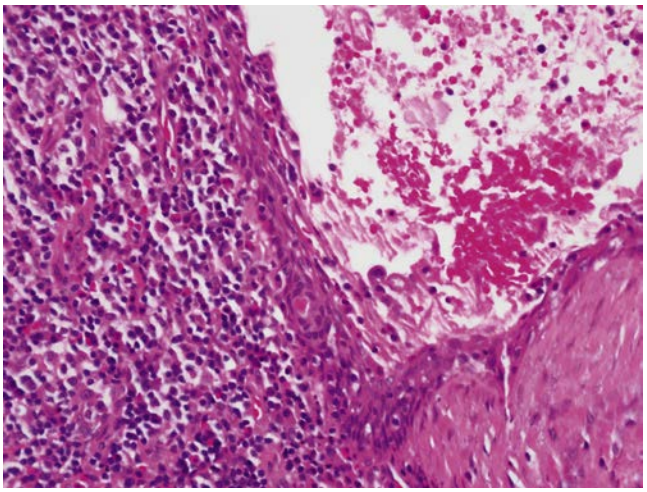
• **Figure 17-49** Axial computed tomography scan showing a large branchial cleft cyst that appears as a well-defined ovoid fluid-filled lesion in the left neck. The cyst is present between the submandibular gland, which is displaced interiorly, and the sternocleidomastoid muscle, which is displaced posterolaterally.



• **Figure 17-50** **A,** Branchial cleft cyst showing thin stratified squamous epithelium lining overlaying diffuse and nodular lymphoid tissue, with germinal centers, in the cyst wall. **B,** Higher magnification.



• **Figure 17-51** Branchial cleft carcinoma. Squamous cell carcinoma is present within the lymphoid tissue in the cyst wall. The cyst lining is benign stratified squamous epithelium.



• **Figure 17-52** Cystic changes in metastatic oropharyngeal nonkeratinizing squamous cell carcinoma in a cervical lymph node. Basaloid epithelial cells with hyperchromatic nuclei form a thin lining of the cystic space.

significant inflammation, surgery may be delayed until it is resolved.[201] Patients who continue to have persistent branchial cleft remnants, with infectious episodes after repeated attempts at surgical excision, may benefit from functional neck dissection.[208]

A recurrence rate of 2.7% has been reported in a large review of cases. Higher recurrence rates were found in cases with a history of infection or previous surgical intervention.[208]

Malignant change in branchial cleft cysts (branchial cleft carcinoma) is extremely rare. In order to correctly make such a diagnosis, it is essential to be able to demonstrate carcinoma developing in the wall of a benign cyst (Figure 17-51). It is also important to rule out cystic changes in metastatic carcinoma in cervical lymph nodes. Such an event is particularly common in metastatic nonkeratinizing carcinomas of the oropharynx.

The lining epithelium in cystic lymph node metastasis may on occasion be very thin and deceptively bland. However, the cells tend to be more basaloid with darker nuclei as compared to the lining epithelial cells of branchial cleft cysts (Figure 17-52).[209] In the great majority of these metastases, human papillomavirus (HPV) can be identified by polymerase chain reaction (PCR) or in situ hybridization (ISH), and the cells react strongly and diffusely with p16 immunostain.[209,210] Thorough clinical evaluation may lead to detection of occult primary tumors, particularly in the tonsils and base of the tongue.

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18

Odontogenic Tumors: Surgical Pathology and Management

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Introduction

The embryologic events that initiate, control, and guide formation of human odontogenic structures take place through an intricate and finely regulated series of inductive interactions between epithelium and mesenchyme, which begin during the fifth and sixth weeks of intrauterine life and are completed about the sixteenth year after birth.[1,2] During this extended period, there is ample opportunity for developmental and growth mechanisms to fail in whole or in part, resulting in the formation of *malformations, hamartomas,* and *neoplasms,* collectively known as *odontogenic tumors*.

Odontogenic tumor, therefore, is an imprecise term that encompasses a wide spectrum of lesions and variants. Distinctions among these three forms of abnormalities may, in part, depend on the embryologic stage of initiation and the histologic and gross appearance of the lesion at the age of clinical discovery. Overlap and combinations among lesions are possible and do occur. A malformation, although neoplastically innocent, because of size and/or anatomic position may cause a functional disturbance or aesthetic liability; a hamartoma by continued growth may eventuate as a neoplasm; and a benign odontogenic cyst or usually self-limiting neoplasm may give rise to an aggressive or malignant neoplasm. Thus, an odontogenic lesion may require surgical management because of physical presence or biologic behavior. Biologic behavior, biologic activity, and growth potential are three interrelated effectors that determine a lesion's ability to harm the host.

Because histologic appearance and biologic behavior are not necessarily linked, assessment of the growth potential of an odontogenic lesion may be difficult. This is true particularly in the case of a "newly discovered" or rarely encountered entity of which long-term clinical experience has not been documented. Even in the instance of ameloblastoma, a lesion that has been recorded extensively for over a century, there are diametrically opposed management philosophies. In addition to so-called radical or conservative modalities, variations and combinations of treatment have been attempted.

The goal of treatment, of course, is eradication of a lesion with the least morbidity possible and the preservation or restoration of function. However, a common all-inclusive algorithm for the management of odontogenic tumors, as well as other maxillofacial jaw lesions, must await long-term treatment and outcome studies. The current basis for the decision whether, when, and how to manage a number of odontogenic lesions is contingent on individual clinical factors and assessment of the lesions' biologic behavior. Several odontogenic tumors have distinct histologic patterns, are well documented in case histories and case series studies, and have known outcome results; however, even among these lesions an occasional rogue lesion may exhibit unexpected biologic behavior.

Such activity may be regarded as chance vagary of the lesion but also may be due to unappreciated histologic or molecular variation with concomitant altered biologic behavior. Because histologic diversity may help to characterize odontogenic lesional behavior, it is prudent to consult an oral and maxillofacial pathologist for evaluation of odontogenic lesions. Presently most hospital pathology departments have an oral and maxillofacial pathologist on staff or routinely consult with them. This is to be expected and encouraged, because odontogenic tumors comprise a specialized area of pathology.

Classifications

It is interesting to read the earlier efforts at classification, especially by the British writers of the later 19th and early 20th centuries up to the 1930s, as they labored to clarify and classify odontogenic lesions.[3-6] The class name they adopted was *Odontomes,* under which the entire gamut of odontogenic lesions, as well as unrelated jaw lesions, were placed. In the United States, Ivy and Churchill[7] also made an effort to bring order to and reclassify odontogenic lesions. In 1946 Thoma and Goldman[8] published their classic paper, which

described a classification of odontogenic tumors based on the tissue cell of origin and eliminated many extraneous lesions from consideration. They recognized lesions derived

Their scheme, and particularly the case illustrations, demonstrated the inductive effects of one tissue (epithelium) on another (mesenchyme) in the pathogenesis of odontogenic tumors.

Several other revisions and refinements were made by Pindborg and Clausen[9] and by Gorlin and other colleagues,[10] who also proposed a classification based on the embryologic inductive interactions of the tissues on each other. These classifications provided a better means to view and catalog lesions in an orderly manner but did not give the surgeon insight into their biologic behavior. In a further departure, the World Health Organization (WHO) published a classification in 1971,[11] a revision in 1992,[12] [13]

but also categorizes odontogenic lesions into benign and malignant types (1971, 1992, 2005). The authors recognize the inherent difficulties in this or any classification that contains lesions of uncertain status as well as lesions for which behavioral information is still being accumulated. As is always the case, the latest efforts at histologic typing of odontogenic tumors have evoked reasonable suggestions and comments from several writers.[14-20] It is apparent that no classification is entirely satisfactory and that all have deficiencies. The order of presentation used in this chapter follows the traditional separation of lesions into epithelial, mesenchymal, and mixed types. In addition, an attempt is made to indicate a progression from the least to the most aggressive lesions. However, we emphasize again that known nonaggressive lesions may exhibit unexpected aggressive behavior.

General Clinical, Diagnostic, and Management Considerations

Clinical

rence reports of odontogenic tumors, expressed as percentage[3] of the total lesions in oral biopsy services of various institutions in the United States and countries throughout

clinical importance of odontogenic tumors is not measured by their numbers, but because some lesions are very destructive and surgical management involves the face, oral tissues, and jaws of both young and old patients. Correlation of clinical, radiographic, and histologic analyses is necessary to prevent over- or undertreatment.

There are no clinical signs, symptoms, or physical findings that permit diagnosis of specific odontogenic tumors. The age and sex of the patient and location characteristics of lesions are derived from pooled data compiled from the literature and unpublished cases. Such information is useful only when combined with other diagnostic features.

Imaging

Because most odontogenic tumors emanate from or involve the jaws, imaging modalities, including plain radiography (periapical, occlusal, panoramic), computed tomography (CT), CT three-dimensional (3D) reconstruction, computer-generated models, magnetic resonance imaging (MRI), and positron emission tomography (PET) scan CT, offer an unparalleled opportunity to view the tumor in relation to the jaws and adjacent soft tissues. Radiographic images do not provide pathognomonic identification of odontogenic lesions, because several odontogenic tumors as well as nonodontogenic lesions may share imaging characteristics. However, highly useful visual information can be gathered to study a lesion for presumptive differential diagnoses, selection of biopsy sites, and management decisions. A lesion's position, size, and shape; presence or absence of lesional calcifications; estimation of soft tissue volume in relation to calcified tissue, cyst formation, and impingement on or inclusion of vital anatomic structures; displacement of teeth or root resorption; and interface boundaries between lesion and host bone help the clinician to form a characterization of the tumor's activity and aggressiveness.

Odontogenic tumors are most often discovered by dental radiography (periapical, occlusal, or panoramic) as part of routine screening during a dental visit, examination of a patient with a specific complaint (e.g., pain or oral soft tissue or facial enlargement), or elective consultation (e.g., orthodontic or orthognathic surgery). The judgment of the clinician will determine the extent and types of imaging that are needed or most useful for the management of a specific case. Yet, in many instances, there is a tendency to use fewer imaging modalities than are desirable—which is usually later regretted, as imaging provides a valuable documentary and study tool.

Overall viewing of bone and soft tissue by consecutive anatomic "slices" and planes is provided by CT and MRI, respectively. The volume of the tumor and the interface margins between the tumor and surrounding bone and soft tissue is roughly revealed by PET-CT, obtained after injection of a glucose isotope conjugate metabolized by the tumor. The 3D CT (three-dimensional computerized tomogram) permits viewing the lesion in almost kaleidoscopic anatomic displays; the 3D CT generated model provides an excellent physical reproduction of the anatomic part and tumor. The model is useful for planning or carrying out a mock surgical

procedure and provides a mechanical frame on which to contour a reconstruction appliance.

Biopsy

Definitive diagnosis is established only after incisional, excisional, or intraoperative frozen section biopsy for histologic analysis. The specific biopsy technique is selected after careful assessment of the patient (age, physical health, and emotional status) and of the use of local, sedation, or general anesthesia to ensure patient cooperation, gain access to the lesion, and obtain sufficient tissue for study. An *incisional biopsy* performed several weeks before definitive management often precludes excision or frozen section diagnostic "surprises." Thus, time is gained to receive a soft or calcified tissue diagnosis, plan the surgical procedure, prepare and/or obtain special presurgical requirements, and fully discuss management with the patient or guardian. *Excisional biopsy* should be performed for completely calcified odontogenic lesions (i.e., malformations radiographically demonstrating only teeth or a cementum-like tissue) in which histologic diagnosis is not immediately essential; for physically impaired patients for whom several anesthetic or surgical exposures should be avoided; or for small lesions (approximately 1.0 to 1.5 cm in diameter) that can be excised completely and can reasonably be expected not to require further operation after histologic study. *Intraoperative frozen section* host bone and/or soft tissue in instances in which extensive resection is not planned. The preparation of a good frozen section is technique-sensitive and requires proper specimen orientation and avoidance of incorporated dense bone (which nicks the microtome blade and disrupts the tissue section).

The biopsy is an important procedure and must be planned and conducted carefully. Because of its key role in the diagnostic process, and later in the definitive surgical procedure, some aspects of the biopsy are discussed here in detail: (1) The lesion is approached, with radiographic guidance, by incision through intact crestal mucosa over intact bone, in order to preserve "noncontaminated" mucosal soft tissue that may be used for wound closure after a postbiopsy surgical procedure. (2) The lesion is aspirated through the intact bone to rule out a vascular lesion masquerading as an odontogenic tumor (other potential radiographic imitators of odontogenic tumors include aneurysmal bone cyst, giant cell lesion, and fibro-osseous disease). (3) Aspiration of cystic fluid neither confirms nor disproves the presence of a cystic odontogenic tumor; the fluid may or may not be retained for a cell-block preparation. (4) Entrance through the bone to the lesion should be selected and obtained without injury to nerves or teeth, if possible. (5) If the radiobordering the lesion–host bone interface. The specimens are incised for removal and not crushed with forceps or hemostats. (6) Before suture closure of the biopsy incision, if desirable, a nonresorbable tissue barrier can be placed over the bone entrance to the lesion to prevent fluid or lesional cell escape into noninvolved periosteum or mucosa.

The specimens are oriented and identified by marking the natural tissue surfaces with indelible ink of the same or a different color (i.e., to represent the biopsy sites such as anterior or posterior), spread flat with the tissue exudate side down on an absorbent surface (e.g., glove wrapper or filter paper), allowed to dry for about 3 to 4 minutes so that the specimen adheres to the carrier and does not curl, and placed into separate labeled containers. This technique

The surgeon or assistant surgeon should complete the pathology laboratory form. This important function should not be assigned to others (e.g., circulating nurse), because accuracy cannot be assured later if questions concerning biopsy sites and histologic findings arise. The pathology laboratory form provides space for a brief history, clinical diagnosis, special instructions to the pathologist, and dia- sent to the pathologist.

The histologic tissue slides should be reviewed by the surgeon alone or with the pathologist. Unusual, problematic, or unexpected findings should be discussed with the pathologist. After histologic study and diagnosis, the biologic activity of the lesion is estimated. An equivocal diagnosis or a choice among several diagnoses should initiate a review by other pathologists.

Management

The objectives of the surgical management of odontogenic tumors are the eradication of the lesion, preservation of normal tissue to the extent possible, and restoration of significant tissue loss, form, and function. All agree that the surgical procedure should be sufficient to the need; however, in many instances there is disagreement among surgeons and pathologists about the extent of surgery that specific tumors require. These differences of opinion are reflected in the literature and account for "conservative" or "radical" approaches to treatment that result from unanswered questions concerning the biologic activity of several odontogenic tumors.

Some surgeons maintain an almost mystical adherence to a conservative surgical approach, in the conviction that all odontogenic tumors are benign. This viewpoint amounts to a planned recurrence for some lesions. The basis for this opinion is the belief that a recurrence or recurrences (more properly, regrowth of residual lesion) can be managed by a simpler procedure that can avoid jaw resection. However,

one of the results of such an approach is the creation of a shotgun pattern of recurrence by which the lesion is spread throughout a larger area, thus compounding the surgical problem. Other surgeons are routinely aggressive in their approach to all odontogenic tumors, and so sacrifice more normal tissue than is necessary to ablate the lesion. The argument has been made that a well-planned and executed resection and reconstruction serves the patient physically and emotionally better than repeated surgical procedures.[22] The defense of or response to both positions lies in the continued accumulation and dissemination of accurate data and knowledge of odontogenic lesions. This can be achieved best by the surgeon and pathologist working together to correlate clinical, surgical, and histologic findings with biologic activity and clinical outcome. This effort would be aided greatly by the adoption of standardized, defined surgical excision terms acceptable to the entire surgical community.

One attempt to provide precisely defined excision terminology applicable to lesions in bone was offered by Gold and co-workers.[23] All excisions involving bone can best be described by the following designations: enucleation, curettage, marsupialization, recontouring, resection without continuity defect (Rs$^-$CD), resection with continuity defect (Rc$^-$CD), and disarticulation. All are definable.[23] Some may be used in combination, and three—Rs$^-$CD, Rc$^-$CD, and disarticulation—can be measured radiographically, grossly, and histologically. This terminology is employed in this chapter where germane. Certainly at present, there are no absolute standards of management for many odontogenic tumors. The treatment of several lesions continues to be debatable, and some suggestions for treatment made in this chapter may be in disagreement with the opinions of other writers.

Epithelial Odontogenic Tumors

Adenomatoid Odontogenic Tumor

The *adenomatoid odontogenic tumor* (AOT) has been known by a number of descriptive names since it was first reported[24] and later recognized as a distinct odontogenic lesion unrelated to ameloblastoma (Figure 18-1). Although it was considered to be a variant of ameloblastoma at one time, surgical and treatment outcome experience has borne out the benign, nonaggressive nature of this lesion. Variously known as adenoameloblastoma, ameloblastic adenomatoid tumor, glandular ameloblastoma, and adenomatoid ameloblastoma, as well as by other designations, the lesion has been extensively recorded in the literature.[25-27]

The acceptance of the more apt name adenomatoid odontogenic tumor[26] recognizes the unique and peculiar ductlike or tubelike histologic structures and odontogenic origin but removes the burden of ameloblastic stigmatization. The AOT can be considered a hamartoma with occasional neoplastic behavior.

Clinicopathologic Considerations

The adenomatoid odontogenic tumor is usually clinically evident during the latter part of the second decade; however, reported cases range in age between 4 and 80 years. There is a slight female over male incidence, an almost 2:1 site preference for maxilla over mandible, and a marked predilection for the anterior jaws (more than 85% of lesions appear anterior to the second premolar teeth).

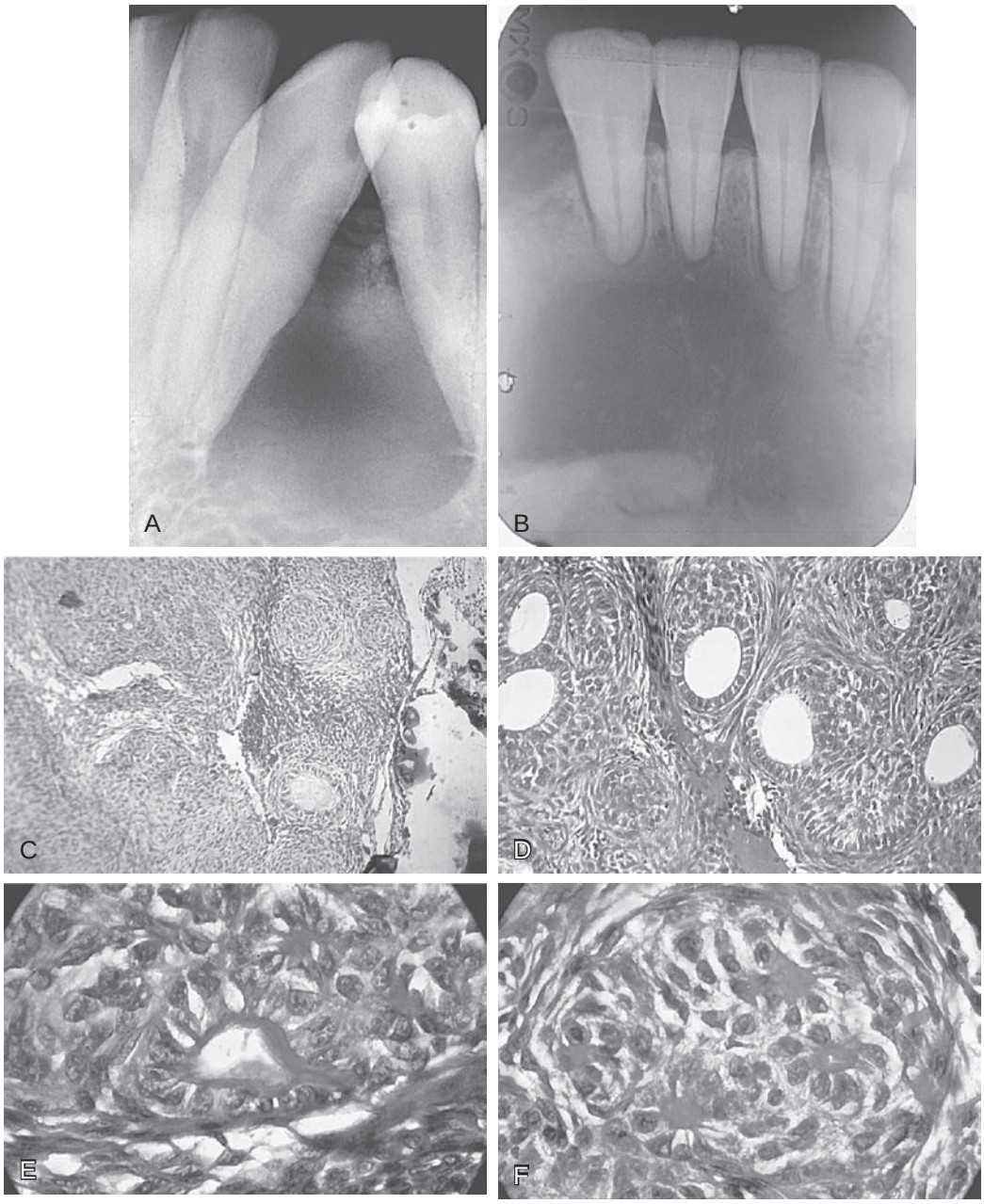
The AOT has several radiographic appearances that may be considered typical but not pathognomonic. The lesion frequently appears as a well-circumscribed, pear-shaped radiolucency (stem portion toward the alveolar surface) lying between divergent roots of the canine and first premolar teeth (or between incisors or premolars); or as a unilocular, radiolucent lesion that is well circumscribed or bounded by a radiopaque margin, lateral to or containing an impacted tooth (similar to a follicular, dentigerous cyst, or occasionally a periodontal cyst) (Figure 18-2, *A-H*). Frequently, small, variously shaped faint or marked radiopaque particles (calcifications) may be distributed throughout the lesional space or are concentrated within a small area of a predominantly radiolucent lesion. Rarely, some lesions appear heavily calcified (see Figure 18-1, *A,B*). Root resorption occasionally occurs but is usually not severe (see Figure 18-1, *B*).

Histologically, the lesion is usually partially cystic and surrounded by a well-developed connective tissue capsule. The luminal surface is lined with a reduced odontogenic epithelium that leads to thickened mural proliferations of the AOT, which project into and partially or almost completely fill a cystic lumen with tumor lobules (see Figure 18-2, *F-H*). The characteristic AOT lesional tissue is composed of a profuse complex of rounded, rosette-like and stream-like aggregates of spindle-shaped odontogenic epithelial cells (see Figure 18-2, *G,H*), similar in size and shape to the stratum intermedium cells of the developing tooth germ (see Figure 18-1, *C*). Within the epithelial masses, some of the rounded and rosette forms appear to become hollow, assume ductlike or tubelike shapes, and are lined with a single layer of cuboidal or columnar epithelium (see Figure 18-1, *D*). Frequently, eosinophilic droplets (likened to enameloid products) are seen within the tubes or lying among the spindled epithelial masses (see Figure 18-1, *E,F*). To a greater or lesser degree, calcifications occur within the lumina of the ducts, scattered among the epithelial masses or in the stroma. These often appear as dystrophic irregular masses or have an annular shape, whereas occasional calcifications have a cementum or dentinlike appearance.

Several cases, personally studied, have demonstrated foci of clear cells within the adenomatoid cellular areas. However, such areas have not influenced treatment. Cases of combined AOT with calcifying epithelial odontogenic tumor (CEOT) have been reported.[28,29]

Management

Because of site, age, and imaging characteristics, lesions such as periodontal cyst, dentigerous cyst, calcifying odontogenic cyst (COC), CEOT, or desmoplastic ameloblastoma can be

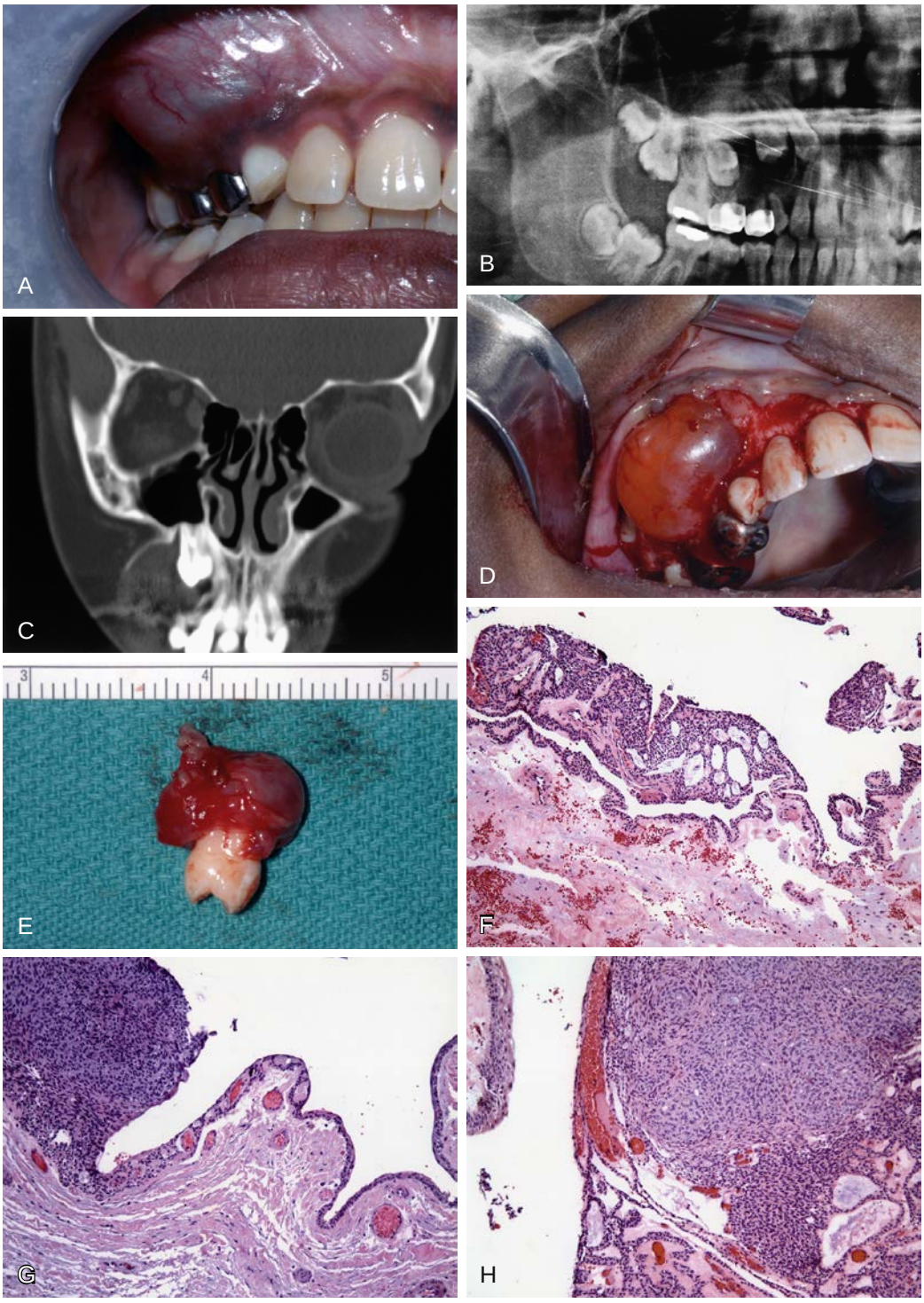


• **Figure 18-1** Adenomatoid odontogenic tumor (AOT). **A**, Radiograph of lesion in canine/premolar region shows wide divergence of tooth roots and pear-shaped radiolucency with intralesional calcifications. **B**, Nonpathognomonic radiograph of anterior mandibular AOT. Note blunting (resorption) of root tips, diffuse radiolucency, and intralesional calcification. **C**-**D**, Low- and medium-power photomicrographs of characteristic histologic morphology: profusely cellular epithelium, rosette-like masses, and ductlike configurations. **E**-**F**, High-power photomicrographs demonstrate ductlike and tubelike structures with an eosinophilic secretory product (possibly enameloid).

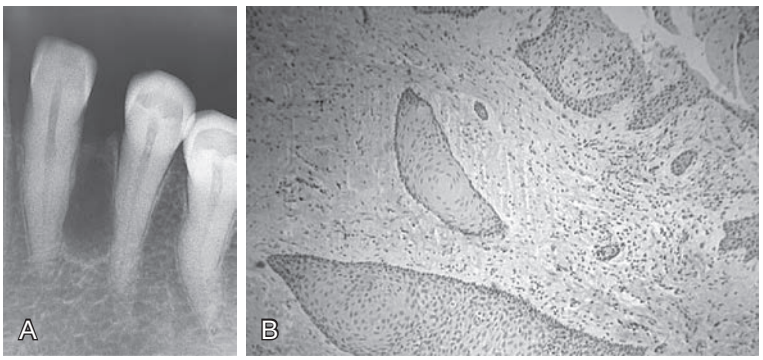
considered in the differential diagnosis. If sufficient suspicion exists that the lesion could be a CEOT or desmoplastic ameloblastoma, one or several biopsies of the lesion should be performed, because treatment varies.

The accumulated world experience with AOT, as reflected in 30 or more years of reports, depicts a lesion in which conservative management produces a uniformly excellent outcome without recurrence, except in one case. Takigami and co-workers[30] reported the case of a 49-year-old woman who had four recurrences of a maxillary AOT, which extended from the maxilla into the maxillary sinus, then extended to the posterior ethmoid and sphenoid sinuses, and finally extended intracranially into the middle fossa with destruction of the sella turcica, dorsum sellae, and anterior clinoid processes. A subtotal resection of the tumor was done.

In almost all instances, the lesion may be removed by surgical enucleation. After reflection of an ample mucosal flap and widened entrance through the usually thinned and expanded cortical bone, the connective tissue capsule of the lesion is encountered. Enucleation is achieved by separation



• **Figure 18-2** Cystic adenomatoid odontogenic tumor (AOT). **A,** An 11-year-old girl and her parents became aware of an enlarging swelling of her right cheek over a 2-month period. **B**-**C,** Panographic and CT radiographs revealed a 2.5 × 2.0 cm. radiolucent lesion in the anterior maxilla, containing severely displaced unerupted permanent teeth. **D,** A presumptive diagnosis of dentigerous cyst and/or AOT was made. At operation, a frozen section biopsy was diagnosed as a cyst with AOT. The lesion was dissected intact from the mucosa, aspirated, and enucleated. **E,** The specimen was thick-walled and contained the permanent first premolar tooth. The canine and second premolar were left in situ for eruption. **F**-**H,** Histologic sections showed characteristic cystic AOT morphology. (Case material courtesy Daniel Taub, DDS, MD, Thomas Jefferson University, Philadelphia.)



• **Figure 18-3** Squamous odontogenic cyst (SOT). **A,** Radiograph of mandibular periodontal cyst with SOT. **B,** Low-power photomicrograph demonstrates several large islands of benign squamous epithelium in the connective tissue wall of the cyst typical of cystic SOT.

of the lesion from bone without perforating the capsule. Portions of the capsule may be thinned or inflamed, permitting fragments of the lesion to escape the connective tissue envelope. Inspection, irrigation, and gentle curettage of the resultant cavity should remove any residual lesion. Primary closure of the wound with a cavity "filler" (e.g., oxidized cellulose, hydroxyapatite, or bone) can be performed. Teeth adjacent to the lesion may have divergently displaced roots (see Figure 18-1, *A*) as well as severely resorbed radicular bone. Such teeth should be removed if endodontic treatment and/or "bone fillers" cannot be provided. Impacted teeth in a follicular, dentigerous or periodontal cystic position can occasionally be salvaged for eruption if the lesion can be completely removed without injury to the teeth (see Figure 18-2, *A-H*).

Squamous Odontogenic Tumor

examples of the lesion (Figure 18-3).[31] SOT is a relatively rare, benign, but locally infiltrative and occasionally aggressive odontogenic epithelial lesion that appears to have hamartomatous and neoplastic characteristics. Since the initial description, a number of papers have amplified details of the clinical presentations and range of biologic activity of SOT.[31-36]

Clinicopathologic Considerations

The SOT is found over a wide age range from the second to the seventh decade, with most cases reported in young adults between 19 and 37 years of age. There does not appear to be a sex or race predilection. The mandible and maxilla are equally affected, and lesions are found singly or multicentrically in all areas of both jaws. The clinical symptoms vary with the circumstances of the individual lesion. Some tumors, within bone only, may be casually discovered by routine radiographs. When lesions occur in dentate areas, alveolar bone resorption around teeth causes mobility and pain. If cortical bone of the mandible or maxilla is penetrated by the lesion, the tumor infiltrates gingiva, occasionally the unattached alveolar mucosa, palatal soft tissue, and rarely the buccal mucosa. Lesions that involve the gingiva as well as alveolar bone, particularly if multicentric in both jaws, give a generalized impression of severe periodontal disease. Overtly aggressive maxillary tumors may infiltrate the maxillary sinus and nasal floor. An interesting study of familial SOTs in three siblings (two male, one female) has been reported.[37]

Radiographically, the SOTs, whether as single or multiple lesions of the mandible and maxilla, usually are seen as irregularly shaped or semicircular radiolucent areas with smooth sclerotic borders involving the superior area of the alveolus or roots of teeth. Some lesions are cystic or are associated with cysts and thus may radiographically appear as dentigerous, periodontal, or periapical in form (see Figure 18-3, *A*).

Histologic characteristics of solid and cystic tumors have been described. The typical solid lesion consists of numerous islands of squamous epithelium dispersed in a connective tissue stroma. The epithelial islands are variable in size, with irregularly shaped trabeculae that sometimes anastomose as well as rounded masses of benign stratified squamous epithelium with prominent intercellular bridges. The epithelial cells are uniform and without pleomorphism or nuclear hyperchromatism. The central areas of islands occasionally show foci of parakeratin or keratin, calcification, or cellular degeneration. Some epithelial nests show a cuboidal epithelial cell layer bordering the mature connective tissue stroma, whereas most rests have a compressed squamous cell layer lying against connective tissue (see Figure 18-3, *B*).

The cystic lesions contain many SOT islands in the connective tissue wall, either completely separated from the odontogenic epithelium lining the lumen or appearing to arise directly from the luminal epithelial lining. Doyle and colleagues[38] (in their study of three cases of SOT) included the first example of a cystic SOT, and Wright[39] (in an excellent study) reported five cystic SOT-like lesions. Hodgkinson and associates,[40] in a report of 79 odontogenic keratocysts, found a cyst that initially had been diagnosed and treated as a well-differentiated squamous cell carcinoma arising in a keratocyst. However, during preparation of their paper, the diagnosis was revised to SOT in the wall

of an odontogenic keratocyst. A case of putative carcinoma developing in a periodontal cyst, reported by Baker and colleagues,[41] appears on close inspection of the photomicrographs to be an example of SOT in a cyst wall. Van der Waal and co-workers[42] reported the case of a SOT-like lesion in bone, the radiograph of which was compatible with that of SOT islands admixed with epithelial islands resembling ameloblastoma. The published photomicrographs demonstrate why the authors were unable to reach a conclusion regarding the identity of the lesion. Similarly, the senior author (L.G.) treated a large posterior maxillary dentigerous cyst (radiographic diagnosis) that histologically revealed an odontogenic keratocystic epithelium lining the lumen, with numerous epithelial islands sharing SOT, ameloblastic, and keratocystic histologic characteristics in the cyst wall, and also emanating directly from the keratinizing epithelial lining of the lumen. A retrospective review of a number of lateral periodontal cysts from a study reported in 1973 revealed one that featured SOT-like islands in the cyst wall[43] (see Figure 18-3).

Management

There are no, or few, readily recognizable clinical or radiographic signs to presage a diagnosis of SOT. A definitive histologic diagnosis is made after biopsy, or histologic study of the excision specimen, if the lesion is removed without benefit of biopsy. The clinician with a strong index of suspicion may include SOT in the differential diagnosis, if lesions are multicentric in the mandible and/or maxilla, if there is gross alveolar bone involvement and bone loss around tooth roots, and if a generalized clinical picture of periodontal disease is present. However, if lesions are in bone and appear to be radiographically periodontal, dentigerous, or periapical cysts, there is no reason to suspect SOT.

Because SOT is benign but infiltrative, complete excision is required but should be tailored to the clinical and radiographic extent of the lesion. Lesions totally within bone can be removed by a combination of enucleation and curettage under frozen section guidance or can be resected without continuity defect if intact noninvolved bone margins can be established. Involved soft tissue overlying lesions that penetrate cortical bone should be included in the excision specimen, as should teeth within the lesional area.

SOTs in the form of cystic lesions (periodontal, dentigerous, or periapical) can be conservatively but completely excised by enucleation and/or curettage and require no further treatment unless histologic study reveals epithelial islands at the border or penetrating the connective tissue cyst wall at the bone interface. Prudence then dictates further excision to a histologically proven safe margin. According to Wright's report[39] of cystic SOTs, none has recurred, but there are no details offered of cyst wall–bone interface studies of the presence or absence of lesional tissue at the bone interface.

SOT exhibits a biologic behavioral pattern of aggression that appears unaccountable in strictly histologic terms; recurrences of incompletely excised lesions have been reported. Further, since SOT is rare, care must be exercised that the unexpected appearance of multiple islands of epithelium infiltrating the investing connective tissue of the lesion, and with occasional variable histologic characteristics, does not result in a mistaken diagnosis of ameloblastoma or squamous cell carcinoma, as has occurred; or conversely, an erroneous diagnosis of SOT instead of squamous cell carcinoma[44] (see Figure 18-22). A squamous cell carcinoma in a bone lesion has been reported in a patient who had multiple SOTs[45]; however, one could speculate whether the lesion was related to the SOT or was coincidental.

Calcifying Epithelial Odontogenic Tumor

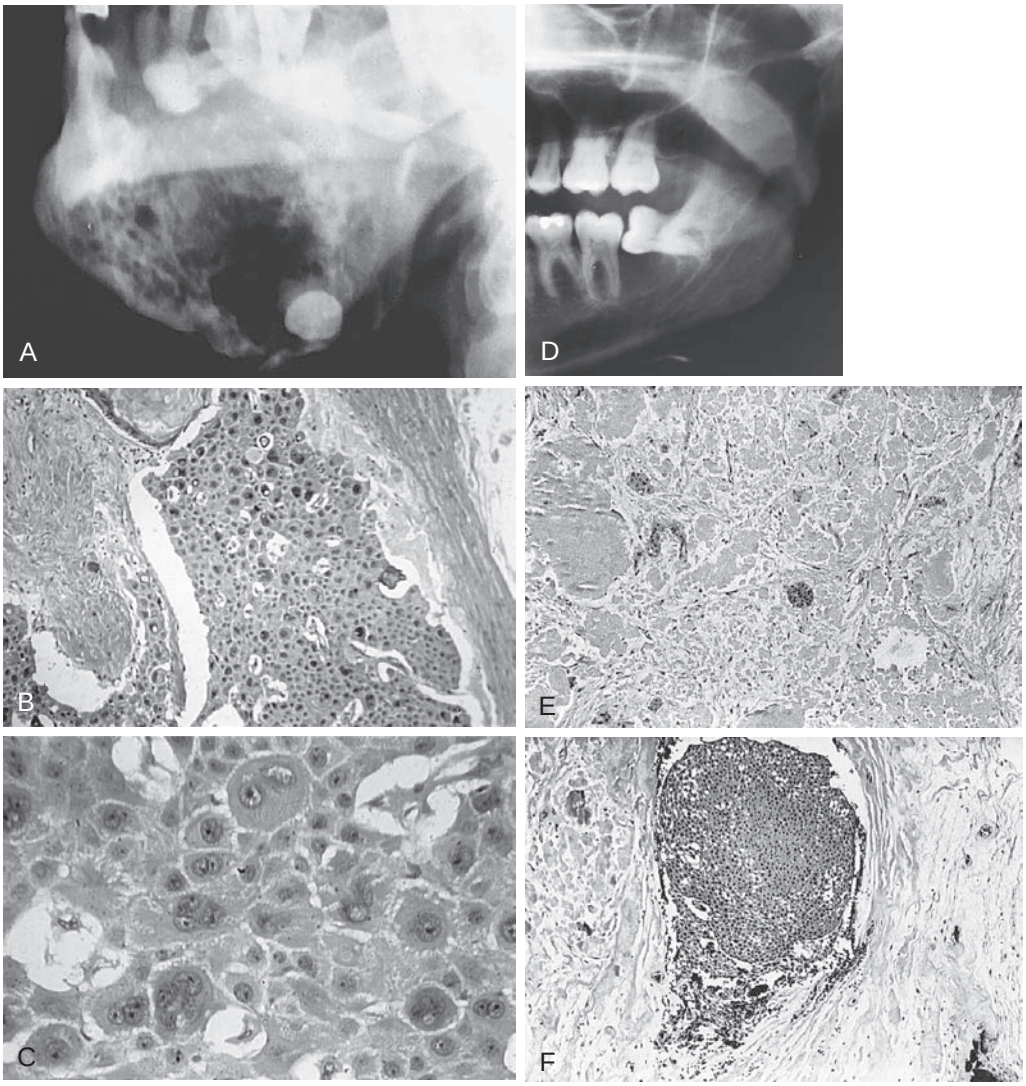
Described in 1955 by Pindborg,[46] the *calcifying epithelial odontogenic tumor* (CEOT) also is known by the eponym *Pindborg tumor* (Figures 18-4 and 18-5). This seldom-occurring neoplasm[47] has distinctive histomorphologic features completely unlike those of ameloblastoma, to which it has been compared clinically. It is interesting that the 1946 Thoma and Goldman[8] report on the classification of odontogenic tumor shows photomicrographs of one of their cases (case 25) labeled adamantoblastoma, adenoid type (now called ameloblastoma) that is clearly recognizable as a calcifying epithelial odontogenic tumor, as is a 1948 case that Ivy[48] erroneously reported as ameloblastoma.

The number of published cases is not large, and the literature expresses conflicting opinions concerning the biologic behavior of CEOT. The lesion appears to occupy a position between hamartoma and aggressive neoplasm; however, there is no question that complete excision of the calcifying epithelial odontogenic tumor is required.

Clinicopathologic Considerations

The calcifying epithelial odontogenic tumor is clinically evident around the age of 40; however, reported cases show an age range between 13 and 80. There is no sex predilection. The mandible is the preferred site over the maxilla in an almost 3:1 ratio. The CEOT may occur in any area of the jaw, but the premolar/molar area appears to be favored. The CEOT is slow growing, locally aggressive, and without clinical signs until a clinically large mass is reached or incidental radiographs reveal the lesion.[46,47,49,50] Several extraosseous CEOTs in the anterior gingiva have been described.[51-54] In addition, CEOT in combination with AOT has been reported.[28,29]

A number of variable radiographic patterns are seen in CEOTs. The lesion may or may not be well circumscribed, mixed radiolucent-radiopaque, unilocular, or associated with an embedded or impacted tooth (see Figures 18-4 and 18-5). Infrequently, the lesion is multilocular with bony septae producing a "honeycomb" effect lacking well-defined margins (see Figure 18-4, *A*). Calcifications in the lesion appear as scattered, irregular radiopaque small or large particles. If the lesion is heavily calcified, a more dense radiopaque aggregation is produced. Thus, there is no radiographic pathognomonic appearance of the CEOT. Other lesions, such as myxoma, hemangioma, or ameloblastoma, may be suspected if the lesion is radiolucent; calcifying

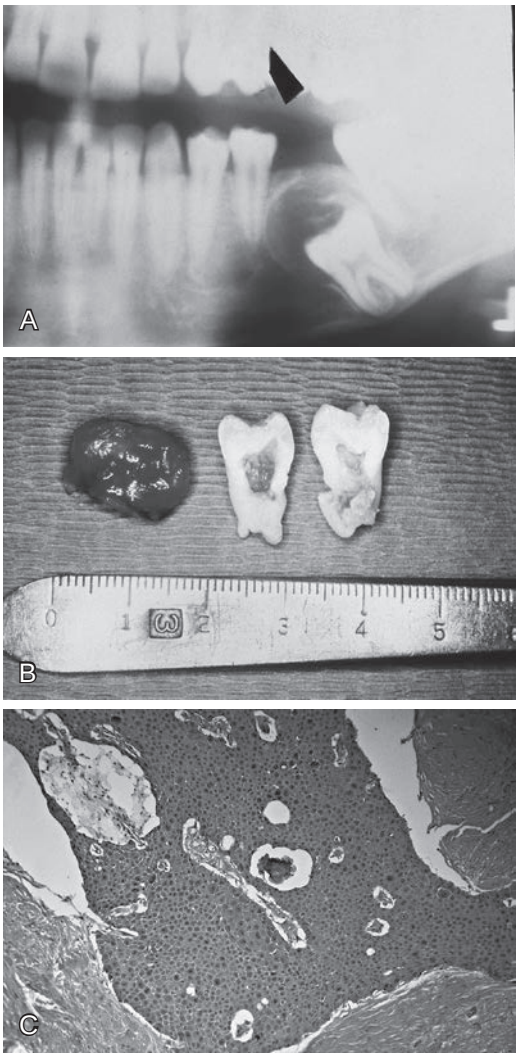


• **Figure 18-4** Calcifying epithelial odontogenic tumor (CEOT). **A,** Radiograph of extensive mandibular poorly circumscribed CEOT with multiple cribriform radiolucent areas and an impacted tooth. **B-C,** Low- and high-power photomicrographs illustrate "classic" CEOT histomorphology: large islands of squamous epithelium with prominent intercellular bridges and variously sized and shaped bizarre cells containing two and three nuclei. **D,** Radiograph of an impacted mandibular third molar in relation to an ill-defined soft tissue mass. The tooth was removed, and the lesion was excised by enucleation and curettage. **E-F,** Low- and medium-power photomicrographs of the soft tissue mass composed of extensive amorphous deposits of amyloid in a connective tissue stroma with scattered islands of odontogenic epithelium recognized as variant CEOT. (Case material **D-F** courtesy Dr. Mansoor Madani, Bala Cynwyd, PA.)

odontogenic cyst and AOT may be suspected if the lesion has radiopacities.

Histologically, the CEOT is characterized by a distinctive picture of trabeculae and/or sheets of large, eosinophilic-staining, squamoid-shaped epithelial cells, frequently with prominent intercellular bridges. The epithelial cells and their nuclei may vary greatly in shape and size. Some nuclei exhibit huge size and odd configurations with large, prominent nucleoli; binuclear and even trinuclear cells may be present. Although bizarre-looking cells are seen, the overall impression is not one of malignancy (see Figures 18-4, *B,C* and 18-5, *C*). The connective tissue stroma is usually inconspicuous between islands and sheets of epithelium. However, occupying the stroma in small areas of some lesions, or seeming to replace the stroma in large areas of other lesions, is a hyaline-like, homogeneous material identified as amyloid (see Figure 18-4, *E,F*).[55-57] Prominent or scattered calcifications, in concentric crenate-like shapes (Liesegang rings), may occur in the amyloid areas and, when present, account for the radiopacities seen in radiographs.

Several distinct histologic pattern variants have also been described, the most important of which include *clear cell* components. Prominent clear cell features in a CEOT appear to be associated with increased aggressiveness of the lesion according to several authors[58-60] (see later discussions of ameloblastoma with clear cells and clear cell odontogenic carcinoma). An excellent paper by Cheng and co-workers[61] discusses a case of CEOT with a conspicuous clear cell



• **Figure 18-5** Calcifying epithelial odontogenic tumor (CEOT). **A,** A 16-year-old boy was referred for evaluation and treatment of an impacted mandibular first molar tooth in an apparent dentigerous cyst. The radiolucent lesion exhibited intralesional calcifications. **B,** The well-circumscribed lesion and tooth were surgically removed. **C,** A medium-power photomicrograph demonstrates classic histomorphology of CEOT. The patient has been followed for 13 years without recurrence.

component that also demonstrated marked cytologic atypia of the epithelial islands. Their case had intralesional vascular invasion, numerous mitotic figures, and an increased proliferating index marker (Ki-67) compared to a conventional CEOT. Despite such evidence, the authors did not regard the lesion to be malignant because demonstrable metastases were absent. They further cautioned that there were still insufficient case studies to confirm a generally aggressive behavior in all CEOTs containing clear cells. Yet, Hicks and co-workers[59], in their 1994 report, record an approximate 14% recurrence rate for conventional CEOT and a 22% recurrence rate for CEOT with clear cell component. The restriction placed by Cheng and colleagues[61] on their case is not justified. Their lesion is malignant with or without demonstrated metastasis.

Two more cases of malignant CEOT have been reported. In 1994, Basu and associates[62] detailed a case with marked nuclear and cellular atypia, perineural invasion around the inferior alveolar nerve, tumor cell invasion of vascular spaces, and metastasis to a submandibular lymph node. Veness and colleagues,[63] in 2001, presented a case of CEOT that recurred twice with increasing cellular atypia, cellular hyperplasia, and vascular invasion with metastasis to a cervical lymph node.

Management

The 1992 and 2005 World Health Organization (WHO) classification[12,13] of odontogenic tumors categorizes the CEOT as a benign, locally invasive neoplasm, but does not describe a recurrence rate (i.e. regrowth of residual lesion). Although Hicks and colleagues[59] describe recurrence percentages in their study (see above), a large body of management data has not been compiled, as it has for ameloblastoma, because of the relative scarcity of reported cases and lack of accurate long-term clinical follow-up evaluations.

Perhaps again, as with ameloblastoma, semantics may play a role in the WHO designation of CEOT as benign and locally aggressive. Locally aggressive CEOT does not appear sufficient to describe the aggressive ability of the maxillary lesion described by Bouchaert and co-workers[64] that involved the maxillary sinus, invaded the orbit and ethmoid sinus, and extended to the cranium with subsequent brain compression. Radiographically, lesions may appear well circumscribed or not well circumscribed, but clinically the tumor is infiltrative and not encapsulated.[65]

The surgical treatment of CEOT should be case specific and based on anatomic location and involvement (e.g., maxilla, mandible, pterygoid areas, nasoethmoidal-sinus region), lesion size (volume of jaw involved), clinical activity (penetration of cortical bone, periosteum, muscle, neural involvement), and histocytologic characteristics (neural or vascular infiltration, cellular atypia, marked clear cell presence, and mitotic index). As with any pathologic entity, an ogy of CEOT not infrequently presents a relatively bizarre microscopic appearance (especially to pathologists unfamiliar with this entity).

Enucleation with curettage is seldom a treatment option, except for very small lesions (i.e., 1.0 to 1.5 cm). Rs$^-$CD or Rc$^-$CD is more likely to result in cure. Obviously, if the lesion is suitable for resection without continuity defect, and an adequate margin of normal bone can be attained, Rs$^-$CD is the procedure of choice. Caution should be exercised with lesions containing aggregates of clear cells, since clear cell follicles and nests tend to be very infiltrative and may extend further into the marrow spaces in a "skip" manner (i.e., cell nests not anatomically contiguous) and are radiographically not well circumscribed (see Figure 18-21, *I,K*).

There are no studies yet that specifically address the issue of "safe" bone margins. Thus a margin of 1.5 to 2.0 cm

may be considered an adequate margin of normal bone, unless frozen sections indicate otherwise. Immediate or delayed reconstruction can be performed as described for ameloblastoma.

Ameloblastoma

The *ameloblastoma* has more than a 100-year history of recognition, reportage, and controversy. Although the most recorded lesion of the odontogenic series, it continues to evoke wide differences of opinion among pathologists and surgeons regarding its position in the neoplastic spectrum, biologic behavior, and management. Ameloblastoma has been described as "benign but locally invasive," "benign and locally invasive with a strong tendency to recur," and "locally malignant." Most opening statements of contemporary reports still quote older papers that depict ameloblastoma as a benign and rare or uncommon tumor. However, ameloblastoma is not rare or uncommon, as measured by present institutional statistics,[66] and its benignity is here denied.

The 1971 and 1992 WHO classifications[11,12] of odontogenic legions categorized conventional ameloblastoma (aka classic ameloblastoma) as a benign but locally invasive epithelial odontogenic neoplasm and also included a category of malignant epithelial odontogenic carcinomas in which *malignant ameloblastoma* and *ameloblastic carcinoma* are separately listed and defined. The WHO described *malignant ameloblastoma* as a neoplasm in which the metastatic lesion(s) continues to resemble conventional ameloblastoma (i.e., there are no microscopic differences between the metastatic lesion and the conventional ameloblastoma from which it emanates), whereas *ameloblastic carcinoma* is described as a malignant tumor in which the lesion demonstrates a spectrum of morphologic/cytologic/histologic characteristics of malignancy, and does or does not necessarily metastasize (see later section on Cytologic Malignant Ameloblastoma).

The WHO 1971 monograph[11] further proscribed that the designation malignant ameloblastoma should not be applied to ameloblastoma that endangers life by direct extension of the growth into vital structures. It appears that it is permissible to recognize a conventional ameloblastoma as malignant if it does metastasize, and to regard the same ameloblastoma as benign if it does not metastasize!

The senior author (L.G.)[17a] was not alone in objecting to this perplexing reasoning. Several writers[14-16] had previously faulted the narrow WHO definition of what constituted malignant ameloblastoma or ameloblastic carcinoma on several counts: (1) that a malignant lesion must produce metastases, (2) that the metastases must be histologically identical to the primary tumor, and (3) that the WHO definition is not consistent with malignancy as applied to other neoplasms. Yet, these authors did not reject the implausible WHO definitions, but accommodated to them with further refinements of the original WHO classification.

It is fitting here to quote several writers directly in order to help place this tumor in proper perspective. Willis[67] (a highly respected British pathologist) believed that clinicians have overemphasized the differentiation between benignancy and malignancy in order to gather prognostic information from pathologists regarding excised tumors. He believes that the question "Is this tumor innocent *or* malignant?" should be replaced by "*How* innocent or malignant is this tumor?" In a specific discussion of ameloblastoma, Willis[67] describes the lesion as "lowly malignant slowly growing" and further writes that "attempts to distinguish between benign and malignant ameloblastoma are futile; they are all malignant in that they are locally invasive and prone to recur." Carr and Halperin[68] in their paper on malignant ameloblastoma stated in their discussion: "Malignant and benign are poor terms when applied generally to this neoplasm, and the use of one instead of the other seems secondary to an understanding of how the tumor may behave and to an approach to treatment based on this understanding."

Consider the following description of the basal cell carcinoma, an acknowledged malignant tumor, offered by Gold[17a]: "slowly growing, infiltrative, capable of great destruction of soft tissue and bone, recurrent when not completely eradicated, capable of invading vital structures (orbit, skull, brain), seldom metastatic but capable of metastasis, presenting a number of histologic patterns, and arising from the epithelial skin surface and skin adnexa. If one substitutes oral epithelium for skin surface and dental lamina/enamel organ for skin adnexa, you are describing the known characteristics of the ameloblastoma." Thus, the ameloblastoma and the basal cell carcinoma share great similarity to each other in their histomorphology, growth, and infiltrative patterns.

If one takes into consideration that within the past 10 years the steadily increasing number of published reports in the world literature, in addition to the numerous previous accounts over many years that also have described "conventional" ameloblastomas that have metastasized, as well as morphologically and cytologically dysplastic ameloblastomas that have metastasized, one is forced to the conclusion that *conventional ameloblastoma is a de novo, low-grade, malignant basaloid tumor with a variable range of histologic patterns, clinical forms, and behavior.*

In 1999, Eversole[18] revised Elzay's[15] modification of the WHO classification of epithelial odontogenic tumors to produce his own version, which he (Eversole) considered more refined, but still not entirely satisfactory. Eversole's thoughtful paper approached but did not reach the essential conclusion that conventional ameloblastoma is a de novo malignancy. Neither did Philipsen and Reichart[19] in their 2002 paper, nor the authors of the 2005 WHO classification,[13] who continue to regard ameloblastoma under benign and malignant categories. None were able to concede the possibility that ameloblastoma is a de novo low-grade malignant lesion.

There are two incontrovertible characteristics that distinguish a malignant lesion: (1) the ability to invade and destroy tissue without regard to anatomic boundaries, and (2) the ability to metastasize. Ameloblastoma, whether in so-called

conventional or in markedly dysplastic form, qualifies by this definition as a malignancy. The recognition of the de novo malignant status of conventional ameloblastoma permits the progressive sequences from low-grade to high-grade cytologic malignancy to be seen as a continuum. It is possible then to eliminate the artificial and confusing terminology—malignant ameloblastoma and ameloblastic carcinoma—from the WHO classification; *ameloblastoma may be described also as a well-differentiated malignancy with or without metastases or poorly differentiated malignancy with or without metastases.*

The long-held traditional belief that ameloblastoma is benign, except in rare instances, will be difficult to reverse. It will require more than a casual alteration in mindset for pathologists and surgeons to accept what they have historically and traditionally regarded as a benign tumor should now be considered a malignancy. However, there are precedents for a change of status among a number of tumors when proof becomes evident, even if, as in the case of ameloblastoma, long delayed (see also morphogenesis of clear cell odontogenic tumor to malignant status in the section on clear cell odontogenic carcinoma). A change in perception is required that ameloblastoma, pari passu, is a de novo malignancy and is not a philosophic or nosologic exercise. It removes this lesion from untenable argumentation regarding its pathologic status. It is important to understand that conventional (classic) ameloblastoma, low-grade malignancy notwithstanding, is a dangerous lesion precisely because of its unpredictable behavior. This realization would have a salutary effect on the study and management of the lesion.

Clinicopathologic Considerations

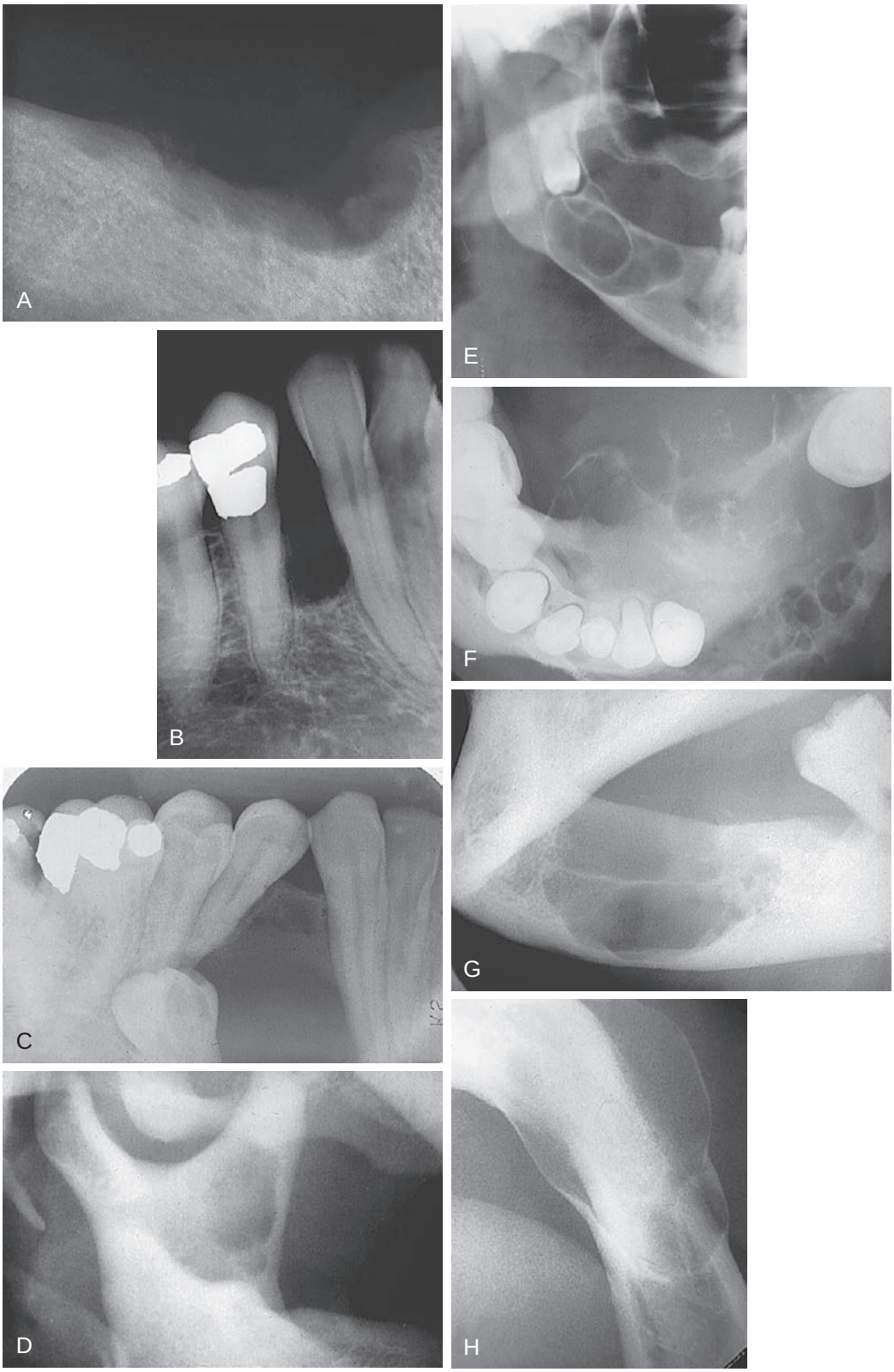
The ameloblastoma is asymptomatic and remains undiscovered until lesional growth produces intraoral and/or external jaw swelling, tooth and dental occlusion disturbances, or incidental radiographic examination reveals a lesion. Paresthesia is an uncommon symptom and pain is rarely a presenting symptom unless the lesion causes root resorption and/or tooth mobility. Depending on the clinical form of the ameloblastoma, the age at which the lesion may become clinically evident is as early as the first decade or as late as the seventh. The lesion may occur in either jaw and in any area, but the sites of predilection are the posterior maxilla and the posterior molar-ramus region of the mandible. The mandible is the favored site over the maxilla by about a 4.5:1 ratio.

Radiographically, the ameloblastoma presents a unilocular or multilocular radiolucent appearance in several different forms and shapes. The apparent lesional edge may be distinct or indistinct. Small or large unilocular or multilocular lesions may contain unerupted deciduous or permanent teeth and give the appearance of a dentigerous cyst. Lesions in dentate areas cause root resorption and tooth displacement. Expansive distortions of normal mandibular or maxillary anatomic features commonly are caused by this lesion. Maxillary lesions often involve the maxillary antrum and change the normal radiolucency of the sinus to a more opacified appearance. One of the ameloblastoma variants—the desmoplastic ameloblastoma, most often found in the anterior maxilla or mandible—projects as a relatively radiopaque lesion because of the dense connective tissue content. The radiographic image of ameloblastoma is at most suggestive and not pathognomonic; other odontogenic and nonodontogenic lesions may simulate it (Figure 18-6, *A-H*).

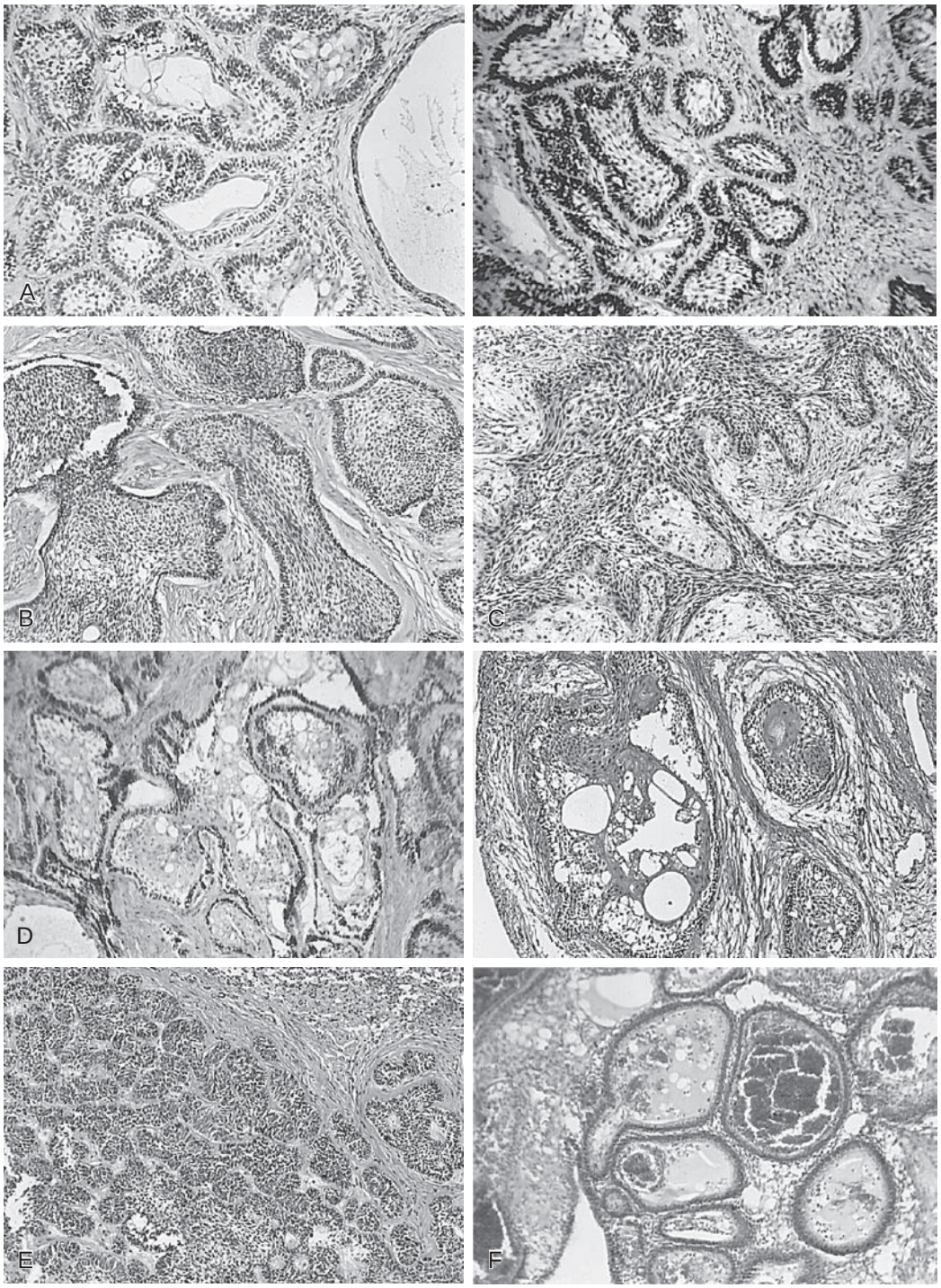
Histologically, most ameloblastomas fall within two major morphologic configurations—the *follicular* and *plexiform* types. Combinations and variations of these two types, as well as other subtypes, are found even within the same lesion. The follicular type consists of small to large odontogenic epithelial nests (the follicles) and variously shaped and sized ameloblastomatous islands. The plexiform type consists of interlacing strands of narrow or wide odontogenic epithelial trabeculae. Both types have a columnar or cuboidal outer epithelial cell layer bordering the connective tissue stroma and enclosing the inner epithelial cells. The characteristic histologic signatures of the ameloblastoma are the orientation of the outer epithelial cell nuclei, which are positioned (polarized) away from the basement membrane (reverse polarity), and the frequent vesicular appearance of the outer cell cytoplasm abutting the basement membrane. In addition, the inner epithelial cells of the follicles are more or less loosely arranged as in a stellate reticulum, imitating the enamel organ architecture. Not infrequently, the strandular narrow configuration of the plexiform lesion has neither the outer epithelial cell nuclear orientation nor the appearance of inner cell stellate reticulum. A variety of subtypes are built around the basic morphologic characteristics. Compression of the stellate reticulum into a squamoid mass with squamous metaplasia and keratinization produces the *acanthomatous type*. The inner follicular and outer follicular cells may assume a basal cell appearance throughout the lesion, causing a striking histologic resemblance to basal-cell carcinoma, in which instance the *basal cell type* is noted. Other ameloblastoma variants also are well recognized such as *granular cell, desmoplastic, vascular,* and *spindle cell (sarcomatoid) types* (Figure 18-7).

Several rare subtypes have been reported, such as ameloblastoma with "ghost-cell" and keratinization as seen in the calcifying odontogenic cyst. More importantly, however, Waldron et al[16] have reported two cases containing clear cell strands and nests biphasically intermixed with follicular ameloblastoma as *clear cell ameloblastoma*. Both cases demonstrated marked cytologic atypia, and one was known to cause the patient's death by uncontrolled growth and metastasis (see later discussion of clear cell odontogenic carcinoma).[17a]

The supporting connective tissue stroma of multicystic and solid ameloblastoma, regardless of histologic subtype, varies from loose to dense, and from scant to plentiful. However, the solid and multicystic forms of the tumor do not produce an effective connective tissue capsule or evoke an encapsulating mechanism by surrounding bone or soft tissue (see Figure 18-7, *A-L*). The unicystic ameloblastoma, however, does have a peripheral connective tissue wall, which may be loose or dense and relatively thin or thick.[17a]



• **Figure 18-6** Ameloblastoma. Variations in radiographic appearance and location of ameloblastoma: **(A)** superficial alveolar crest, **(B)** periodontal cystlike, **(C)** dentigerous cystlike, **(D)** ramus, **(E-H)** multilocular.

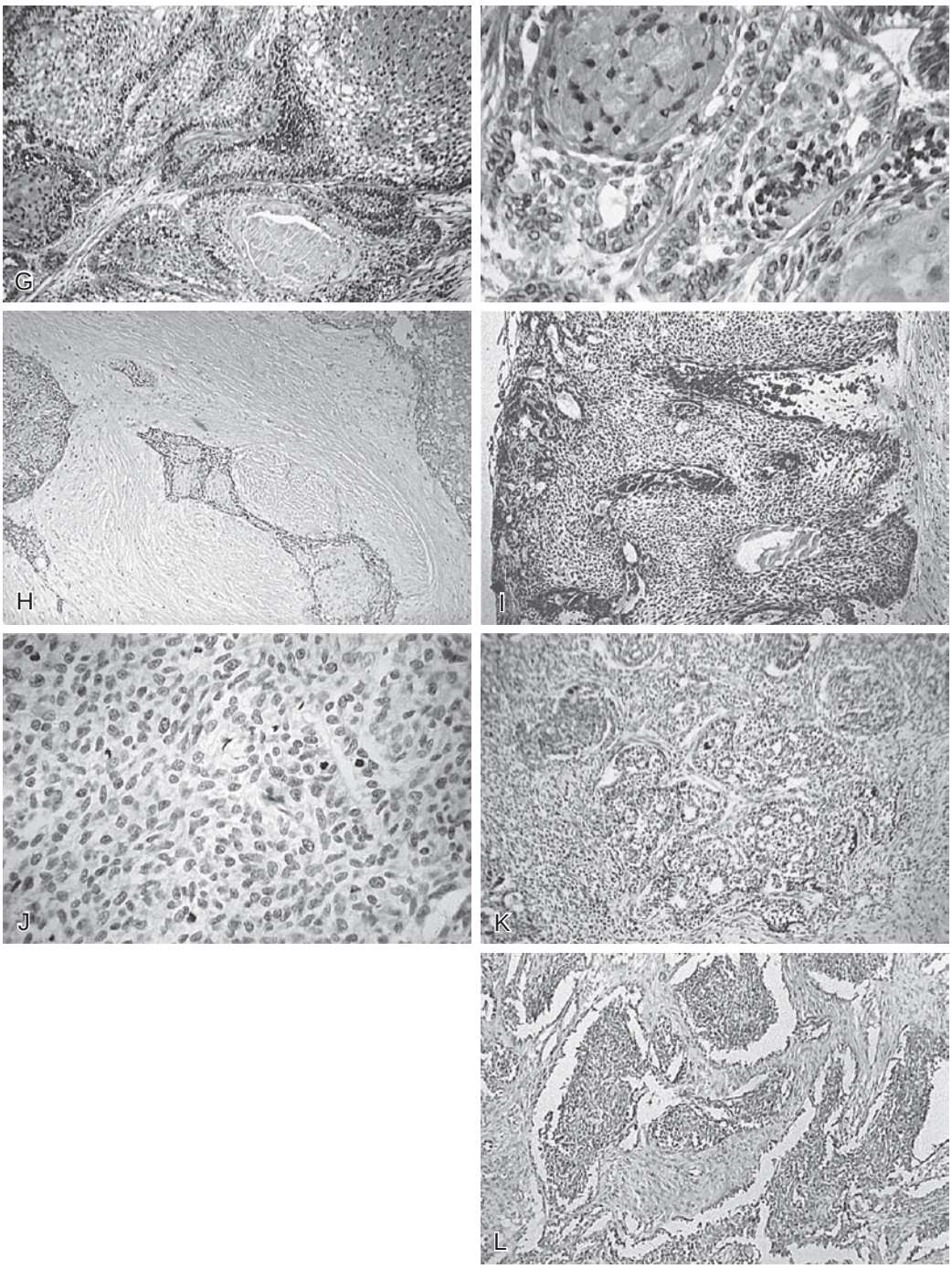


• **Figure 18-7** Ameloblastoma. Common and uncommon histologic patterns of ameloblastoma: **(A)** follicular (two examples are shown), **(B)** trabecular, **(C)** plexiform, **(D)** acanthomatous (two examples are shown), **(E)** basal cell, **(F)** vascular,

Clinical Forms and Mechanisms of Growth

Conventional ameloblastoma presents several clinical (physical) forms as well as histologic types; however, neither physical form nor histologic type is immutable, and combinations of form and type occur. The major intrabony (central) clinical forms are *unicystic* (unilocular) (Figures 18-8 to 18-11), *multicystic* (multilocular), and *solid* (Figures 18-12 to 18-14). The *peripheral* ameloblastoma is the visibly extraosseous soft tissue form of the lesion found in the gingiva and mucosa of the alveolar process (Figures 18-15 to 18-17).

Mixtures of histologic types of ameloblastoma in the original or in a recurrent lesion are not unusual; for example, a unicystic granular cell ameloblastoma, when recurrent years later, showed a multicystic follicular lesion,[69] and a large unicystic lesion simultaneously displayed elements of plexiform, granular cell, follicular, and acanthomatous types.[17a]

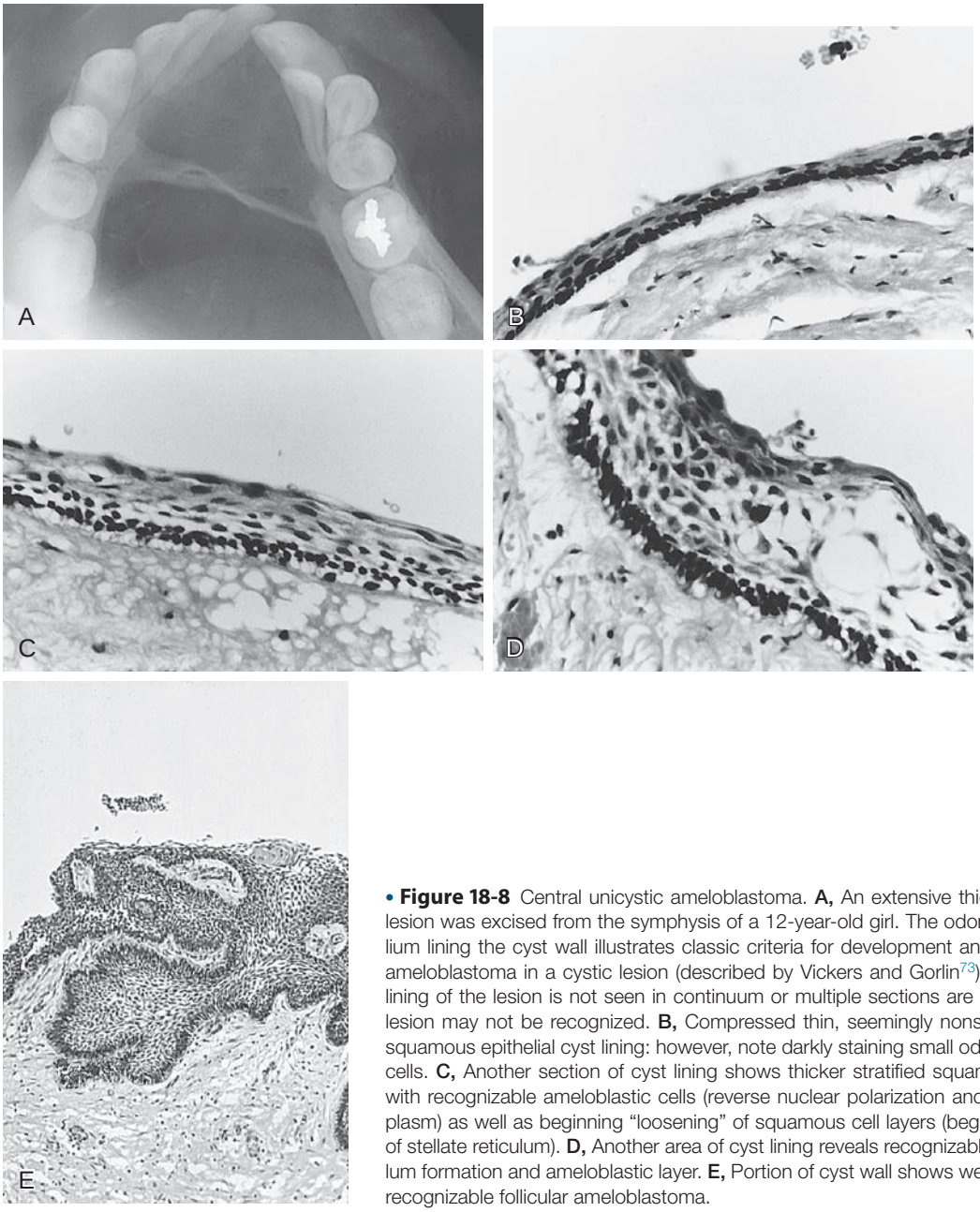


• **Figure 18-7, cont'd** **(G)** granular cell (low and high power are shown), **(H)** desmoplastic, **(I)** spindle cell (hyperplastic stellate reticulum), **(J)** hyperplastic stellate reticulum with mitoses, **(K)** undifferentiated, **(L)** anaplastic.

Unicystic Ameloblastoma

A *unicystic ameloblastoma* may form de novo or develop secondarily in an odontogenic keratocyst or dentigerous cyst.[70,71] The lesion may remain small, become large, or even develop into a multicystic form (see Figures 18-9, 18-11, and 18-13). Occasionally small satellite cysts, separated from the main cystic lesion, may be undetected clinically or radiographically.[72] Small or large unicystic lesions that contain unerupted (impacted) teeth, or those without unerupted teeth, are usually identified radiographically as a dentigerous cyst or odontogenic keratocyst. However, an often-overlooked radiologic feature of unicystic ameloblastoma involving a dentate area is the partial resorption of tooth roots (permanent or deciduous), a rare occurrence in dentigerous or odontogenic keratocyst.

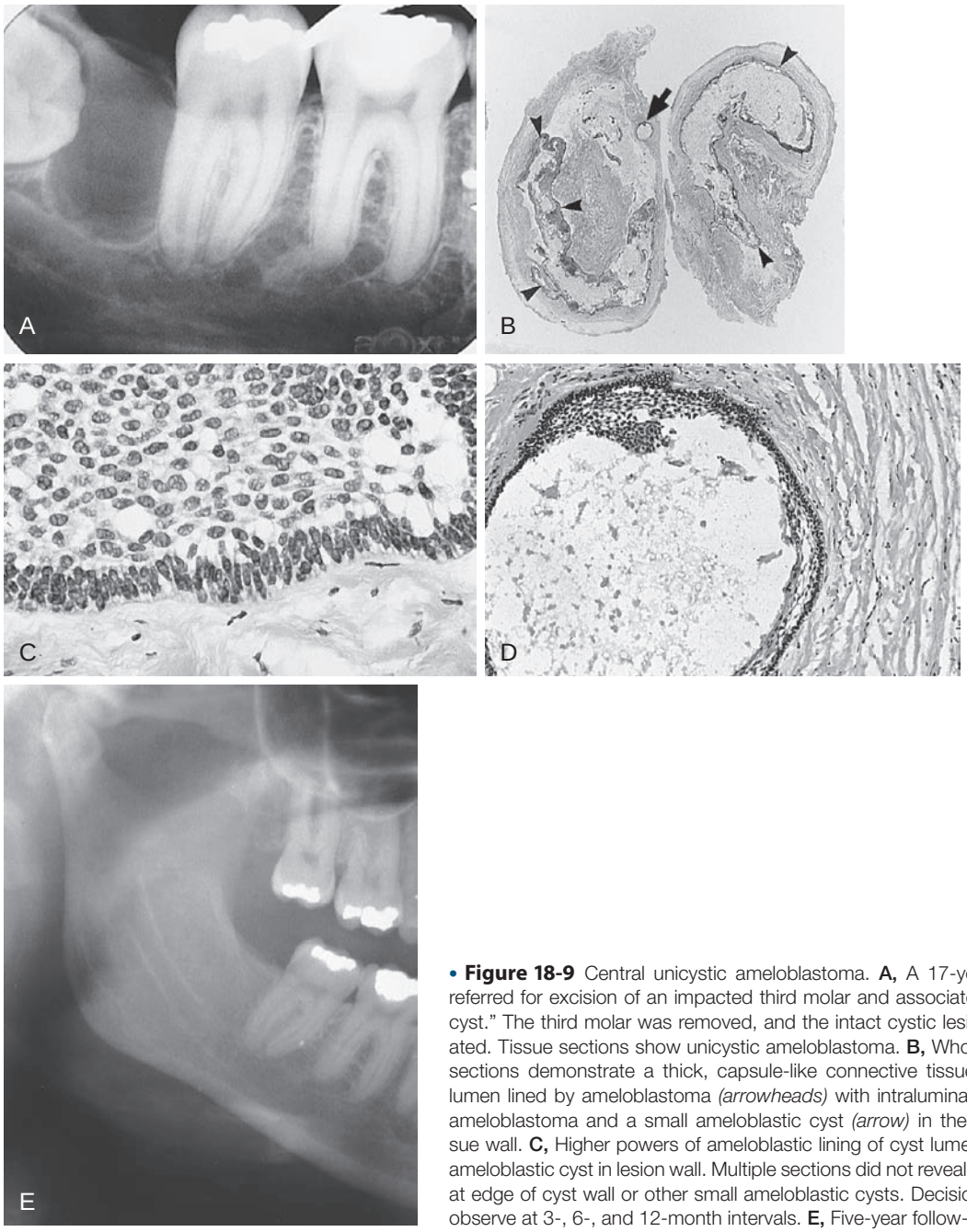
The unicystic ameloblastoma exhibits two other notable clinical differences from the multicystic, solid, and peripheral forms, besides its physical shape. First, the lesion usually occurs in adolescents, teenagers, and young adults; and second, the lesion exhibits the previously described



• **Figure 18-8** Central unicystic ameloblastoma. **A,** An extensive thick-walled cystic lesion was excised from the symphysis of a 12-year-old girl. The odontogenic epithelium lining the cyst wall illustrates classic criteria for development and recognition of ameloblastoma in a cystic lesion (described by Vickers and Gorlin[73]). If the epithelial lining of the lesion is not seen in continuum or multiple sections are not studied, the lesion may not be recognized. **B,** Compressed thin, seemingly nonspecific stratified squamous epithelial cyst lining: however, note darkly staining small odontogenic basal cells. **C,** Another section of cyst lining shows thicker stratified squamous epithelium with recognizable ameloblastic cells (reverse nuclear polarization and vesicular cytoplasm) as well as beginning "loosening" of squamous cell layers (beginning formation of stellate reticulum). **D,** Another area of cyst lining reveals recognizable stellate reticulum formation and ameloblastic layer. **E,** Portion of cyst wall shows well-formed, easily recognizable follicular ameloblastoma.

peripheral-encompassing connective tissue wall of varying thickness.

A diagnosis of unicystic ameloblastoma is influenced by several clinical and microscopic decisions: (a) The surgeon may elect to excise a cystic lesion, especially if not extensive, without a preceding biopsy. Thus, a microscopic diagnosis of unicystic ameloblastoma will be unexpected and will occasion further surgery or none, depending on a proper study of the excision specimen (see laboratory discussion [point d] later). (b) The surgeon changes may not extend along the entire cyst lining. (c) A correct microscopic diagnosis will not be made if the hospital pathologist fails to recognize the sometimes subtle early or evolving ameloblastic changes described by Vickers and Gorlin[73] (see Figure 18-8) or misinterprets a plexiform ameloblastic lining as hyperplastic nonspecific epithelium (see Figure 18-10). (d) Gross sectioning of the unicystic specimen in the laboratory must be done in proper plane orientation so that histologic sections will reveal the ameloblastic proliferation in relation to the cyst lumen, lumen lining, and cyst wall. Recognition of the proliferative pattern of the unicystic ameloblastoma has clinical importance. Growth within the cyst cavity

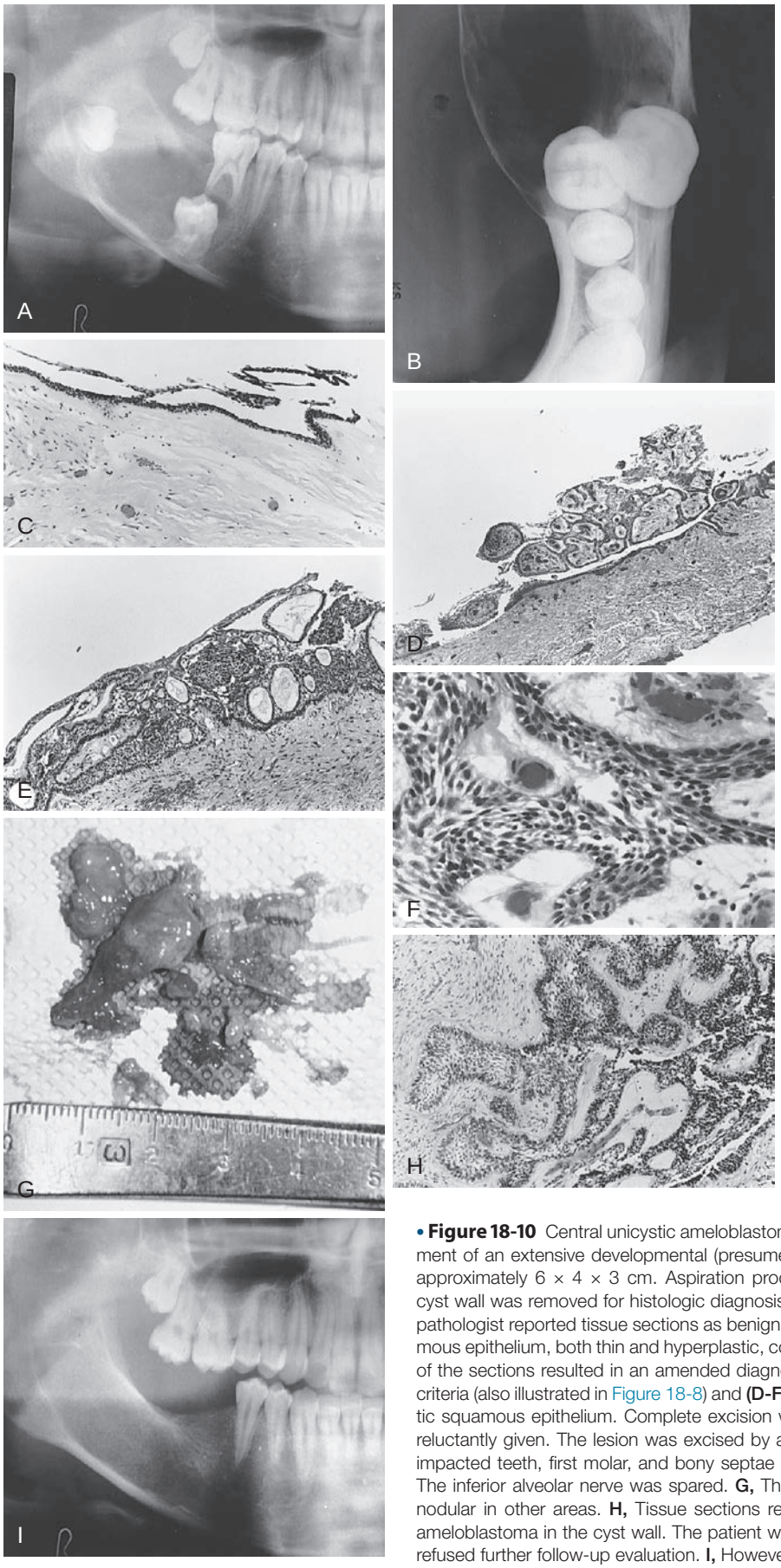


• **Figure 18-9** Central unicystic ameloblastoma. **A,** A 17-year-old girl was referred for excision of an impacted third molar and associated "dentigerous cyst." The third molar was removed, and the intact cystic lesion was enucleated. Tissue sections show unicystic ameloblastoma. **B,** Whole mount tissue sections demonstrate a thick, capsule-like connective tissue wall and cyst lumen lined by ameloblastoma *(arrowheads)* with intraluminal proliferation of ameloblastoma and a small ameloblastic cyst *(arrow)* in the connective tissue wall. **C,** Higher powers of ameloblastic lining of cyst lumen and **(D)** small ameloblastic cyst in lesion wall. Multiple sections did not reveal ameloblastoma at edge of cyst wall or other small ameloblastic cysts. Decision was made to observe at 3-, 6-, and 12-month intervals. **E,** Five-year follow-up panograph.

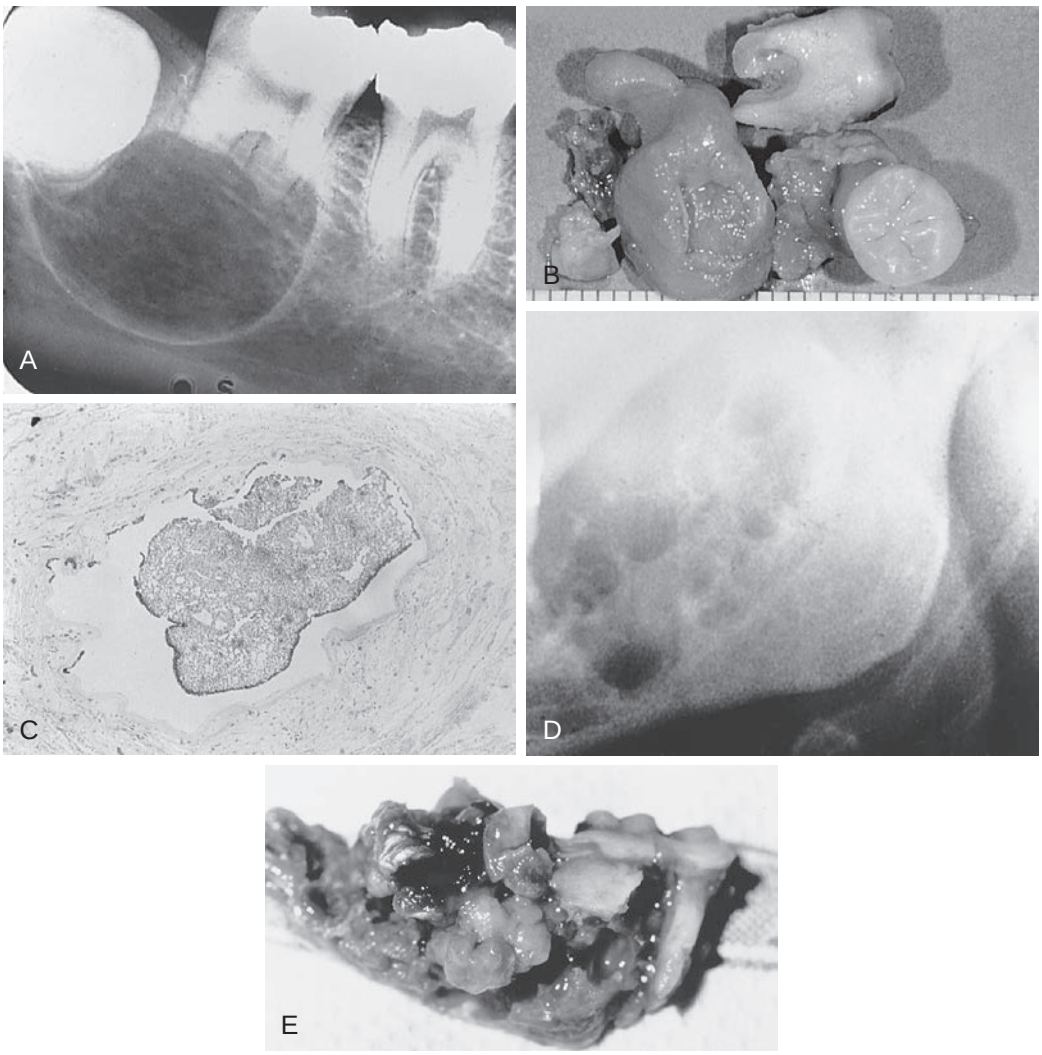
(intraluminal), growth along the cavity surface *(luminal),* or proliferation into the connective tissue of the cyst wall *(mural)*[74a] greatly affects treatment (see discussion under Management).

Solid and Multicystic Ameloblastomas

Solid and *multicystic ameloblastomas* may have similar origin in a field of neoplastic change (see Figures 18-12 and 18-13). Small foci of ameloblastoma spread out in a three-dimensional manner; the foci become masses and retain a solid form (see Figure 18-14) or make microcystic and/or macrocystic spaces lined by ameloblastic epithelium. Intraosseous ameloblastoma grows slowly but inexorably, by invasion of medullary spaces and resorption of cancellous and cortical (compact) bone. Ameloblastic epithelium or lesional connective tissue (stroma) is seen to directly abut resorbing trabecular bone, which still contains endosteal osteocytes and osteoblasts lining the side opposite to the resorbing trabecular surface. There rarely appears to be compensatory bone formation as a reaction to the presence of the tumor. Osteoclastic cellular activity is very rarely seen microscopically.[17a] The often cited "impenetrable barrier" of the compact (dense) bone of the



• **Figure 18-10** Central unicystic ameloblastoma. **A-B,** A 13-year-old boy was referred for treatment of an extensive developmental (presumed dentigerous) cyst of the mandible, measuring approximately 6 × 4 × 3 cm. Aspiration produced copious thin fluid. A large section of the cyst wall was removed for histologic diagnosis, and the lesion was marsupialized. The hospital pathologist reported tissue sections as benign fibroconnective tissue wall, focally lined by squamous epithelium, both thin and hyperplastic, consistent with dentigerous cyst. My routine review of the sections resulted in an amended diagnosis of unicystic ameloblastoma: **(C)** with classic criteria (also illustrated in Figure 18-8) and **(D-F)** with plexiform type misinterpreted as hyperplastic squamous epithelium. Complete excision was strongly advised, and parental consent was reluctantly given. The lesion was excised by a combination of enucleation and curettage. The impacted teeth, first molar, and bony septae projecting from the cortical walls were removed. The inferior alveolar nerve was spared. **G,** The cyst wall was thin in areas and thickened and nodular in other areas. **H,** Tissue sections revealed a combination of plexiform and follicular ameloblastoma in the cyst wall. The patient was followed periodically for 1 year, after which he refused further follow-up evaluation. **I,** However, the patient was seen 4 years later, because he was applying for health insurance.



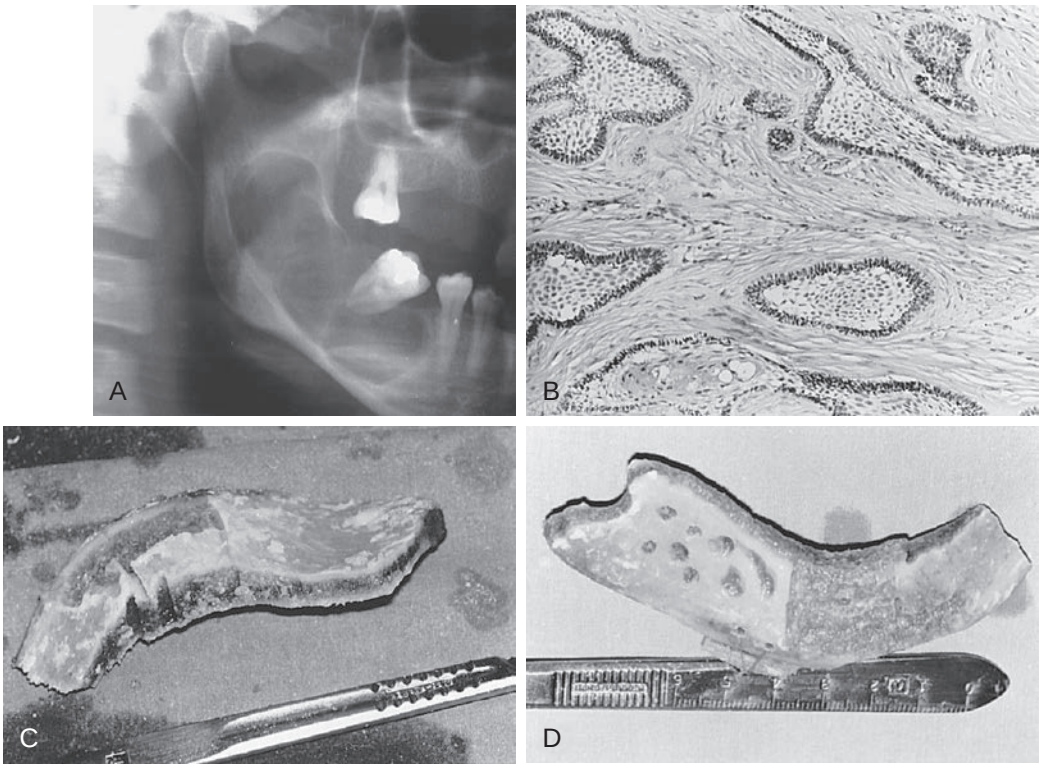
• **Figure 18-11** Recurrent central unicystic ameloblastoma. **A,** A 21-year-old man had excision of an impacted third molar, associated cyst, and second molar with root resorption. **B,** The gross specimen showed a fleshy, thick cystic structure attached to the impacted tooth and follicular sac. **C,** Tissue sections revealed a unicystic ameloblastoma with intraluminal ameloblastic proliferation and no apparent tumor in the cyst wall. **D,** Extensive recurrence 8 years later was treated by continuity resection and bone graft reconstruction. **E,** Gross specimen bisected to show recurrent ameloblastoma.

mandibular inferior border is mythical. The inferior border is resorbed by the tumor, sooner or later, dependent on the growth vectors of the lesion.[17a]

The pathophysiologic mechanism of the resorptive process is not yet completely known; however, contributing factors have emerged. In 1989, hypercalcemia was reported in two patients with metastasis of ameloblastoma to the lungs, thus suggesting evidence of an osteolytic humoral factor.[74b] A report published in 2004 by Abdelsayed and colleagues[75] found that a parathyroid hormone-related protein (PTHrP) was expressed by all lesions (100%) in a study of 30 unicystic and multicystic ameloblastomas. This local expression of PTHrP by tumor cells may readily provide a humoral cause of bone resorption and aggression by the tumor. Other genetic and molecular studies have contributed and will contribute to further understanding of this tumor.[76,77]

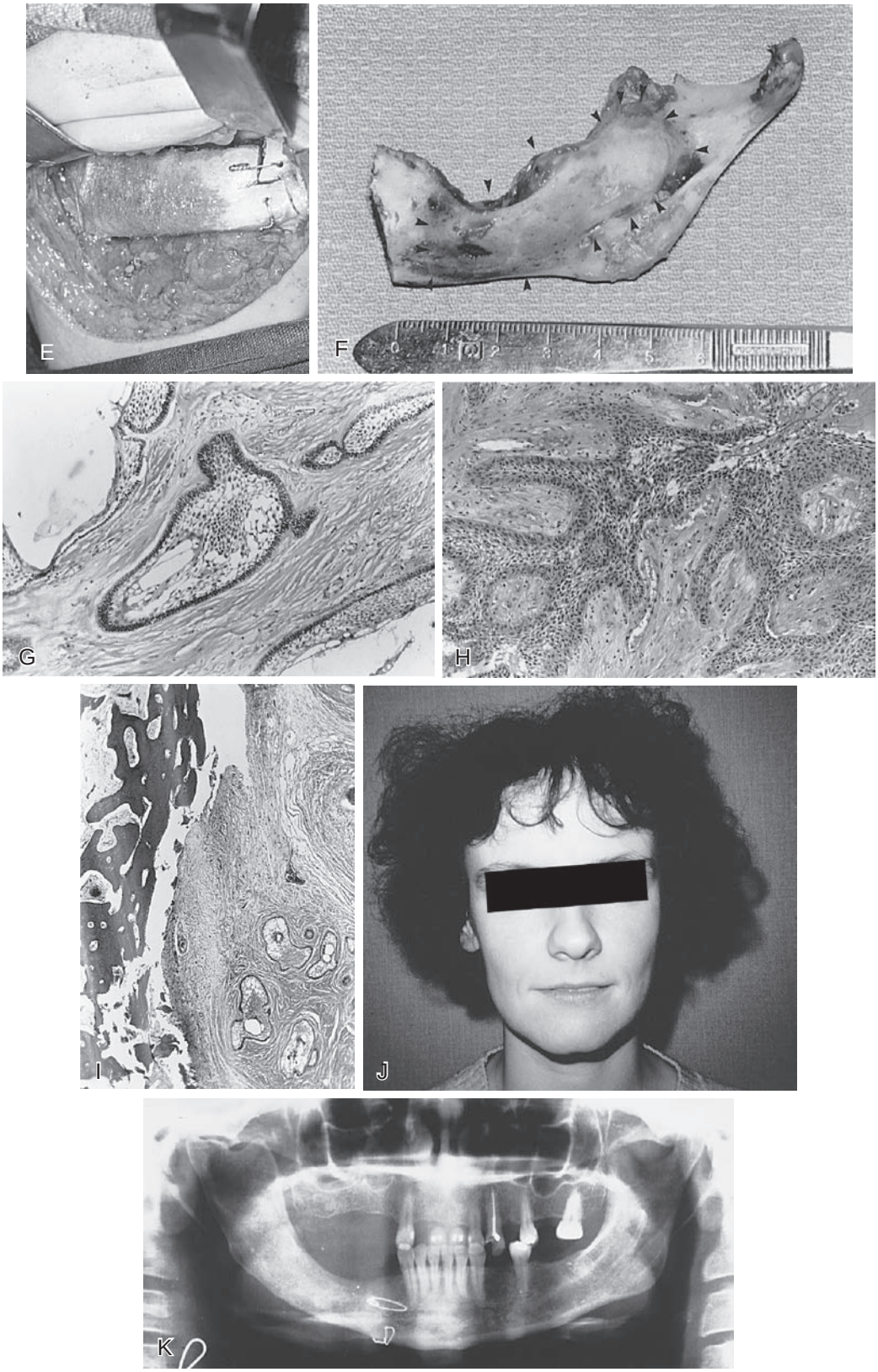
Peripheral Ameloblastoma

The *peripheral ameloblastoma* (by definition) is presumed to originate from residual or displaced odontogenic epithelial tissue in the gingiva or mucosal surface overlying the alveolar process (see Figures 18-15 and 18-16) and is the soft tissue counterpart of the intraosseous ameloblastoma, occurring on the gingival and mucosal covering of the alveolar process of the jaws.[78] The lesion may present a smooth sessile shape if the tumor is contained entirely within connective tissue well below the surface epithelium, and a warty or papillomatous shape if the lesion infiltrates the surface epithelium.[79,80] Like the intrabony ameloblastoma, *the peripheral ameloblastoma is not encapsulated but is strongly circumscribed by stromal connective tissue through which it can infiltrate surrounding mucosa as well as penetrate periosteum and involve bone*. The peripheral tumor has

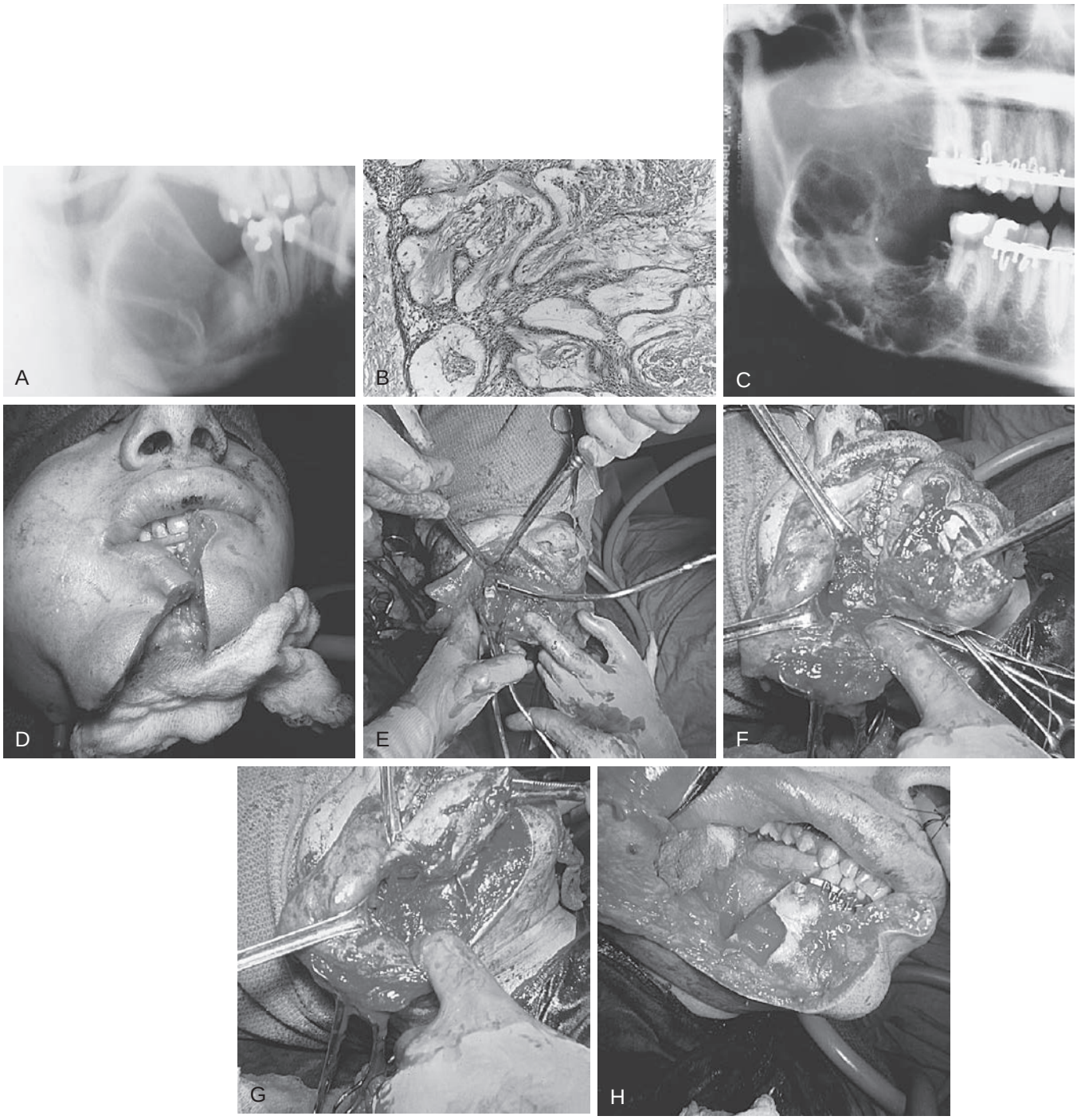


• **Figure 18-12** Central multicystic ameloblastoma of mandible. A 29-year-old woman was referred for diagnosis and treatment of intraoral and extraoral right facial swelling. The patient reported having intraoral drainage the previous day. Examination showed buccal and marked lingual mandibular expansion. The lingual surface was compressible, and the remaining molar tooth was mobile and displaced. **A,** Periapical, occlusal, and panographic films showed an extensive multicystic (multiseptated) radiolucent lesion with molar root resorption, buccal and lingual expansion, and cortical thinning. The molar was removed and biopsy specimens were taken through a crestal incision from the posterior, middle, and anterior cystic and solid lesional areas. **B,** Tissue sections revealed follicular ameloblastoma. Preoperative preparation included extraction of the maxillary right third molar and mandibular right first and second premolars; maxillary impression and model to fabricate a splint with incorporated arch bar; and cephalometric radiograph on which a mock resection of the involved mandible was done, from which to fashion a malleable lead pattern of the resected part to be used as a measurement guide for the bone graft. Two months after the patient was first seen, the operation was performed: (1) application of arch bar to remaining mandibular teeth reinforced with circummandibular wires, and application of maxillary splint to remaining upper teeth, reinforced with circumzygomatic arch wires; (2) intraoral buccal and lingual incisions to circumscribe narrowly and excise the healed previous gingival crestal incision biopsy site; (3) extension of crestal incision to ramus and to canine area for buccal and lingual subperiosteal reflection of mucosa for exposure and exploration to the inferior surface of mandibular body with extension of exploration to ramus coronoid notch area on buccal, release of temporal muscle to condyloid process with resection of process, and medial ramal exposure to lingula for visual inspection of cortical bone integrity; (4) the buccal and medial cortices of the body and ramus were intact, and the incision(s) were closed with running horizontal mattress and vertical interrupted sutures; (5) an extended submandibular extraoral incision was made from an area posterior to the angle to the area below the canine tooth, sharp and blunt dissection exposed the mandible to join the buccal and medial intraoral dissection (with care taken not to lacerate the oral mucosa

from the mandible; (6) the mandible was divided just posterior to the canine tooth to produce a continuity defect, then rotated laterally as blunt and sharp dissection continued superiorly along the ramus to expose the lateral condylar area, and medially to divide the inferior alveolar nerve from the mandibular branch as it entered the mandible at the lingula, with continued lateral rotation of the resected mandible, the lateral pterygoid muscles were exposed and cut at the insertion to the condyle and condylar neck, the lateral aspect of the condylar capsule was dissected and cut, and the resected specimen was disarticulated from the joint space and removed, leaving the temporomandibular joint (TMJ) disc intact and in place; **(C)** (7) a contralateral full-thickness (bicortical) extended anterior iliac crest graft was harvested to take advantage of the iliac curvature using the prepared lead pattern as a size and shape guide; **(D)** the graft was turned end over and reversed to simulate the curvature of the right side of the mandible, and sculpted, with preservation of cortical bone in the ramal and anterior areas for strength and ability to retain fixation wires, and decorticated in areas to permit rapid vascularization; (8) the cut end of the inferior border of the intact mandible and anterior end of the graft were prepared for a butt-and-inset step joint;

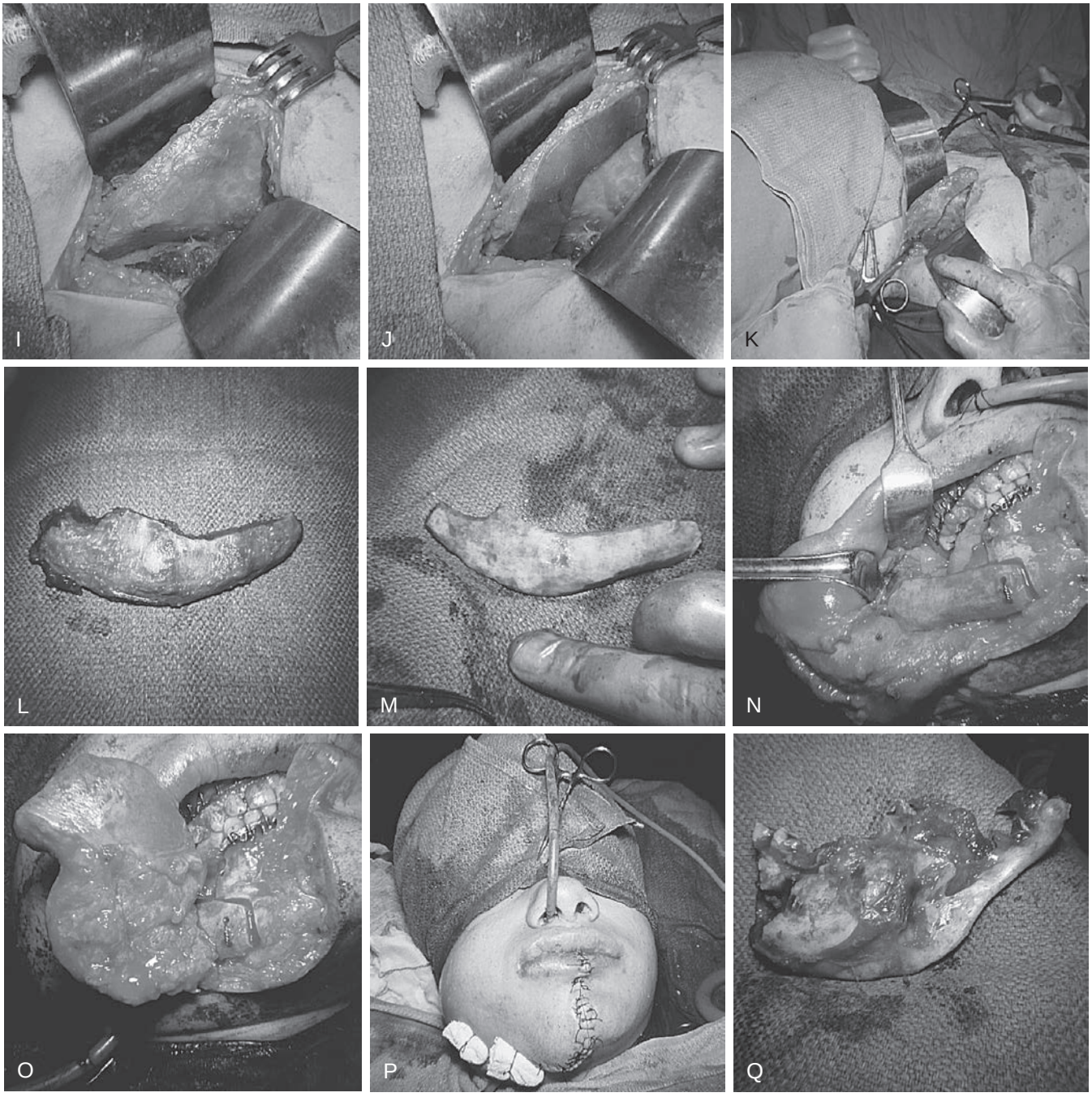


• **Figure 18-12, cont'd** **(E)** (9) intermaxillary fixation was secured, and the graft was inserted into the resection space in contact with the TMJ disc superiorly and fastened to the intact mandible with single horizontal graft angle, and the combined extraoral-intraoral periosteal and superficial tissues were firmly sutured in layers around the graft to provide tissue contact and eliminate "dead" space; no drain was inserted. **F,** Gross specimen, cross sections in the mental foramen area revealed a multicystic soft lesion filling interstices between buccal and medial cortices; the cortices were intact.**G-I,** Histologic sections showed follicular ameloblastoma with cyst formation and bone resorption. **J,** A clinical photograph 2 months postoperatively shows facial symmetry. A partial denture was constructed 10 months after the procedure; oral opening is satisfactory without mandibular deviation. **K,** A panographic film taken 10 years postoperatively.



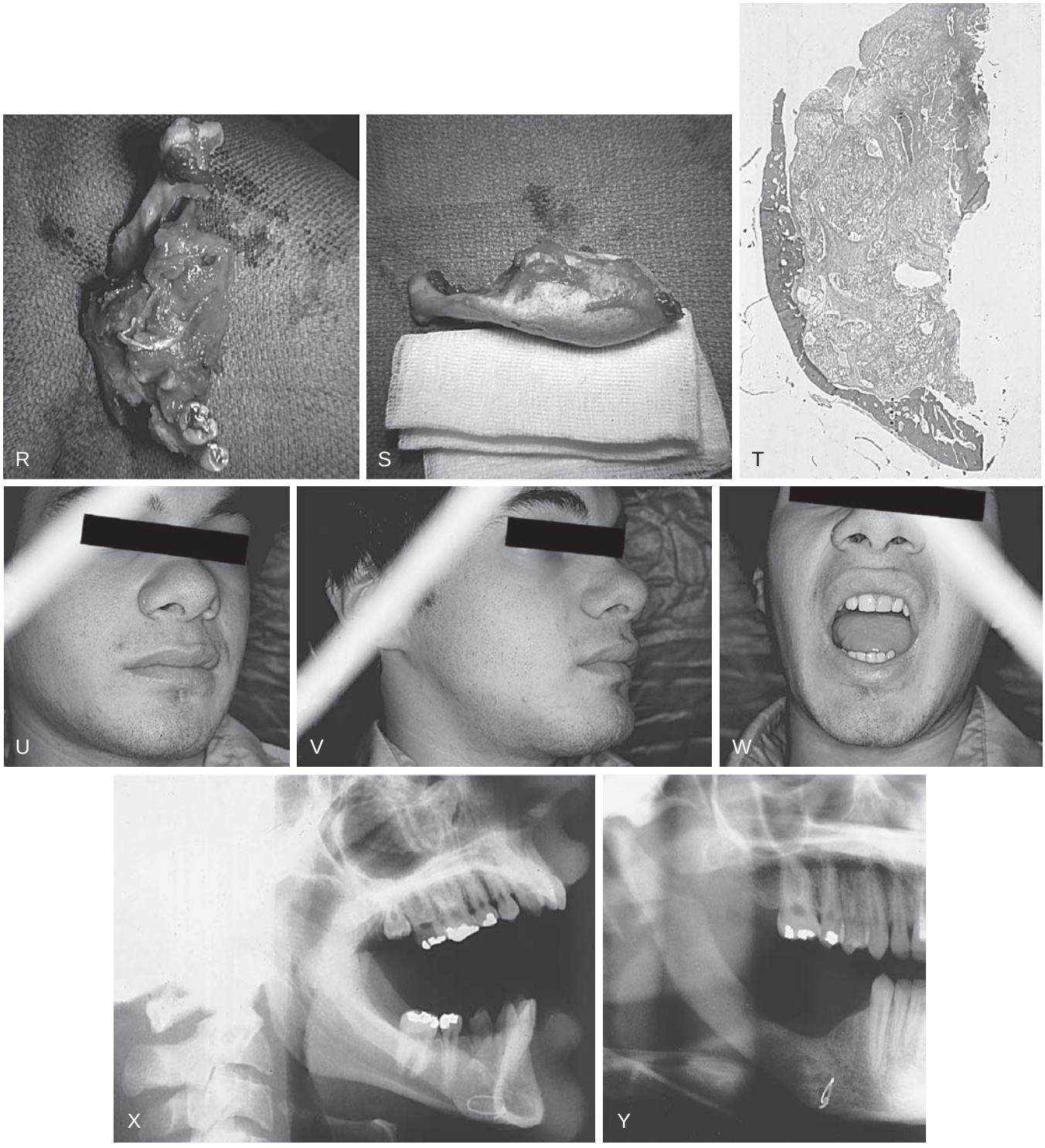
• **Figure 18-13** Central multicystic ameloblastoma of mandible. **A,** A 21-year-old man, operated on 3 taken during the initial consultation and examination revealed a plexiform ameloblastoma. Preparation for the resection of the ameloblastoma began with application of mandibular and maxillary arch bars in the office, with further imaging including panographic, tomographic, and cephalometric radiographs. **C,** Note the conversion of a unicystic to a multicystic lesion. A malleable, thin lead pattern, later used for bone graft measurement, was fashioned from a mock resection performed on the cephalogram. Two units of autologous blood were banked for the procedure. A mandibular resection with continuity defect at the canine–first premolar interspace and disarticulation with preservation of the temporomandibular disc was performed. Because preoperative clinical and radiographic study determined that the lesion extended to the sigmoid notch and pterygoid areas with a significant extramandibular medial component, maximum access was required. Therefore, a combined extraoral and transoral approach utilizing a lip-splitting procedure was employed. A tracheostomy was done; the procedure included the following steps: **D,** The lower lip was vertically divided just past the midline with extension of the incision through the chin, in a slightly curvilinear manner, and continued submentally and submandibularly to the ramus area past the mandibular angle. **E**-**G,** The dissection was then carried out as detailed in Figure 18-12, but more supramandibularly to incorporate the extramandibular components of the lesion with muscle cover. **H,** The resected mandible was disarticulated, and a step was prepared in the intact mandible.

a basaloid pattern primarily, but frequently is mixed with follicular and acanthomatous elements, and in the absence of other subtypes appears identical to basal cell carcinoma.[81-83] Even a clear cell variant has been described.[84] Some lesions appear to emanate from surface epithelium or fuse with the surface (see Figure 18-16, *F*). Radiographs of the alveolar process contiguous with the lesion show varying involvement of the underlying bone and occasional resorption of adjacent tooth roots. The underlying bone is occasionally resorbed medial to the lesion or sometimes appears cupped out by a pressure phenomenon (see Figures 18-15 and 18-16). There is no certain knowledge that the lesion cannot simultaneously originate from bone and soft tissue and grow centrifugally rather than centripetally.

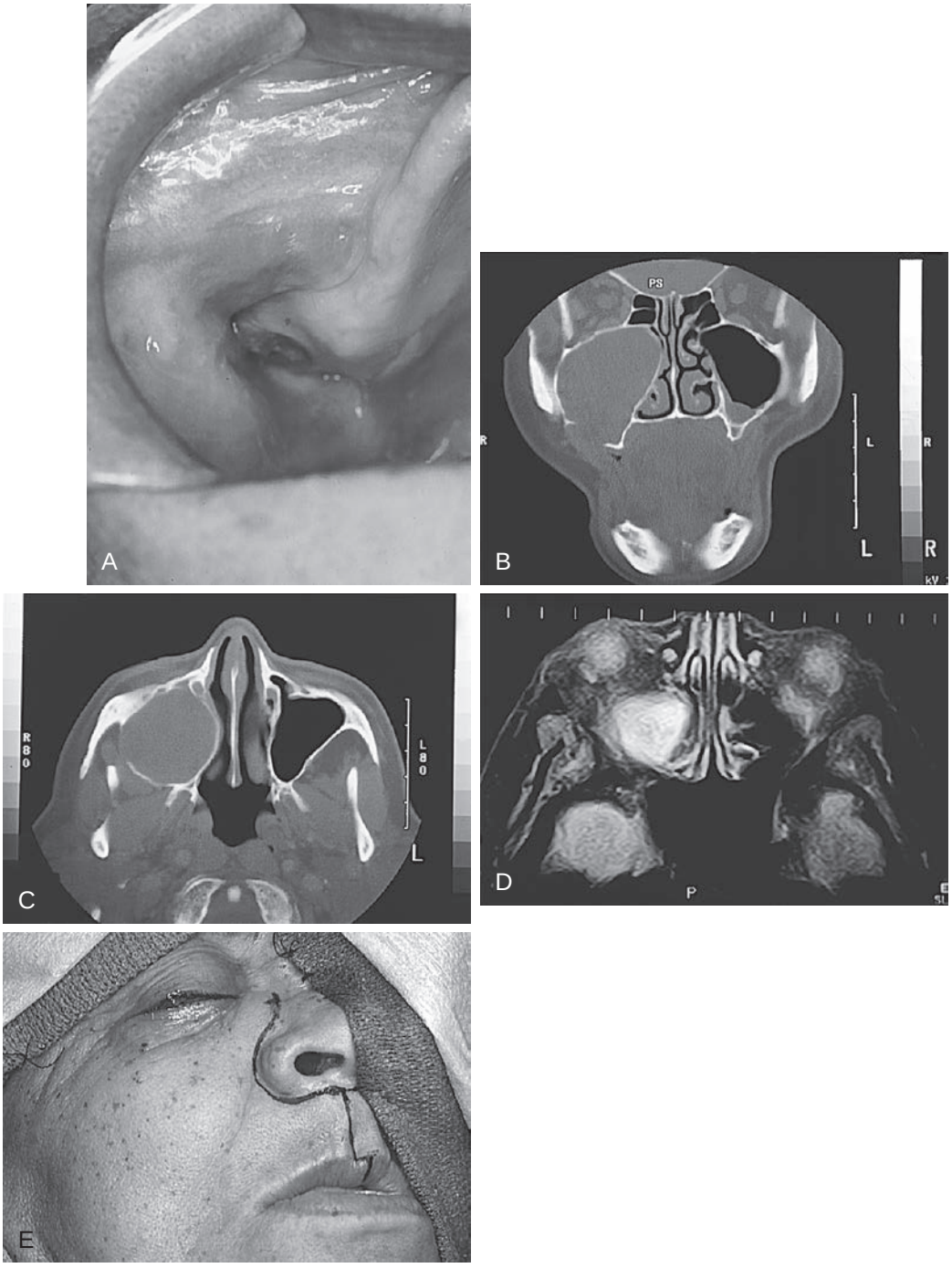


• **Figure 18-13, cont'd** **I-L,** A full-thickness (bicorticated) graft was harvested from the contralateral anterior iliac crest, using the lead pattern as a guide **(M)** and sculpted without decortication. **N,** The graft was placed into the intact mandibular step and against the temporomandibular disc and fixed to the mandible with a single vertical mattress wire. **O,** A drain was inserted, and the wound was firmly closed in multiple layers. **P,** Several "wrap-around" vertical mattress sutures were placed from the medial side to exit through the skin and were tied over bolsters to adapt the soft tissues more firmly around the graft. **Q,** The specimen as seen from the lingual (medial),

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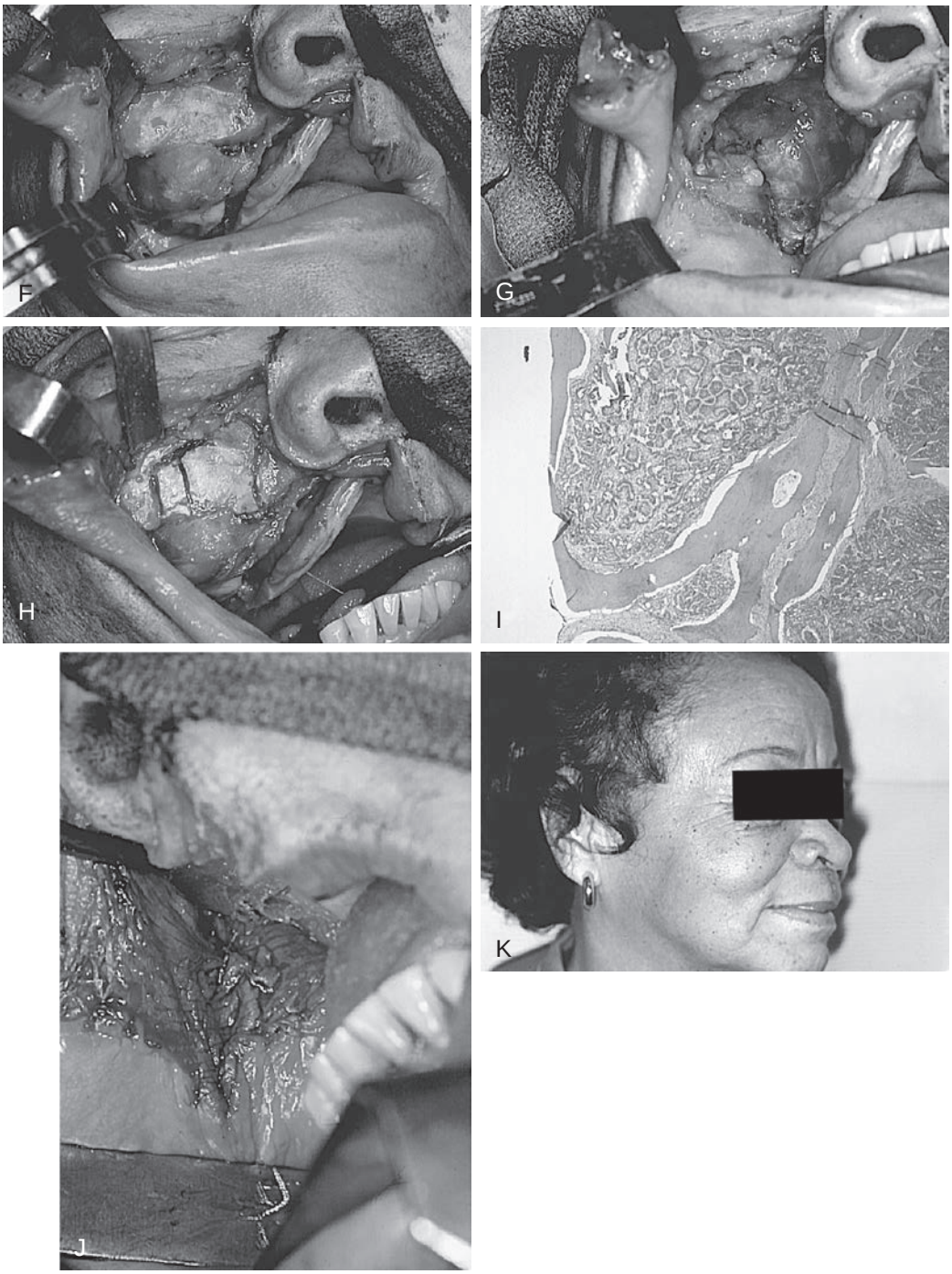


• **Figure 18-13, cont'd** **(R)** superior, and **(S)** buccal aspects (the soft tissue is removed to demonstrate classic gourd shape of the thinned expanded inferior border). **T,** Low-power photomicrograph of hemi-cross section taken through a portion of the specimen to demonstrate the solid and cystic tumor replacing the medullary spaces and resorbing cortical (compact) bone. The tumor was a predominantly solid lesion. **U-Y,** A good cosmetic and functional result was achieved. The patient was lost to follow-up evaluation after 9 months. (Patient left area and refused follow-up.)

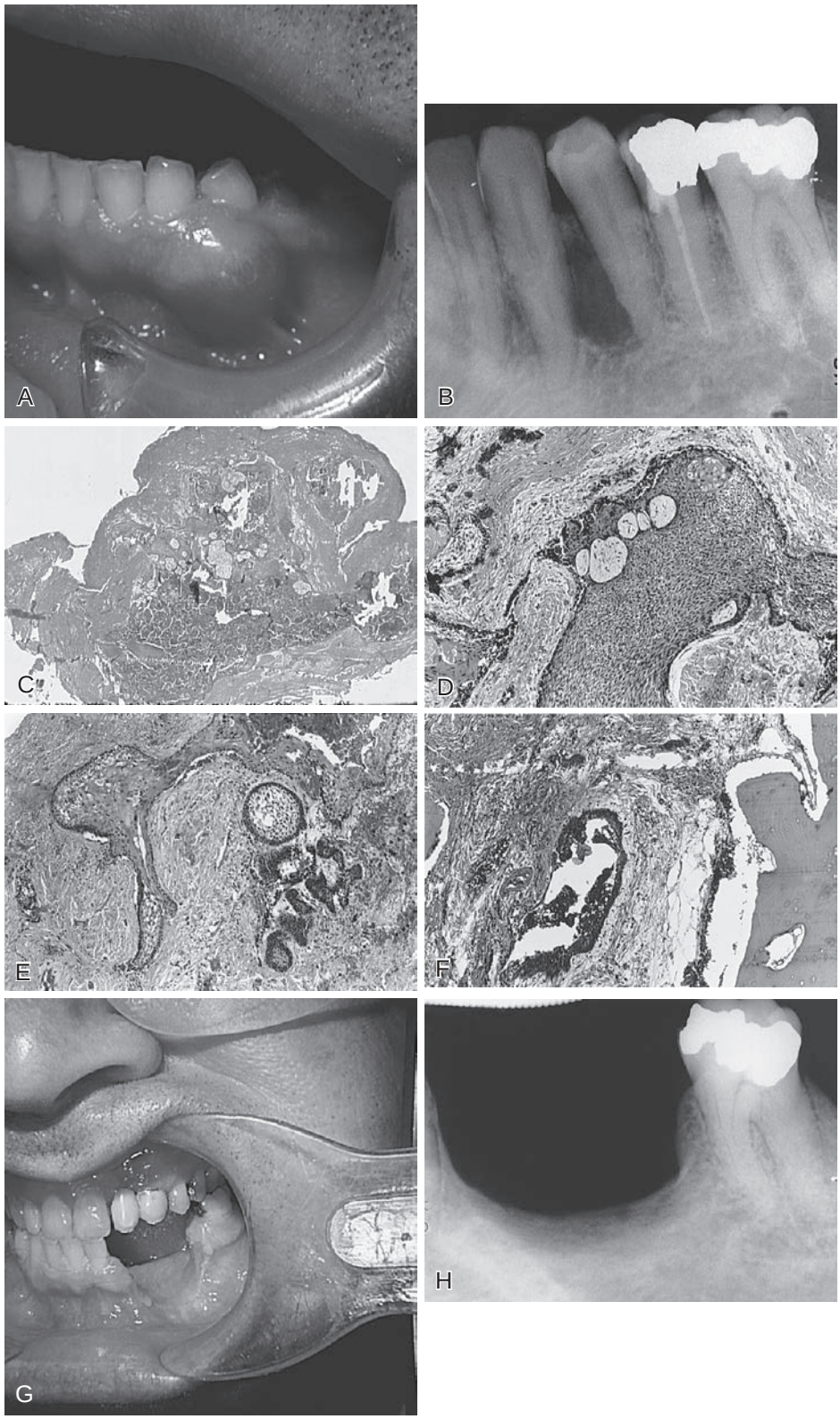


• **Figure 18-14** Solid ameloblastoma of the maxilla and maxillary sinus. A 77-year-old woman was referred for management of a previously biopsied follicular ameloblastoma of the right maxilla. **A,** The lesion expanded the buccal aspect of the maxilla and had resorbed the alveolar process and was palpable through the mucosa. The posterior biopsy site was ulcerated. **B-C,** Panographic, computed tomographic, and magnetic resonance imaging (MRI) revealed a circumscribed lesion occupying the maxilla and maxillary sinus, compressing the lateral nasal wall, involving the turbinates, and extending to the pterygoid plate. **D,** The infraorbital rim and floor of orbit and the ethmoid sinus were intact. The contrast MRI showed a solid lesion with suggestion of intralesional cystic spaces. **E,** A maxillectomy was performed, employing a Weber-Fergusson skin incision (without a horizontal infraorbital extension), combined with a transoral incision that spared uninvolved mucosa but included the biopsy site in the specimen.

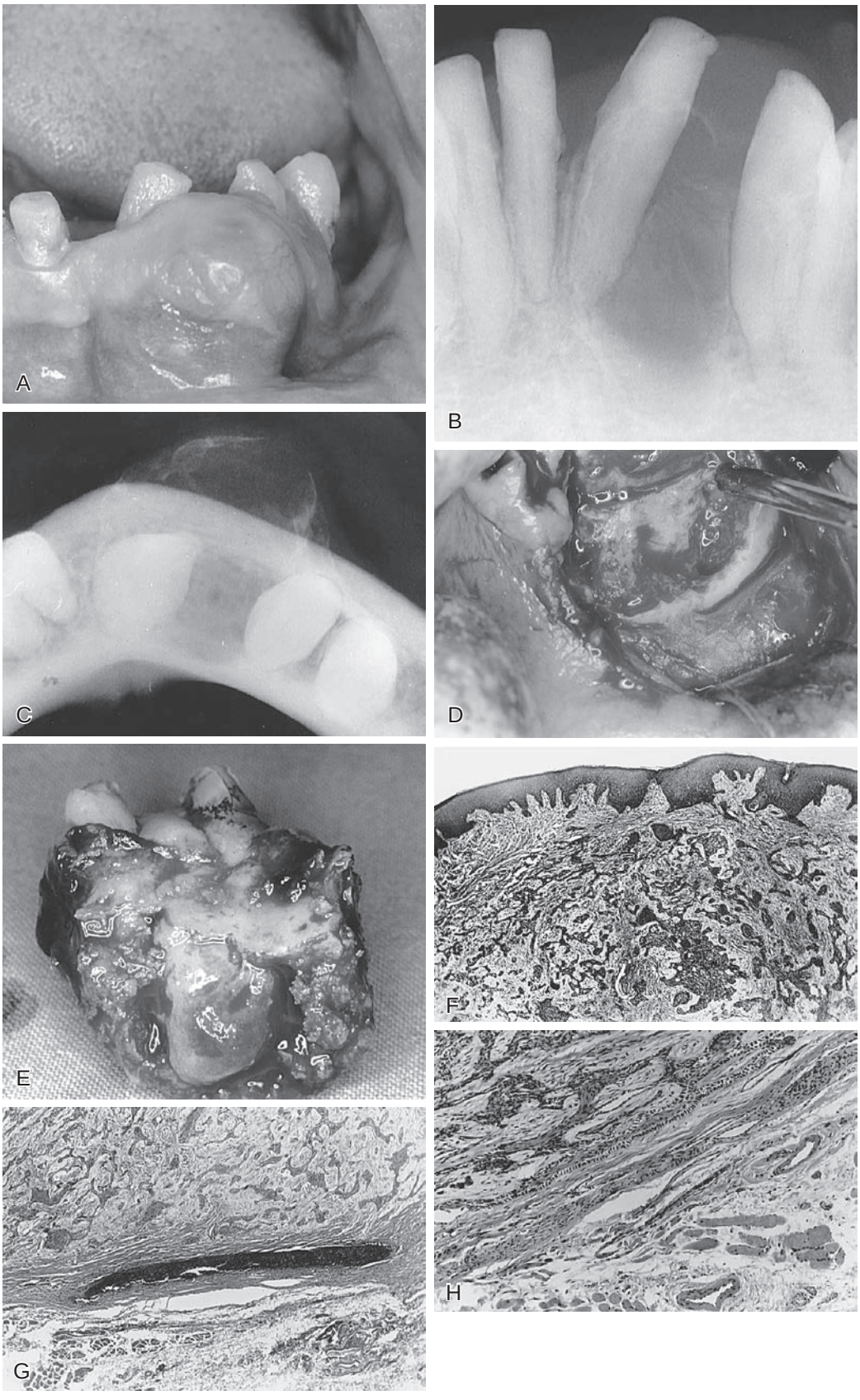
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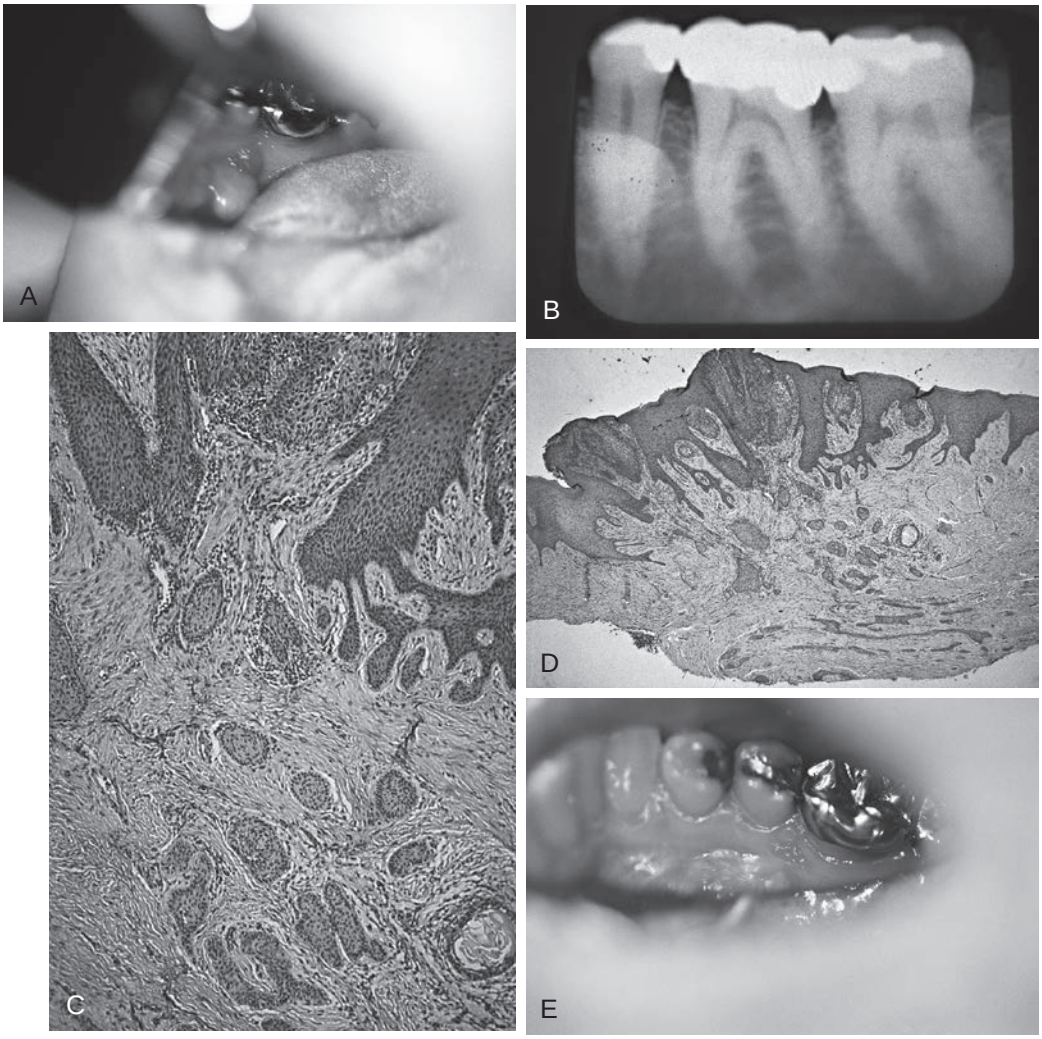
• **Figure 18-14, cont'd** **F**-**H,** The lesion had resorbed the posterior sinus wall but was **(I)** encased in remnants of the bone and circumscribing soft tissue. **J,** A meshed split-thickness skin graft was sutured to the inner raw surface of the facial flap and pterygoid area. Soft gauze, infiltrated with antibiotic ointment, was packed into the wound to obliterate space and support the skin graft. The pack was sutured in place across the palate. A temporary obturator was constructed within the mouth, and a permanent obturator was fabricated 2 months later. **K,** Facial appearance 2 months post operation.



• **Figure 18-15** Peripheral ameloblastoma. **A,** A 46-year-old man was treated for a smooth-surfaced sessile 1.5 × 1.5 cm mass, involving the gingival and alveolar mucosa between the mandibular left canine and premolar teeth, that had been present for several years. **B,** Periapical, occlusal, and panographic radiographs showed a radiolucent lesion with irregular bone resorption, beginning root resorption, and possible extension to the lateral incisor. Block resection of the soft tissue mass, with deep curettage of the bone base, exposed the roots of the lateral incisor, canine, and first premolar teeth. **C**-**E,** Tissue (microscopic) sections showed a mixture of squamatoid, follicular, basaloid, and acanthomatous ameloblastic patterns. **F,** Microscopic sections of the bone bed revealed basaloid follicles adjacent to the bone. A resection without continuity defect of the tumor bed was done that incorporated the involved teeth and extended to a level below the tooth apices; residual tumor was not found. **G**-**H,** Clinical and radiographic examination 5 years later showed some bone regeneration with no recurrence.



• **Figure 18-16** Peripheral ameloblastoma (possible central origin). **A,** A 55-year-old woman was referred for treatment of a smooth-surfaced, sessile mass, measuring 2.5 × 2.5 × 2.0 cm, involving the gingival and vestibular mucosa and covering the lateral incisor and canine that extended to the premolar. **B**-**C,** Periapical and occlusal radiographs showed a faintly septated radiolucent lesion causing separation of lateral incisor and canine teeth, with apparent thin bone covering a portion of the lesion's periphery. **D,** A block resection without continuity defect included the mass below the vestibular fornix and the three teeth, sparing the inferior lingual cortex. **E,** Specimen shown from the lingual and inferior surface. **F,** Tissue section of mucosal aspect reveals irregular large and small islands of mixed basaloid, acanthomatous, and occasional follicular ameloblastoma in a loose and dense stroma. **G,** The tumor abuts resorbing cortical bone and **(H)** periosteum separating tumor from muscle in the vestibule.



• **Figure 18-17** Recurrent peripheral ameloblastoma. **A,** A 55-year-old man was referred for evaluation and treatment of a 5-mm ovoid, reddish, slightly elevated lesion, with a pebbled surface on the lingual aspect of the gingival and alveolar mucosa, just superior to a mandibular torus. **B,** Panographic and periapical radiographs did not reveal bone involvement. The lesion was excised, and a microscopic diagnosis of peripheral ameloblastoma was made. **C,** Medium-power photomicrograph shows area of lesion in relation to surface gingival epithelium. The lesion recurred 8 months later and was re-excised with a 2-mm soft tissue margin, including the underlying periosteum. **D,** Scanning power photomicrograph demonstrates lesion at base of the tissue section. **E,** A second recurrence was seen within 3 months. The lesion was re-excised, again, with a perimeter of 5 mm of soft tissue and 3 mm of underlying bone (and the mandibular torus). There have been no recurrences (i.e., regrowth of residual tumor) in an 11-year follow-up period.

For a discussion of further potential links between peripheral ameloblastoma and intraosseous ameloblastoma, the reader is referred to papers by Ide et al[85] and Gold.[17a]

The peripheral ameloblastoma, because of its surface accessibility is the most readily managed of the ameloblastomas by relatively conservative surgery. However, growth characteristics such as tumor extension to the surface and medial and lateral infiltrating growth with circumscription but without true encapsulation must be taken into account. Recurrence, although uncommon, has been reported[78,79,83] (see Figure 18-17) (see discussion under Management).

Philipsen et al,[86] in a review of 160 cases of peripheral ameloblastoma culled from the world literature, identified 6 cases reported as malignant variants. These lesions were described as basal cell carcinoma[87] or squamous cell carcinoma.[88-90] One of the six cases was excluded (because of incomplete documentation) by Wettan et al[91] in a paper that also reviewed reported malignant peripheral ameloblastomas, and discussed their own cases of recurrent peripheral ameloblastoma with severe dysplasia.

In a letter to the editor in 2004, Ide and Kusama[92] discussed a paper published by them in 2001[93] of a maxillary peripheral ameloblastoma which "in spite of seemingly innocuous histology, showed unusual mitotic activity." The lesion was described as "partially malignant." In 2003, they studied an excised submandibular lymph node from the same patient, which was diagnosed as metastatic

well-differentiated peripheral ameloblastic carcinoma secondary to the original lesion. Ide and Kusama[92] now suggest that, in view of this retrospective diagnosis, mitotic activity in a peripheral ameloblastoma is possibly correlated with malignancy. They also find a corollary between the "conventional" appearance of peripheral ameloblastoma and "conventional" intraosseous ameloblastomas that have metastasized.

Their excellent discussion demonstrates the dilemma faced by pathologists who are reluctant to diagnose a lesion as malignant unless there is clear morphologic and cytologic evidence of malignancy, but also may represent an overly cautious desire not to over diagnose a lesion, which may influence a surgeon to perform what may be unwarranted, aggressive surgery.

Cytologic Malignant Ameloblastoma

As previously argued in the introduction to the section on ameloblastoma, the authors consider conventional ameloblastoma a low-grade de novo malignant tumor. Numerous reports document conventional ameloblastomas that aggressively invade adjacent and regional tissues as well as metastasize to the bronchopulmonary system, local and distant lymph nodes, and distant organs.[74b,94-100] Accounts suggest that nothing distinguishes some metastatic lesions from conventional ameloblastoma,[101-103] but several writers[17a,104,105] have commented that a number of photomicrographs reveal pronounced histologic dysplastic differences from conventional ameloblastoma that should have been recognized.

There is a tendency among some pathologists, once the histologic diagnosis of ameloblastoma is made, to dismiss the lesion from further consideration, since common knowledge holds that all ameloblastomas, of whatever subtype, behave in a similar manner. However, it is reasonable to expect that increased clinical aggression beyond the apparent slow progression of conventional ameloblastoma will be accompanied by histologic evidence of cytologic or gross atypia. It is probable that subtle morphologic histologic alterations are not recognized or are dismissed as unimportant, and obvious and blatant evidence of increased cellular atypia is regarded as "atypical," rather than an extension of the lesion's know biologic potential.

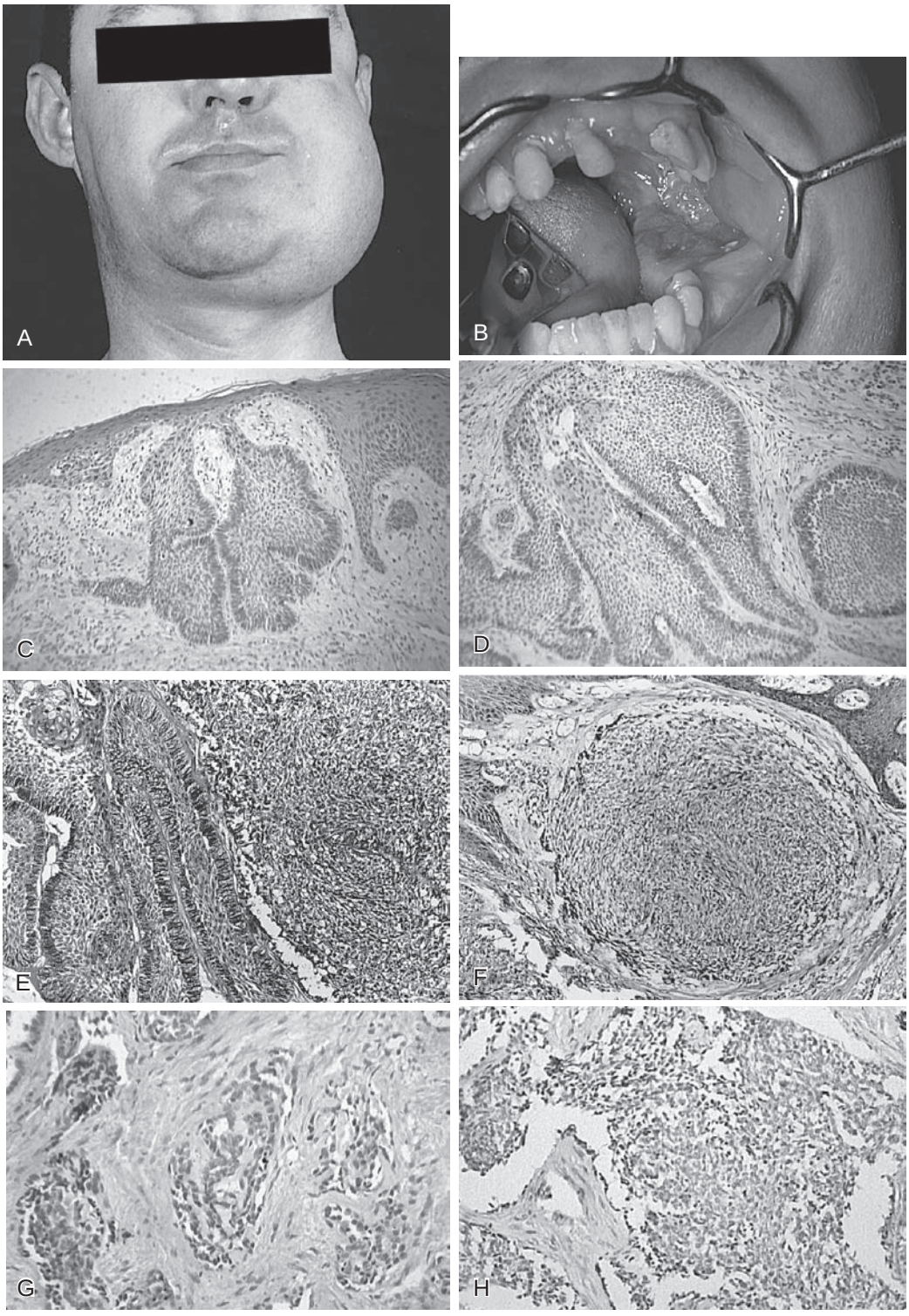
Subtle cytologic mutations can occur in ameloblastoma without physical or symptomatic awareness. *However, sudden, rapid, intraoral expansion of bone or soft tissue, and marked facial or cervical swelling, often accompanied by sensory loss and/or pain, may signal significant morphologic and cytologic changes in a lesion*. Imaging (panographic, CT, MRI) also may show extensive jaw bone destruction.

In unusual instances, clinical examination and imaging of maxillary lesions may reveal tumor masses, which extend into the maxillary sinus, nasoethmoidal, and pterygoid spaces or the skull base.[106,107] Mandibular lesions may infiltrate the floor of the mouth, parapharyngeal, and cervical regions.[108,109] *A clinically symptomatic patient may be the first sign of the presence of a de novo ameloblastic cytologic malignancy. However, more typically they will be patients who have been treated previously, sometimes years before, or have had numerous, intermittent unsuccessful procedures*.

In addition to imaging the primary jaw lesion when cytologic malignancy is proved or suspected, CT and PET examination should be extended to the chest, and bone scan to the skeletal system.[110] Isolated and multiple lung and pleural metastases as well as vertebral, hip, and other bone lesions may occur.[111] Metastases to brain, kidney,[112] and even myocardium[113] have been reported. Metastases to the skull, spine, lymph nodes, and distant organs do not occasion dispute concerning their metastatic credentials. However, metastasis to the lungs, often recorded as a favorite site, has raised the suggestion that aspiration occurred during a surgical procedure. Although implantation can and perhaps does occur, given the protective measures used to guard against aspiration, it must be a rare event measured against the numerous reports of metastases to the lungs. MacIntosh[114] has voiced the convincing argument that a common site of metastasis of oral salivary gland malignancy (e.g., mucoepidermoid carcinoma) is also to the lung, about which there has been no question of validity (Figure 18-18).

The histologic changes that accompany the progression from low-grade to high-grade malignancy range from relatively subtle to extreme atypia and produce marked deviation in epithelial cytologic characteristics as well as tissue pattern. Inner cell layers (such as stratum reticulum) become hypercellular and hyperchromatic and display mitotic activity with change in shape and size (often rounded with loss of polygonal shape). Masses of inner cells, no longer bound or restrained by an outer cell layer, infiltrate surrounding tissue as rounded or irregularly shaped islands. The peripheral (outer cell layer) cells also show atypia and hyperchromicity, change shape and size, lose nuclear polarity and identity as an outer cell layer, and proliferate as strands of undifferentiated carcinoma cells. Some lesions may retain segments of recognizable ameloblastic pattern or appear as undifferentiated carcinoma (see Figure 18-18).[17a] Clear cells may be present as islands and strands, or intermixed with squamous carcinomatous cells in irregularly shaped islands.[115]

An earlier discussion noted the production of a parathyroid hormone-related protein (PTHrP) by ameloblastic tumor cells in the local jaw lesion and a humoral factor in metastatic lesions in lung and bone, resulting in hypercalcemia.[75,76,94] An excellent study and case report by Cox and colleagues[116] demonstrates the relationship of PTHrP and hypercalcemia in a protracted case of ameloblastic carcinoma emanating from a conventional ameloblastoma (ex ameloblastoma) of the mandible. These findings suggest that *hypercalcemia may be a marker of metastatic disease in some instances, and that calcium levels should be routinely obtained*.



• **Figure 18-18** Central anaplastic ameloblastoma with metastases. A 32-year-old man was seen for a "lump on the left jaw" of 8 weeks' duration. The patient reported that he had had an "abscess in the jaw 15 years ago and never felt right since." **A-B,** Examination showed facial enlargement and an extensive intraoral lesion. Radiographs (unavailable) revealed almost complete replacement of the left mandible by a massive lesion. A biopsy was reported as anaplastic ameloblastoma. An extensive continuity resection of soft tissue and disarticulation of the mandible with neck dissection was done. Cervical lymph nodes were negative. The patient was hospitalized 6 months later in another hospital and died after 2 months. Pelvic and cervical vertebral metastases were proved at autopsy, but tissue slides of the metastatic lesions were never received. **C-H,** Photomicrographs of sections from the resection specimen demonstrate a spectrum of morphologic changes from areas of recognizable ameloblastoma to increasing anaplasia (undifferentiated carcinoma).

The cytologically malignant lesion that produces massive local disease or is combined with disseminated disease to organs and bone offers little to no possibility of salvage. Radiation and chemotherapy have had limited and temporary success[117,118] and are most suited, at this time, for palliation (not adjunctive therapy). Wide resection of the primary lesion and isolated metastatic lesions remains the best prospect for cure.

Management

The inability of the pathology community to resolve the continuing controversy surrounding the neoplastic classification of ameloblastoma has had a direct effect on surgeons' ability to deal unequivocally with this lesion. The pathologists who continue to deny low-grade malignant status to the tumor have hindered clinicians' understanding of the lesion's biologic behavior and potential, have given license to ineffective management, and must share with surgeons responsibility for the compromised treatment that some patients with ameloblastoma receive. Extensive knowledge of and clinical experience with ameloblastoma permit some general and specific principles of management to be enumerated. A recent paper by Carlson and Marx[119] is recommended for an excellent perspective on management.

General Principles

- Treatment must be guided by consideration of the behavior and potential of the tumor, the growth characteristics of the various physical forms, the anatomic site of occurrence, the clinical extent and size of the tumor, and the histologic assessment of the specific lesion.
- Unless precluded by the patient's physical and mental status and ability to withstand the surgical procedure and the postoperative recovery period, the goal of treatment is the total removal of the tumor by whatever surgical procedure or combination of procedures is necessary. *Less than complete excision is equivalent to planned recurrence (regrowth).*
- Present-day anesthesia, instrumentation, reconstructive surgical techniques, and materiel offer a number of choices for excellent functional and aesthetic restoration. Philosophic arguments about "radical" and "conservative" surgical approaches are irrelevant considerations, when weighed against the obligation to eradicate the lesion. The first procedure should be planned to be definitive and offer the best opportunity for cure, with the least psychological distress imposed on the patient.
- Curettage and enucleation of ameloblastoma, either separately or in combination, have resulted in recurrence (regrowth). The following recurrence rates of curetted lesions, compiled from relatively small series, are approximate and probably not completely accurate:
  - Intraosseous solid or multicystic lesions: 55% to 100%
  - Intraosseous unicystic lesions: 18% to 35%
  - Peripheral lesions: unknown, but occur
- Curettage as a primary or single surgical modality must be condemned. Curettage can disperse the tumor into uninvolved areas and make necessary subsequent procedures more tissue destructive. It is difficult to follow healing by radiographic examination of a lesion that has been treated by curettage, because recurrence may appear radiographically similar to formation of bone.
- Cancellous bone of the mandible and maxilla and cortical bone of the maxilla are readily infiltrated and resorbed by the tumor; the tumor spreads covertly through the bone.
- The dense cortical bone of the lateral and medial borders, as well as the inferior border and symphysis of the mandible, are temporary barriers. The dense bone of these sites can be and is invaded and destroyed by the tumor.
- The lesion microscopically infiltrates bone beyond the tumor-bone interface seen in imaging. Until anatomic and histologic studies prove the presumption incorrect, a safe margin of uninvolved bone is approximately 1.5 to 2 cm for solid and multicystic lesions, and 1 to 1.5 cm for unicystic and peripheral lesions.
- Resorption of cortical bone by the tumor permits growth into the periosteum; if the periosteum is penetrated, growth into surrounding muscle and soft tissue occurs.
- The peripheral connective tissue of ameloblastoma, whether dense or loose, may appear to circumscribe the lesion but cannot be considered a capsule. The tumor can and does grow into and through the peripheral connective tissue.
- Post-treatment patients should be followed for 15 to 20 years or longer.

Specific Principles

Intraosseous Solid, Multicystic, and Solid/Multicystic Ameloblastoma

- Mandibular excision, by block resection without continuity defect ($Rs^{-}CD$) or block resection with continuity defect ($Rc^{-}CD$), should be performed on lesions that, respectively, do not and lesions that do involve the superior-inferior diameter of the mandible, provided the general management principles (cited previously) are observed.
- The inferior alveolar nerve should be sacrificed if it lies within the lesion. If the surgical plan includes nerve grafting, it is best to perform the procedure at the time of resection whether bone reconstruction is immediate or delayed.[120]
- Resection should be exterior to a tumor-involved tissue plane (e.g., if cortical bone is resorbed and penetrated, the resection should include the periosteal layer of that area; if periosteum is infiltrated, the resection should include that portion of overlying muscle or mucosa).
- A thin inferior border of the mandible preserved in an $Rs^{-}CD$ may fracture even if supported by a reconstruction plate placed to span and support the segment. Retention

of an inferior border less than 1 cm in thickness is not practical, and Rc-CD should be performed.
- Resection by sharp cutting instruments permits radiographic and histologic assessment of the resection margins. The technique of "grinding" bone away with a burr does not allow microscopic evaluation of the tumor-bone interface.
- Immediate reconstruction can be performed, by several techniques, if there is surgical, specimen radiographic, or intraoperative frozen section certainty of complete excision of the tumor. However, if there is uncertainty about the resection margins, reconstruction should be delayed until permanent tissue sections are studied.
- If sufficient uninvolved soft tissue is locally available to cover the resection bed, an autogenous free bone graft or bank allogeneic bone crib and patient marrow may be used with a reconstruction plate or wire fixation of the graft. Platelet-rich plasma[121] mixed into a particulate cortical/cancellous/marrow bone graft is an excellent binder and may promote bone formation.
- If insufficient soft tissue is locally available to cover the resection bed, a vascularized composite pedicle graft of bone and myocutaneous tissue can be used.
- Delayed reconstruction also may be employed in the instance of insufficient soft tissue at the resection site by application of a plate to maintain the resection space, and rotation of a vascularized regional myocutaneous flap. Bone grafting should immediately follow healing of the soft tissue bed, in order to prevent fracture of the reconstruction plate and subsequent infection.
- Maxillary lesions must be resected aggressively because of the ease with which the tumor can spread through the less dense cancellous and cortical bone, with access to the pterygoid region, sinuses, infratemporal space, and skull base.

Intraosseous Unicystic Ameloblastoma

- Most unicystic ameloblastomas are clinically and radiographically diagnosed initially as dentigerous cysts or odontogenic keratocysts and therefore are often treated without prior biopsy; the management selected (i.e., enucleation or marsupialization if the lesion is thought to be a cyst) is determined by patient-related clinical factors. Seldom is unicystic (mural) ameloblastoma considered in a differential diagnosis. Although often overlooked, an important radiographic diagnostic sign of a unicystic ameloblastoma is tooth root resorption in the lesional area. Cystic lesions such as dentigerous, calcifying odontogenic, and glandular odontogenic may also cause tooth root resorption, all of which should arouse sufficient suspicion to warrant performing a biopsy. Biopsy of a unicystic ameloblastoma does not guarantee correct diagnosis. The biopsy site may not include ameloblastic sites in an attempt to obviate selection of nondiagnostic areas.
- Careful radiographic examination can help determine whether small satellite cysts are present and are separated from the main cyst cavity by bony septae.
- The physical basis for attempted enucleation of a mural (unicystic) ameloblastoma is the integrity of the cyst wall: a property conferred by the density of the collagenous connective tissue and the ability to find a cleavage plane between the lesion and bone.
- Fragments of torn cyst wall that remain attached to bone and friable areas of cyst wall should be submitted for intraoperative frozen section to detect the presence or absence of ameloblastic foci.
- The absence of satellite cysts, physical integrity of the cyst wall, and negative intraoperative frozen section finding (i.e., absence of ameloblastic elements in the cyst wall adjacent to or abutting bone) are essential to a successful enucleation attempt.
- Curettage of the bone is discouraged because it may implant foci of ameloblastoma more deeply into bone. Adjunctive treatment of the bone tumor bed by chemical fixation with Carnoy solution[122] is of theoretical but unproven value, and cryosurgery gives inconstant benefit, as well as risk of sequestration or pathologic fracture.[123-126]
- If frozen sections or final microscopic sections of the tumor reveal foci of ameloblastoma within the cyst wall (so-called *mural* occurrence) at or near the bony tumor bed, it should be assumed that ameloblastoma is within adjacent bone. In such an instance, further management should be by Rs-CD or Rc-CD, depending on the extent of anatomic involvement. Reconstruction can follow in the same manner as outlined for intraosseous solid or multicystic lesions.
- *There is no surgical imperative that enucleation be the preferred management modality.* Indeed, there are some compelling reasons not to select enucleation, but to employ Rs-CD or Rc-CD with reconstruction from the outset. These are (1) a lesion so extensive as to result in pathologic fracture, soon or late, if enucleation alone is attempted; (2) the presence of small satellite cystic lesions (or invisible microscopic foci) in addition to primary lesions; (3) an intraoperative frozen section finding of ameloblastoma in the cyst wall at the cyst-bone interface; and (4) the ability to select a 1- to 1.5-cm resection margin distant to the radiographic lesion-bone interface, as a presumptive "safe" distance from the lesion.

Peripheral (Extraosseous) Ameloblastoma

- Peripheral ameloblastoma is seen as a sessile gingival and mucosal mass, with frequent separation of teeth in dentate areas, a smooth or warty (pebbled) surface, and a radiographic image that reveals the extent, if any, of alveolar bone involvement. Because there are no pathognomonic clinical characteristics, unless

a biopsy is performed, the lesion probably will be excised. Microscopic sections of the tumor will reveal the extent of involvement of surface mucosa, periosteum, and bone.

- With prior biopsy and identification of the lesion, Rs-CD should be done, with clinical and radiographic guidance, to excise a block containing the tumor, overlying mucosa, underlying periosteum, alveolar bone, and teeth. A 1- to 1.5-cm resection margin of clinically uninvolved soft tissue and bone should be included. Healing by wound dressing usually is sufficient.
- If the lesion has been removed without biopsy, and microscopic sections of the specimen reveal ameloblastoma at the excision margins, a secondary Rs-CD block centered on the previously excised area should be performed as described.

Cytologic Malignant Ameloblastoma

- A cytologically malignant ameloblastoma (CMA) will frequently exhibit a combination of characteristic features:
  - A history of a lesion treated previously (in instances years before) or multiple periodic operations without effective containment, except in instances of a de novo CMA.
  - Clinical signs of facial enlargement with sudden, rapid jaw and soft tissue expansion and symptoms of pain or sensory impairment in the jaw.
  - Past or present roentgenograms that reveal a lesion with indistinct borders merging with host bone and extensive destruction of cortical bone.
- Definitive diagnosis must be based on microscopic analysis of several biopsies taken from the lesion.
  - Tissue diagnosis should be performed by a pathologist familiar with the nuances of histologic atypia possible in ameloblastoma, as well as the spectrum of dysplastic changes displayed by CMA.
  - Fine-needle aspiration is not recommended as a biopsy technique and should not replace incisional biopsy of the primary lesion or metastatic sites.
- A positive diagnosis of CMA should initiate a roentgenographic survey for the presence of paragnathic tumor masses and metastases to regional lymph nodes, lung, and skeleton.
  - Metastatic lung and bone lesions may be present without clinical symptoms.
  - Serum hypercalcemia may indicate the presence of metastasis.
  - CT, MRI, PET-CT, and bone scan imaging are indicated for head, neck, chest, and skeletal survey.
- Physical and mental status permitting, and if surgically feasible, wide resection and reconstruction should be performed on the primary and metastatic lesions by a surgical team.
- Radiation and chemotherapy are questionable modalities for adjunctive treatment and should be reserved for palliation.

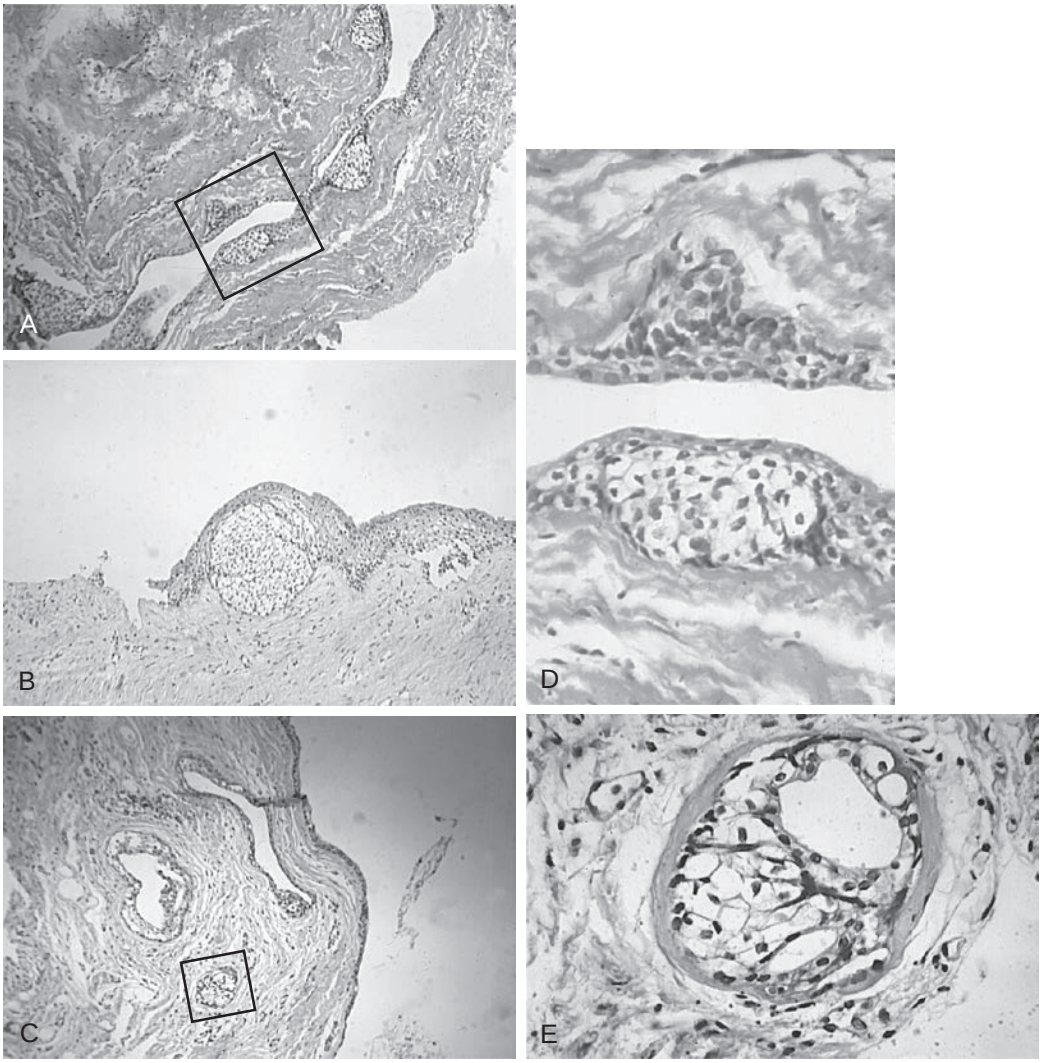
Clear Cell Odontogenic Carcinoma

A chronologic account of the recognition of the odontogenic "clear cell" from histologic curiosity to identification of its potential neoplastic and malignant behavior is interesting and instructive (Figures 18-19 to 18-21). The odontogenic epithelial cell, known as clear cell, has its origin in the embryonic oral ectoderm of the dental lamina. It was described by the early dental histologists as a basal cell whose cytoplasm did not stain in histologic preparations, because of a rich glycogen content, giving an empty appearance.[1] Pathologists through the years also have observed small and large islands of clear cells in follicular sacs and dentigerous cyst walls (in two reports,[127,128] the clear cell nests were erroneously described as sebaceous cells).

A study of epithelial nests in the human periodontal ligament by Reeve and Wentz[129] revealed three morphologic types, one of which consisted of large islands of clear cells, either densely packed or loosely arranged like a stellate reticulum, sometimes surrounded by a connective tissue capsule.

Clinical and histologic studies of the lateral periodontal cyst and gingival cyst by a number of investigators[43,130-132] showed the lesions to be unicystic or polycystic (also known as botryoid odontogenic cyst[133,134]), capable of recurrence,[135,136] and containing clear cells. Several reports pointed out the distinctive clear cell as one of the types of epithelium lining the cystic lumen and present in the connective tissue wall as nests, sheets, and lining of microcysts. Some periodontal cysts showed lumina lined by stratified squamous or cuboidal epithelium in combination with clear cell follicles or clusters (see Figure 18-19, *A-D*). One study[43] identified the neoplastic potential of the clear cell and helped tumor composed primarily of clear cells. This patient, after several Rs-CD and Rc-CD procedures, appeared to be cured in 1971 but later exhibited metastases to lung and ribs, survived for 18 years, and succumbed to the lesion now identified as clear cell odontogenic carcinoma (see Figure 18-21).

After the description of the classic CEOT as an entity by Pindborg in 1955,[46] CEOTs and variants were reported by a number of writers, including several who described CEOTs containing large areas of clear cells or composed chiefly of clear cells.[59,137-139] These tumors also were viewed as variants of the CEOT because the lesions contained areas of calcification and apparent amyloid (presumed collateral hallmark of CEOT). Greer and Richardson,[58] in a report titled "Clear Cell Calcifying Odontogenic Tumor Viewed Relative to the Pindborg Tumor," described a lesion composed entirely of clear cells except for a central radiopaque nidus. However, the authors, in this instance, expressed vexation with the assignment of the lesion to the CEOT category. They considered "unique tissue formations ill-used by compulsive subclassification." They knew the lesion was not primarily



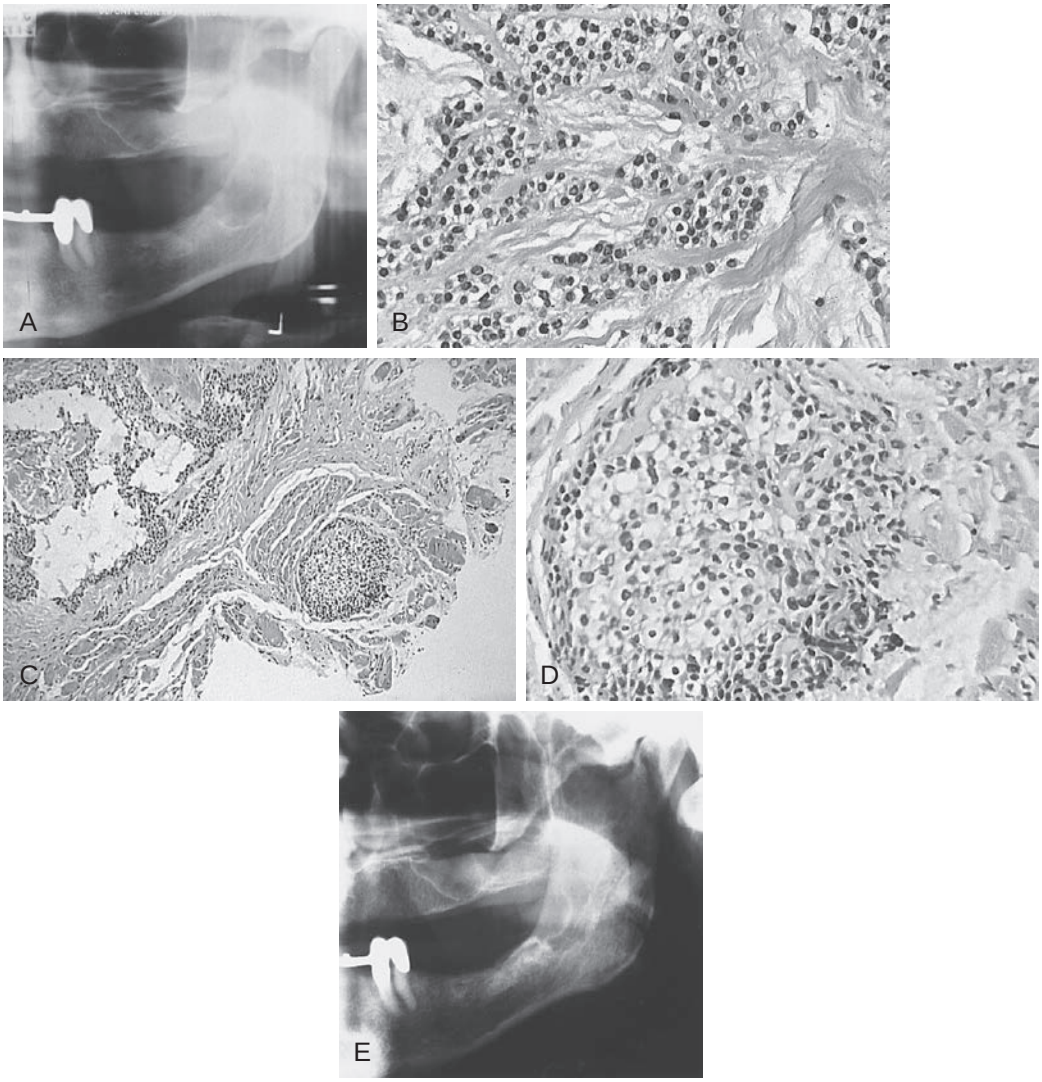
• **Figure 18-19** Periodontal cysts with clear cells. Photomicrographic patterns of clear cell follicles in the luminal lining and walls of several periodontal cysts. **A-C,** Low powers. **D,** High-power area of luminal lining in **(A). E,** High-power area of wall in **C**.

cell odontogenic tumor or carcinoma. Hicks and colleagues[59] reviewed the literature on clear cell variants of CEOT and presented an aggressive case example (see the previous section on CEOT).

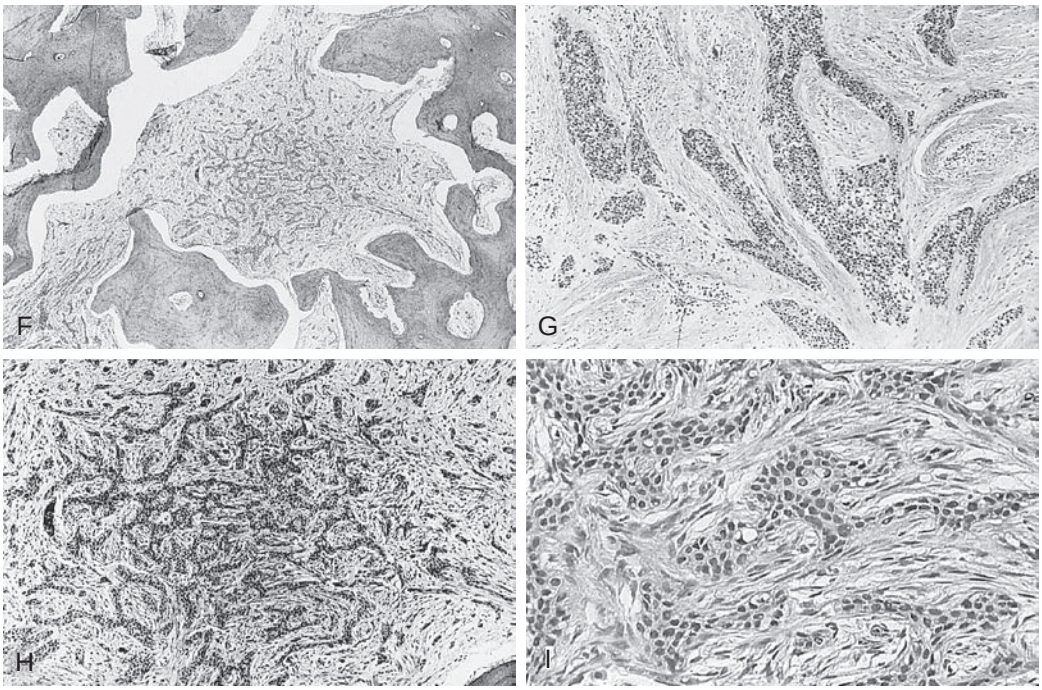
Waldron and colleagues,[16] in a report characterizing *clear cell ameloblastoma* as an odontogenic carcinoma, described two cases of a malignant odontogenic neoplasm that exhibited a biphasic pattern of follicular ameloblastoma, with dysplastic follicular features and a very pronounced and prominent clear cell component. One patient apparently survived (6½ years of follow-up) and the other patient died of extensive and uncontrolled growth (infratemporal fossa, retro-orbital region, skull base, facial tissue) and cervical metastases. The authors regarded both lesions as malignant clear cell variants of ameloblastoma and took the occasion of their report to reexamine critically the neoplastic position of ameloblastoma and the WHO concept and classification of malignant odontogenic neoplasms.

A short report by Müller and Slootweg[140] discussing clear cell differentiation in an ameloblastoma described an anterior mandibular multilocular ameloblastoma in a 14-year-old boy, which in addition to typical follicular and plexiform patterns showed extensive fields of clear cell differentiation where normally stellate reticulum was expected. The tumor was treated by "conservative marginal resection with additional bone removal with burs." Examination 15 years later showed no recurrence. Because of this experience, the authors proposed to extend the family of ameloblastoma types to include a clear cell variant but cautioned that other nonodontogenic sources of clear cells must be ruled out (see later discussion).

In 1985, reports by Eversole and colleagues[141] and Hansen and colleagues[142] described and delineated the histochemical, ultrastructural, and clinical features of a rare, distinctive, aggressive odontogenic neoplasm, which they termed *clear cell odontogenic tumor* (CCOT). Although the lesions were aggressive, the authors were reluctant to characterize the CCOT as malignant, since none of the three cases evidenced regional or distant metastasis (parenthetically, between the time of Hansen and colleagues' original



• **Figure 18-20** Clear cell odontogenic carcinoma with recurrence. A 59-year-old man complained of a nontender swelling in the left retromolar pad area of the mandible. **A,** A panograph revealed an approximate 3 × 2-cm radiolucent lesion with fairly well-defined margins. Aspiration did not produce aspirant; however, a solid "gritty" tissue was felt. The mandible was exposed by an intraoral mucoperiosteal flap distal and proximal to the mass; however, the buccal and lingual mucosa overlying the lesion was firmly attached and appeared infiltrated by tumor. The tumor mass with intact overlying mucosa was enucleated from the mandible. It was noted that the tumor had involved the mylohyoid muscle and anterior lateral pharyngeal wall. **B,** Tissue sections revealed a clear cell odontogenic carcinoma with muscle involvement: **(C)** low power; **(D)** high power. **E,** Fourteen years later the patient, then 73 years old, was seen again with evident recurrence. A biopsy again showed clear cell odontogenic carcinoma. Computed tomography demonstrated a 2-cm tumor mass in the superior medial retromolar region of the mandible with bone involvement. There was no evidence of lymph node metastasis. A combined extraoral-transoral approach (with lip incision) permitted good visualization of the mandible and the mucosa-covered tumor mass. A reconstruction plate was contoured, fitted, and screwed to the mandible, and then removed and set aside for later use. Continuity resection was completed with adequate distal and proximal bone margins. The specimen included the mucosal extension of the tumor. The plate was attached to the mandible and the oral and extraoral wounds were closed. The patient subsequently had mandibular reconstruction with a cadaveric mandible. Examination of the patient 1½ years after the surgery revealed no recurrence.



• **Figure 18-20, cont'd** Tissue sections of the resection specimen demonstrated greatly increased squamatization of the tumor (**F,** low power; **G,** high power) with decreased evidence of clear cells (**H,** low power; **I,** high power) as seen in the first excision 14 years previously. (Case material courtesy David J. Furman, DDS, Huntsville, AL, and Herman M. Teachey, MD, Huntsville, AL.)

1985 report[142] and Eversole and colleagues' 1995 report,[143] one of the three patients died of recurrent disease).

Within several years, however, Bang and co-workers,[144] Fan and colleagues,[145] Milles and associates,[146] and Eversole and co-workers[143] had published well-documented and illustrated cases that recorded local, regional, and distant malignant and metastatic behavior of the clear cell tumor and justified a change in designation from CCOT to *clear cell odontogenic carcinoma* (CCOC). This abbreviated account undoubtedly omits some who have contributed to the recognition of the neoplastic potential of the odontogenic clear cell (see discussion by Hansen,[142] who credited Rick with assigning a diagnosis of clear cell odontogenic carcinoma to a puzzling case presented in a 1981 seminar). Although an uncommon tumor, the CCOC probably has been unrecognized, misdiagnosed, and/or unreported in the past.

Clinicopathologic Considerations

The CCOC offers no distinctive clinical aids for differential diagnosis. The age of affected patients extends from the fourth to the eighth decade, with a markedly biased occurrence rate in women over men in an approximate 4:1 ratio. Almost 75% of lesions are found in the mandible and 25% in the maxilla. The anterior mandible is the site of predilection, followed by the body and angle regions. The anterior area also is favored in maxillary lesions. Radiographically, lesions show a radiolucent unilocular or multilocular appearance, with poorly defined irregular borders. Imaging reveals evident bone destruction in small or large lesions. Tooth root resorption is seen in areas of lesional involvement (see Figures 18-20, *A* and 18-21, *A*).

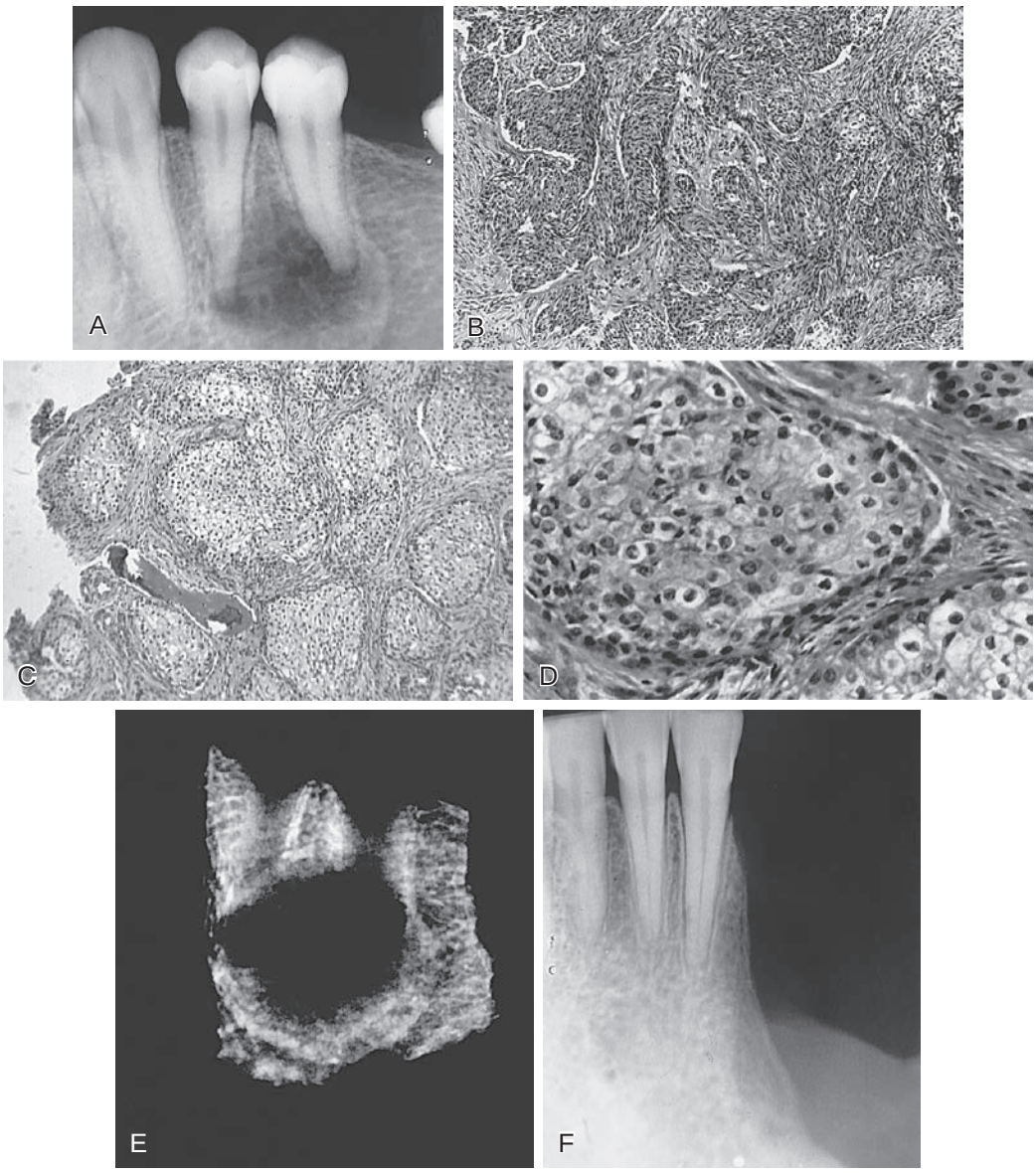
Presenting clinical symptoms and signs of the quiescent or slowly growing lesion are not diagnostic. Mild pain or discomfort may be experienced in the lesional region, with jaw enlargement and loosening of teeth in dentate areas of the lesion. Interestingly, none of the patients in the study by Eversole and co-workers[143] reported a sensory deficit.

Sudden and rapid jaw enlargement or massive swelling, without apparent provocation, usually signals overt, invasive, malignant behavior. Mandibular lesions may penetrate bone and infiltrate oral soft tissue and adjacent facial areas, including muscle and the cervical region.

Maxillary lesions may infiltrate and involve the nose, sinuses, orbit, adjacent zygomatic and facial bones, and skull base. Case reports illustrate cervical node metastasis as well as lung and liver metastases.

Some patients appear to have been successfully treated after local recurrence required further surgical procedures, and several appear to be living with disease. At least 5 patients have died of tumor—in some instances because of uncontrolled regional disease; in other instances patients have died after 7, 10, 18, or even 20 years with recurrent disease (see Figures 18-20 and 18-21).

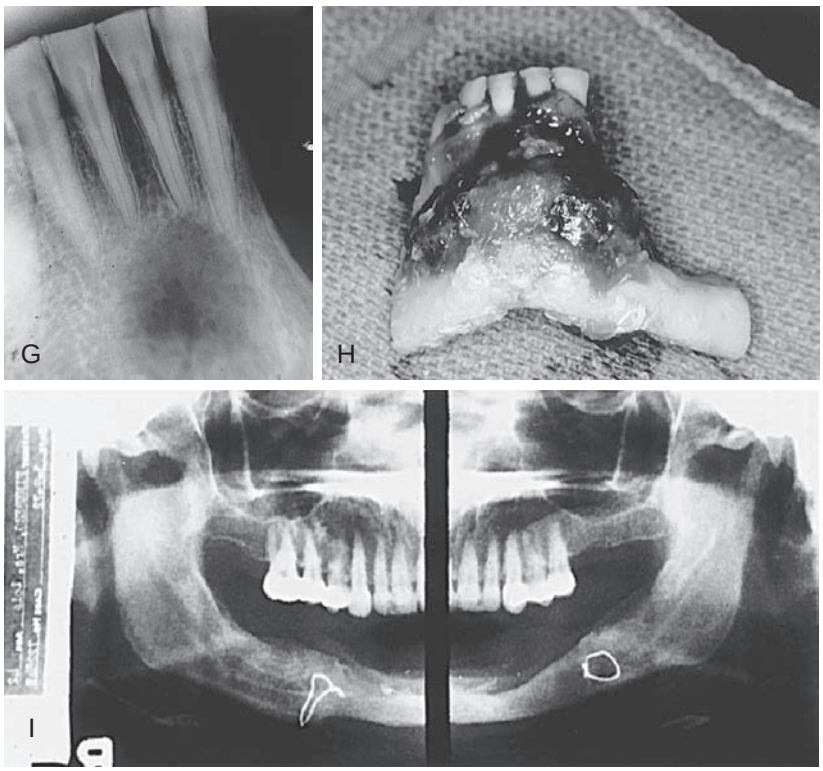
Histologically, the clear cell odontogenic carcinoma is primarily and prominently composed of small and large nests and islands of clear cells—cells that are ovoid or round and have vacuolated clear cytoplasm, with small, round, often eccentric, pyknotic nuclei and distinct cytoplastic borders. The clear cells exhibit bimorphic as well as



• **Figure 18-21** Clear cell odontogenic carcinoma with metastases. **A,** A 36-year-old woman was referred for treatment (May 1966) of a localized gingival swelling and radiolucent lesion in the left mandibular first and second premolar area. The lesion was enucleated and curetted, and the two teeth were extracted. It was noted that the bone walls were not smooth. A tissue diagnosis of ameloblastoma variant was made by the hospital pathologist. My interpretation conceded vague similarity to ameloblastoma but favored some form of odontogenic tumor with clear cells, specific entity not known. (A study of periodontal cysts in 1971 revealed clear cells similar to those of the tumor [see Figure 18-19].) **B,** Photomicrographs of the enucleated lesion demonstrated a biphasic tumor pattern of squamatoid islands admixed with clear cells **(C-D)** and a predominant pattern of clear cell follicles. **E**, Specimen radiograph of a limited resection without continuity defect performed within a month of the original procedure. The patient had frequent follow-up evaluation. **F,** Radiograph (Jan. 1967) of the anterior edge of the resection border showed no tumor.

polymorphic phases. Other tumor cells are polygonal and have cytoplasm with faint eosinophilia, and nuclei that are somewhat larger and vesicular. The bimorphic and polymorphic phases show strands, sometimes branching; more compressed and hyperchromatic appearing clear and squamoid cells; as well as squamous islands that are both innocuous and carcinomatous in appearance. Occasionally, clear cell islands exhibit reverse nuclear polarity and columnarization of peripheral cells lying against the basement membrane of the connective tissue stroma, similar to the peripheral cell arrangement of an ameloblastoma. The connective tissue stroma may be thin or somewhat dense and narrowly separate the islands of clear cells, or it may be more abundant in areas of the small nests and strands of tumor cells (see Figures 18-20 and 18-21).

The CCOC is seen to invade and resorb medullary and cortical bone as sheets and islands of tumor. Nests of clear



• **Figure 18-21, cont'd** **G,** Follow-up radiograph (Sept. 1967) showed anterior recurrence. A transoral resection (Nov. 1967) with continuity defect was performed from the mandibular right canine to the left second molar area (frozen sections of bone marrow curetted from the left resection end showed no tumor), with an immediate autogenous iliac crest graft. **H,** Specimen section, and **(I)** periodic panographs taken in 1972. Almost 9 years later (1976), a lung scan revealed a 1.5 × 2.0 cm tumor nodule in the left lung lingula and a lesion in the sixth rib. Rib resection was done and a course of chemotherapy was given.

Continued

cells infiltrate bone at some distance from the main tumor mass, as well as soft tissues after the bone barrier is breached.

Mitotic activity may or may not be present, either in the primary lesion or in the metastatic deposits. A diagnosis of malignancy is not dependent on the mitotic index of the tumor. CCOC is a de novo malignancy from onset.

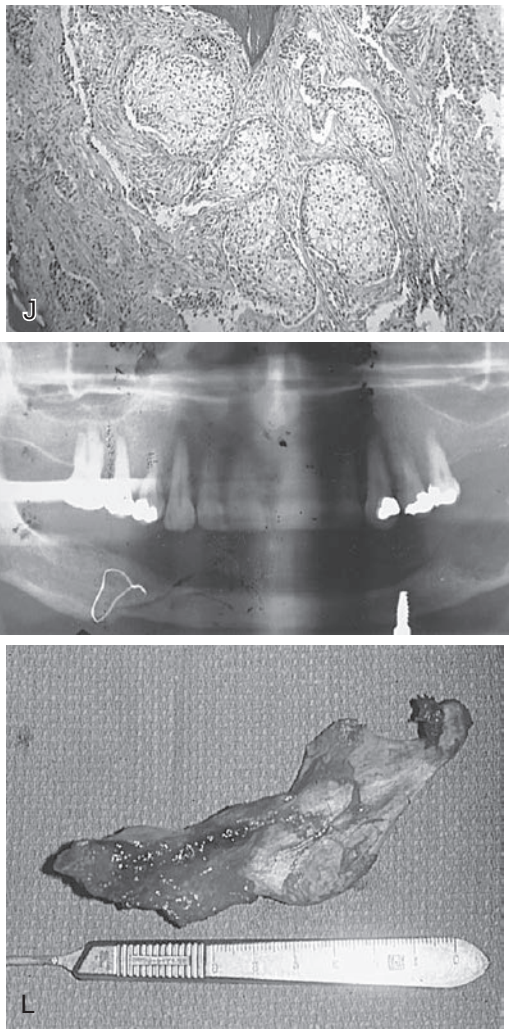
The lesion called clear cell ameloblastoma is well illustrated in reports by Waldron and associates[16] and Müller and Slootweg.[140] In addition to the varied forms of clear cell islands previously described, conventional ameloblastic follicles incorporate clear cells that replace the stellate reticulum. The columnarization and reversed nuclear polarity of peripheral clear cells in some clear cell nests, the coexistence of clear cell islands and conventional ameloblastoma in the clear cell ameloblastoma, and histologically dysplastic ameloblastomatous configurations appear to point to a relationship between a "pure" CCOC and ameloblastoma. Is there a question of homology? Is CCOC a more embryologically dedifferentiated and virulent form of ameloblastoma, or is CCOC a distinct lesion that may, to an extent, neoplastically differentiate toward ameloblastoma? In either respect, it is apparent that the appearance of clear cells within a nominally conventional ameloblastoma confers further aggressive biologic behavior and metastatic capability.

Clear cell nests described in CEOTs[59,137-139] prompt similar questions. Is there a numerical percentage of clear cell islands in a CEOT necessary to convert a tumor from CEOT with clear cells to a CCOC with Pindborg features, and does the presence of calcifications and/or amyloid preclude a diagnosis of CCOC? There have not been sufficient cases with follow-up evaluation to answer these questions.

Discrimination between CCOC and other lesions containing or primarily composed of clear cells may present a differential diagnostic problem. The neoplasm may histologically resemble a number of clear cell adenocarcinomas of salivary gland origin,[147] squamous cell carcinoma with clear cells (also glycogen containing), or metastatic adenocarcinomas (e.g., kidney, ovary). The cells of CCOC demonstrate glycogen (strongly or weakly) in frozen sections with periodic acid-Schiff (PAS) and diastase digestion staining and are mucicarmine negative. Immunohistochemical staining variably discloses cytokeratin, epithelial membrane antigen, and S100 protein.[143]

Management

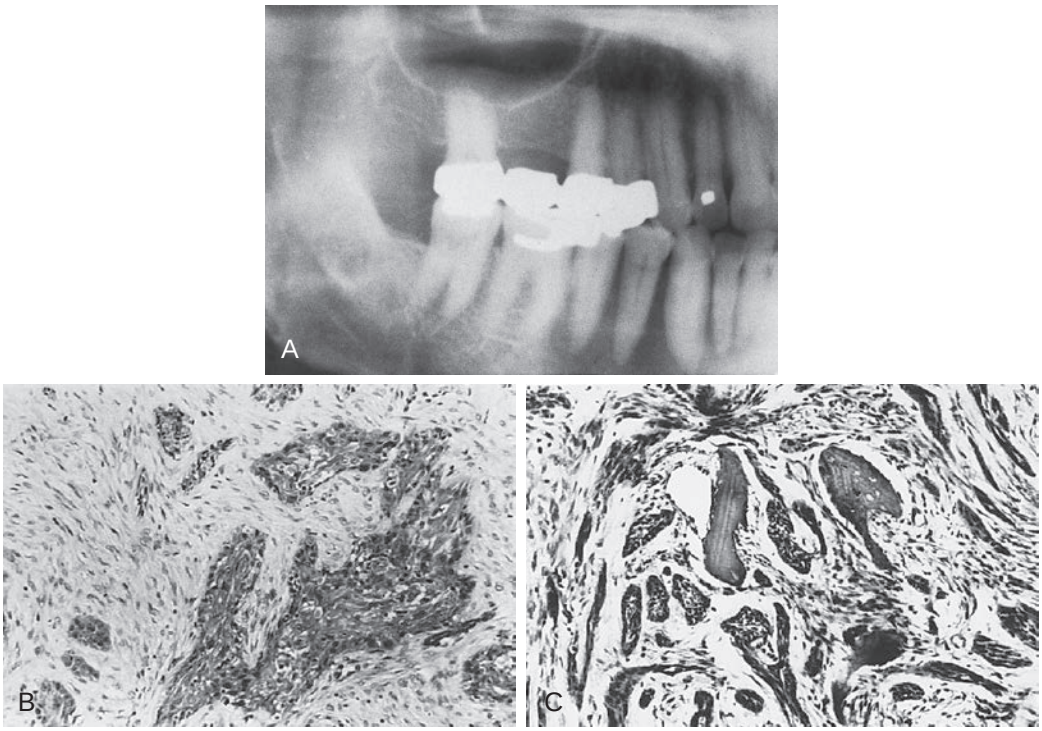
The preceding discussion is explicit: CCOC should be regarded as a de novo malignant odontogenic neoplasm, capable of uncontrolled local and regional growth and regional and distant metastases. The 1995 tabulation of CCOC cases by Eversole



• **Figure 18-21, cont'd** **J,** Tissue sections from the rib demonstrated metastatic clear cell odontogenic carcinoma. **K,** Four months later clinical and radiographic examination revealed recurrence at the left (proximal) end of the graft. **L,** A left mandibular resection with continuity defect from the premolar area with disarticulation was done (Oct. 1976). No further reconstruction was considered. The patient's facial form was little affected, and the patient remained free of local tumor until her death 18 years after discovery of the oral lesion. The cause of death was considered to be progressive tumor disease and cardiac myopathy (autopsy was not performed).

and co-workers[143] showed, in addition to other details, that 4 of 14 patients died of disease within a 7- to 21-year follow-up period. A suggested management protocol is offered, supported by known characteristics and probable behavior of the lesion:

- Rule out metastatic disease and regional tumors that histologically simulate CCOC.
- Microscopic assessment of malignancy should not be based on the presence or absence of mitoses.
- CCOC, from the time of discovery, should be considered malignant and a potential metastasizing tumor.
- Ameloblastoma with microscopic evidence of ameloblastic atypia and a substantial clear cell component should be regarded as a CCOC.
- The position of CEOT with a substantial clear cell component has not yet been clearly established in the spectrum of CCOC lesions.[58-61] It appears best to regard such a lesion as malignant.
- The lesion must be resected aggressively.
- A definitive first surgical procedure offers the best opportunity for cure.
  - Resection should be guided by preoperative CT and/
  - Sacrifice neural structures in proximity to the lesion and soft tissue overlying cortical bone penetrated by the lesion.
  - Bone and soft tissue resection must maintain wide tumor-free margins in all dimensions to the extent, or beyond, that is recommended for ameloblastoma.

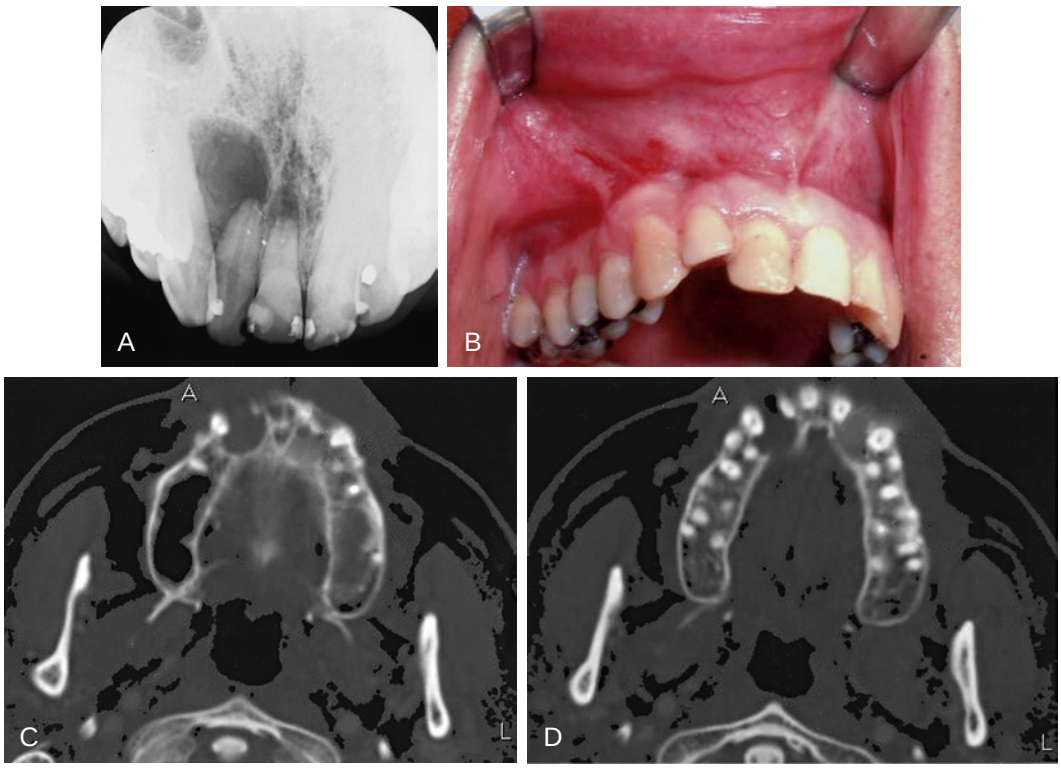


• **Figure 18-22** Intraosseous odontogenic squamous cell carcinoma. **A,** Panograph of a 67-year-old man who was seen by his dentist for a nonpainful, elevated, smooth mass in the right lateral mandibular canine-premolar alveolar ridge area. Under local anesthesia, five teeth were removed and the lesion was enucleated. **B,** A microscopic diagnosis of squamous odontogenic tumor was made. Eight months later, the patient was seen because of pain at the surgical site. A radiograph showed an ill-defined lesion. A biopsy was performed, and a microscopic diagnosis of acanthomatous ameloblastoma was given. The patient was referred to the University of Nebraska Medical Center, Department of Oral and Maxillofacial Surgery. On the basis of the biopsy report and radiographic appearance, a resection without continuity defect and immediate bone graft was performed. **C,** Tissue slides of the decalcified specimen showed cords and islands of epithelial cells with a hint of palisading, admixed with fragments of resorbed bone, consistent with a pattern of well-differentiated squamous cell carcinoma. A recommendation for mandibular resection and radical neck dissection was declined by the patient. Eleven months later, the patient complained of pain in the right mandible. A panograph showed a pathologic fracture and an ill-defined radiolucency. In the following month, numbness occurred in the right mandible. Examination showed a fungating mass in the anterior mandible. Bone scan revealed probable metastases in first lumbar vertebra, manubrium, second rib, and mandible. Combined chemotherapy and radiation therapy did not alter the progress of the disease. The patient died 38 months after first being seen. (From Ruskin JD, Cohen DM, Davis LF: Primary intraosseous carcinoma: report of two cases, *J Oral Maxillofac Surg* 46:425, 1988.)

- Follow-up and periodic visits should be scheduled every 3 months for the first year, every 6 months for the next 5 years, and yearly thereafter for more than 20 years.

Intraosseous Odontogenic Carcinoma

Intraosseous odontogenic carcinoma (IOC) is a malignant epithelial squamous cell tumor (squamous cell carcinoma) derived from odontogenic epithelium within the jaws (Figures 18-22 and 18-23). This definition explicitly excludes carcinomatous intraosseous involvement (invasion) of the jaws from nonodontogenic sources. The concept and proof of IOC has evolved over this century by publication of case reports, critical reviews, and analyses of case series, and by suggestions and arguments for an improved classification first enunciated by the WHO.[12] A number of writers have contributed greatly to this effort (including Shear,[148] Gardner,[149] Eversole and co-workers,[150] and Elzay[151]). The term primary intraosseous odontogenic carcinoma (PIOC) in the WHO classification indicates IOC derived from odontogenic rests only, excluding other IOCs derived from cysts or tumors; however, in Elzay's modification of the classification[151] PIOC represents the entire gamut of IOC lesions, which are then categorized into types and subtypes. Elzay's modification of the WHO classification was intended to permit closer scrutiny and study of cases of IOC. A further useful modification was presented by Waldron and Mustoe.[152] In its strictest sense the word *primary* implies the archetypical primordial odontogenic epithelial cell; however, even odontogenic rests represent an advanced



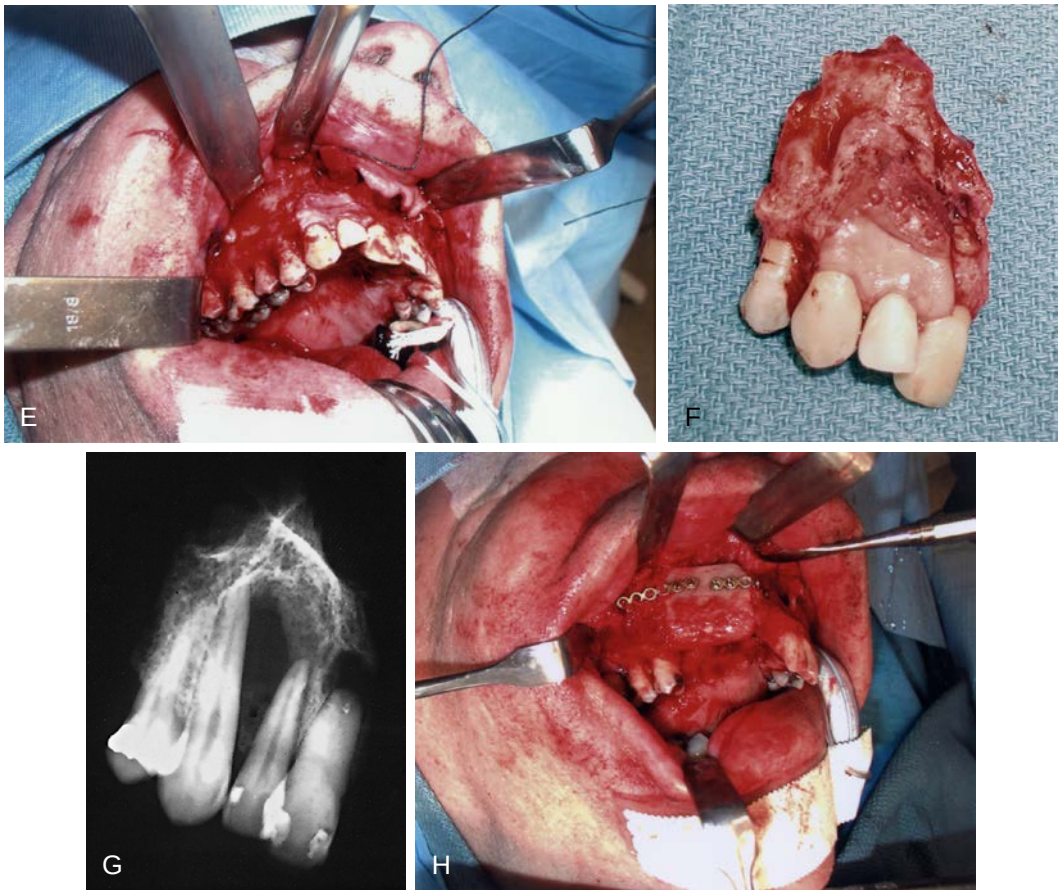
• **Figure 18-23** Intraosseous odontogenic squamous cell carcinoma with clear cells versus clear cell odontogenic carcinoma with squamatization. A 66-year-old man was seen in a practitioner's office complaining of "pain in his two upper front teeth with looseness of one for the past year." **A,** An occlusal radiograph showed a small periapical radiolucency over the carious maxillary right central incisor and a well-circumscribed significant radiolucent lesion between and above the diverging roots of the lateral incisor and canine teeth. The patient had a retrograde endodontic procedure and curettage on the central incisor and an incisional biopsy of the maxillary lesion, performed in the office (Jan. 2006). A microscopic report of "ameloblastoma with atypia" was received for the maxillary lesion, and acute and chronic inflammation for the periapical central incisor area. The patient was referred to Thomas Jefferson University, Department of Oral and Maxillofacial Surgery, for definitive treatment. **B,** Examination of the patient showed a modest, diffuse swelling with a slight central depression in the well-healed surgical site of the anterior maxilla, and a displaced right lateral incisor. The canine, lateral and central, exhibited decreased sensation on palpation. A restudy of the biopsy microscopic slides and further sectioning of the biopsy tissue block resulted in an amended diagnosis of odontogenic carcinoma. Panographic, computed tomographic, magnetic resonance, and positron emission tomography (PET) scan imaging did not reveal evidence of local or regional metastasis.**C**-**D,** The maxillary radiographs revealed labial and palatal cortical bone perforation, with a questionable overlying soft tissue component.

developmental progression. Therefore, further clarity can be achieved by elimination of the word *primary*. The senior author (L.G.) has previously expressed his opinion of the fallacies of the WHO classification as it relates to ameloblastoma in the preceding discussion of that lesion. This entire area still calls for clarification and simplification.

Reports published in the first half of this century considered IOC to be rare, but by the late 1990s the number of published reports showed that it is not rare but uncommon. In addition, extensive literature on IOC has accumulated, and critical analyses by writers have eliminated many reports for lack of convincing evidence; still a continual culling process has maintained many acceptable instances of IOC. Yet, even as more cases of IOC are presented, critical examination and proof of validity should continue to be demanded.

The sources of nonodontogenic carcinomas that invade the jaws are well known, and for obvious clinical reasons nonodontogenic carcinomas should be differentiated from intraosseous carcinoma of odontogenic origin. Nonodontogenic sources include carcinoma originating in the oral mucosa, maxillary sinus, nasal mucosa, submucosal salivary glands, intraosseous salivary gland inclusions, and metastasis from a distant primary site.

It should be noted that a surface mucosal carcinoma may arise in an unseen crypt or ulcer and directly invade underlying bone without apparent surface involvement, or a maxillary sinus carcinoma may involve the tooth-bearing segment of the maxilla before detection, and a submucosal salivary gland malignancy can invade bone without surface indication. Carcinomas from nonodontogenic sources may also be confused with odontogenic lesions (such as



• **Figure 18-23, cont'd** **E,** A partial maxillary resection without continuity defect was performed (Mar. 2006). The resected specimen consisted of a block of the right anterior maxilla incorporating the right central incisor to the right first premolar and measured 5 cm from the teeth to the floor of the maxillary sinus, pyriform rim, and nasal spine. **F,** The specimen was 2 cm thick from anterior to posterior and included the palatal bone and periosteum. Soft tissue from all borders was taken for frozen sections, as well as peripheral bone for later sections. **G,** An intraoperative radiograph of the specimen was taken to help confirm adequate bone margins. **H,** The maxillary defect was reconstructed with an iliac crest cancellous bone block and iliac cortical bone chips overlaid with platelet-rich plasma and secured with small reconstruction bars. The soft tissue was generously undermined, permitting a tension-free closure.

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histologic misinterpretation of adenoid cystic carcinoma for ameloblastoma or a maxillary sinus lesion that collides with a dentigerous cyst and thus obscures origin) or with metastatic lesions (which may simulate an odontogenic carcinoma).

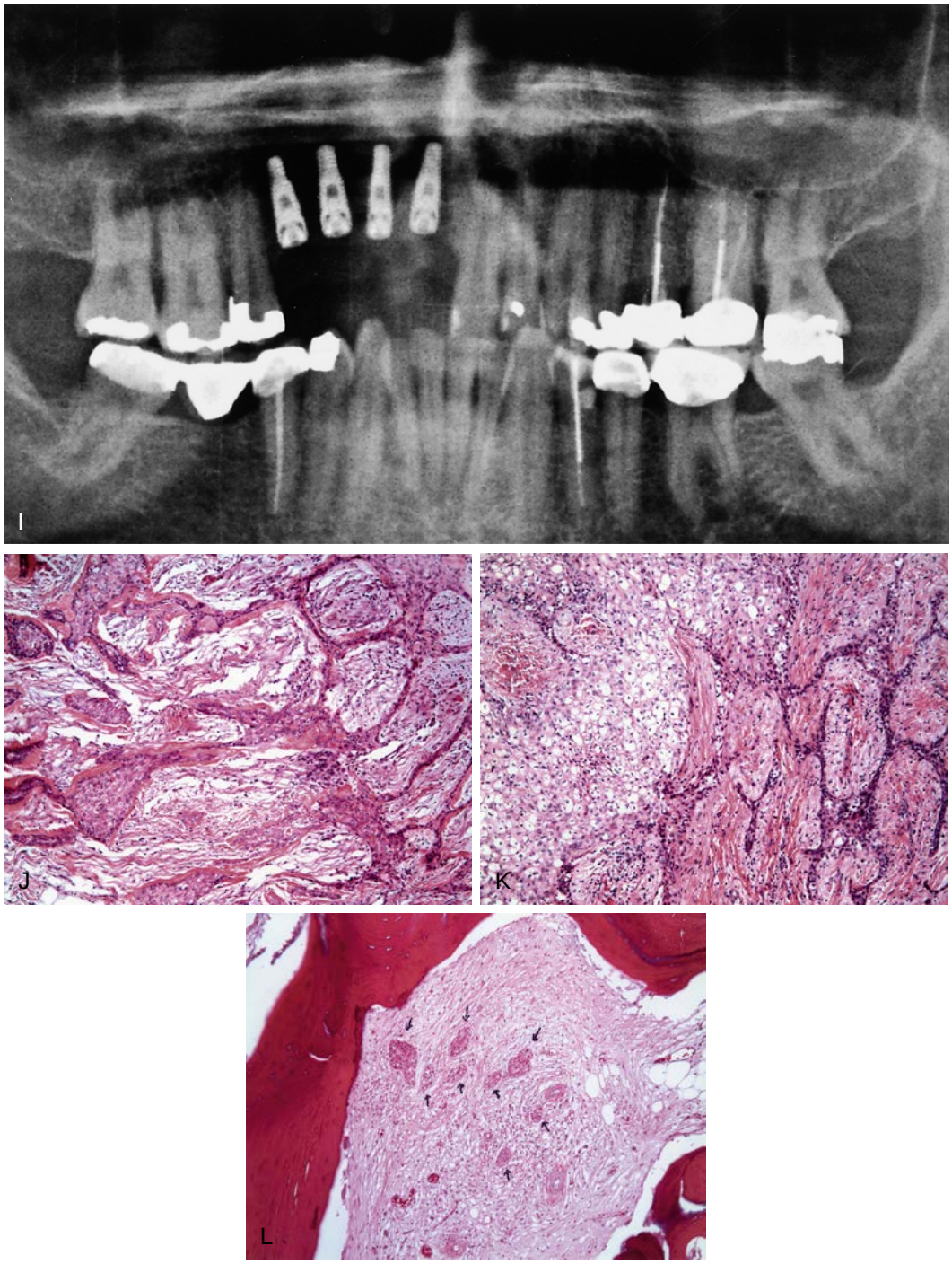
After elimination of nonodontogenic sources of intraosseous carcinoma, a malignant epithelial neoplasm may be considered to have an odontogenic origin, principally originating in endosseous epithelial residue remaining after tooth development or in the epithelial lining of odontogenic cysts[153] and epithelial odontogenic neoplasms.

Intraosseous Carcinoma from Odontogenic Residue

IOC derived from endosseous epithelial "residue" by definition must include rests scattered in the medullary bone areas of the jaws, as well as those in the periodontal ligament and epithelial rests within follicular sacs. Proof of such origin may be difficult or impossible, since many lesions have a predominant squamous cell carcinoma pattern, not distinguishable from a surface mucosal source. If a lesion has odontogenic epithelial histologic characteristics in addition to a squamoid appearance, the possibility of a high-grade ameloblastoma cannot be excluded. As with all IOCs, careful clinical and radiographic documentation is necessary, especially since there is no histotypic appearance of IOC derived from epithelial rests.[40,152,153]

Intraosseous Carcinoma from Odontogenic Cysts

Numerous case reports have been published that describe origin from a variety of preexisting odontogenic cysts,[153] including dentigerous,[154-160] residual,[161,162] and keratocyst.[163,164] In addition to exclusion of carcinoma from nonodontogenic sources, photomicrographs must convincingly illustrate the histologic conversion of innocent epithelial cyst lining to a malignant epithelial lining or carcinomatous proliferation.



• **Figure 18-23, cont'd** **I,** Healing was uneventful, and implants were placed 6 months later. **J,** Gross sectioning of the specimen revealed a white-tan to red-brown, rounded, well-circumscribed tumor composed of numerous strands and nests of atypical squamous epithelium in a fibrous stroma and **(K)** large areas of clear cells admixed with squamous epithelial islands and strands also containing clear cells exhibiting mild atypia. The squamous epithelial strands are encased by homogeneous collagen. Scattered mitotic figures are present. **L,** Note small tumor nests in the bone separated from the main tumor mass. A cytokeratin stain (AE1/AE3) is especially positive in clear cell areas. These features support a diagnosis of intraosseous odontogenic squamous cell carcinoma with clear cells or clear cell odontogenic carcinoma with a squamatization. (Case material courtesy Robert J. Diecidue, DMD, MD, Thomas Jefferson University, Philadelphia.)

Intraosseous Carcinoma from Epithelial Odontogenic Tumors

All epithelial odontogenic tumors previously discussed in this chapter are theoretically capable of conversion to an IOC, and two should be considered IOCs from inception.

The *squamous odontogenic tumor* is a possible precursor of IOC. In one interesting, detailed report, an IOC was first histologically misinterpreted as squamous odontogenic tumor before clinical events led to a correct diagnosis.[44] Conversely, a squamous odontogenic tumor arising in a keratocyst was first incorrectly diagnosed as squamous cell carcinoma,[40] and a report of squamous cell carcinoma arising in a periodontal cyst is probably a cyst with SOT.[41]

In the discussion of *ameloblastoma*, the senior author (L.G.) expressed his opinion that ameloblastoma is a de novo low-grade malignancy, and that instances of conversion to a high-grade malignancy with metastasizing capability is not unexpected.

Since the 1980s the former clear cell odontogenic tumor, now properly termed *clear cell odontogenic carcinoma,* has demonstrated its position de novo as an IOC with metastasizing capability. The *clear cell ameloblastoma* described by Waldron and colleagues[16] combines odontogenic clear cells with ameloblastoma into a single IOC entity.

Malignant calcifying epithelial odontogenic tumors with and without a prominent clear cell presence have been documented.[61-63] Several malignant and metastasizing variants of *calcifying odontogenic cyst or tumor* have been reported under the names *odontogenic ghost cell tumor* and *ghost cell carcinoma.*[165-167]

Clinicopathologic Considerations and Outcome

The outcome of IOC is influenced by several factors—patient recalcitrance and refusal to be treated, time of discovery during the course of the lesion's development, correct (or incorrect) diagnosis, and definitiveness (or nondefinitiveness) of the initial surgical procedure appropriate for the cli

lar
higher occurrence in males than in females and in the mandible (particularly the posterior areas) rather than in the maxilla by a high ratio.

Signs, symptoms, and radiographic features are case specific. Patients may be seen with or without extraoral and/or intraoral swelling, or clinical evidence of metastasis. Pain is variably present. Edentulous patients may complain of inability to wear dentures because of pain or swelling. Paresthesia is an inconstant finding in mandibular lesions.

Radiographically, IOCs are radiolucent, sometimes suggestive, but not pathognomonic. They present a differing image dependent on the progression of the disease—from well-outlined radiolucencies to diffusely infiltrating lesions. IOCs that develop in odontogenic cysts may be innocuous in appearance.

Histologically, IOCs may not be suspected and may be a surprising microscopic finding after excision. All cystic lesions that show "skip" areas of unaffected odontogenic epithelial lining alternating with areas of dysplastic to malignant epithelial lining, which may not be detected if insufficient sections are prepared. A report by Suei and co-workers is recommended for a discussion of diagnostic criteria.[168]

The outcomes of IOCs presented in published reports vary from apparent cure to protracted clinical course and fatal outcome, whereas some lesions are rapidly aggressive and lead to death with or without metastases. Cases demonstrate that conservative operations fail. An exception can be made for the instance of an odontogenic cyst in which only the epithelial lining shows malignant change, without involvement of the cyst wall. Early recognition and definitive oncologic procedures may result in successful management.

Mesenchymal Odontogenic Tumors

Odontogenic Fibroma

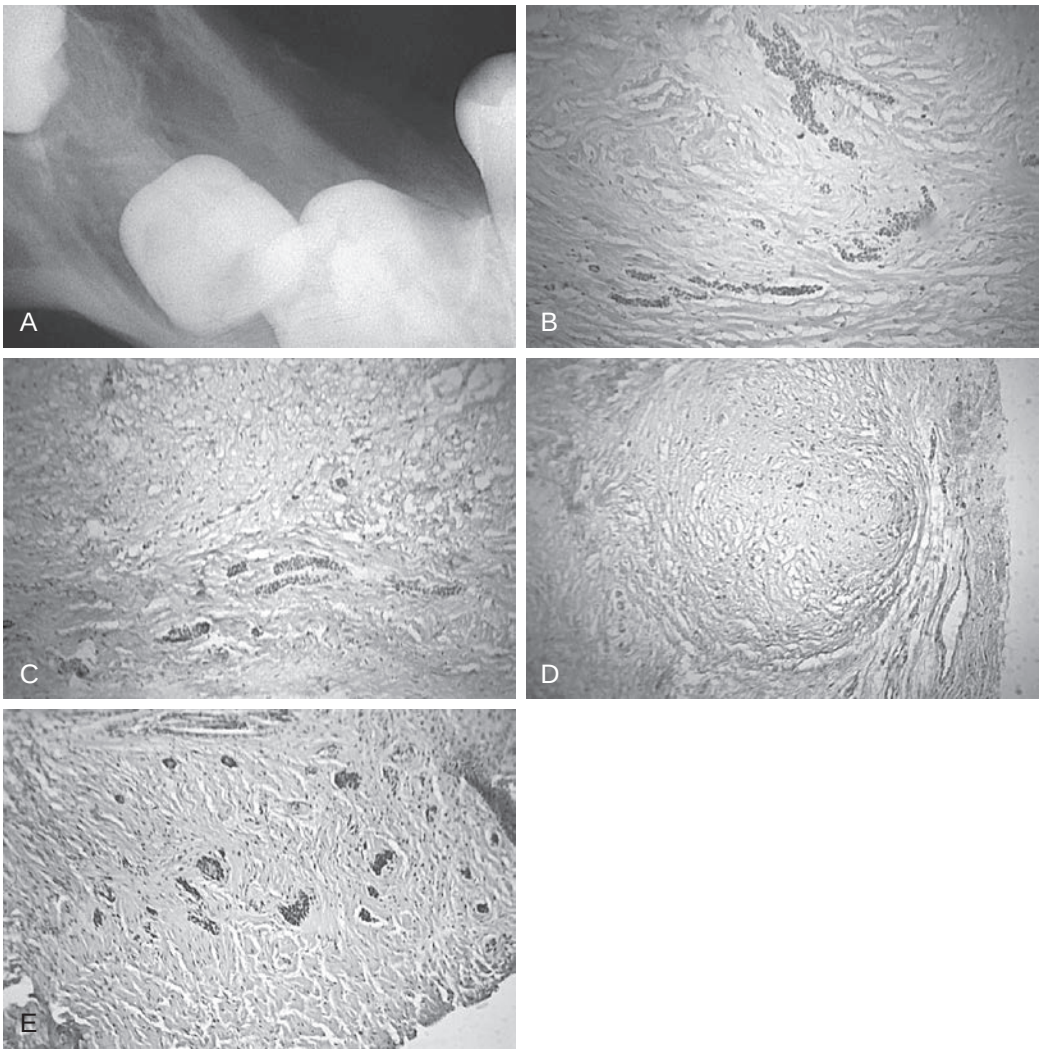
The WHO classifies *odontogenic fibroma as a benign, relatively rare connective tissue tumor that contains a variable amount of inactive odontogenic epithelium.*[11-13] The monograph's explanatory notes recognized that the parameters of the lesion were still evolving and that variants under this designation might, or might not, be acceptable in the future. Present convention finds it expedient to permit some flexibility in the histologic composition of odontogenic fibroma, especially since all agreed-upon types of the lesion pursue a benign behavioral course. The odontogenic fibroma is found intraosseously—*central odontogenic fibroma*—and extraosseously, on the gingiva—*peripheral odontogenic fibroma.*

Clinicopathologic Considerations

The infrequent occurrence of central odontogenic fibroma (Figure 18-24) is illustrated by Regezi's 1978 analysis[169] of 706 odontogenic tumors, which included 12 categories of lesions but did not record an odontogenic fibroma, and by Gorlin and co-workers' 1963 classification and extensive discussion[170] of odontogenic tumors, which also omitted the lesion. However, in 1970 Gorlin's discussion of odontogenic tumors[171] included the odontogenic fibroma and provided a succinct description of the lesion. The intraosseous lesion is not inconsequential and, despite benign behavior, may be responsible for significant tissue destruction.

Central Odontogenic Fibroma

The clinical features and analysis of a large series of central odontogenic fibroma[172-176] show a wide age range at identification from 14 to 72 years, with a mean of approximately 37 years. There appears to be a striking female occurrence and predilection for the maxilla, anterior to the first molar. Most lesions are asymptomatic and are discovered by radiograph; however, occasional clinical enlargement and root resorption produce discomfort.

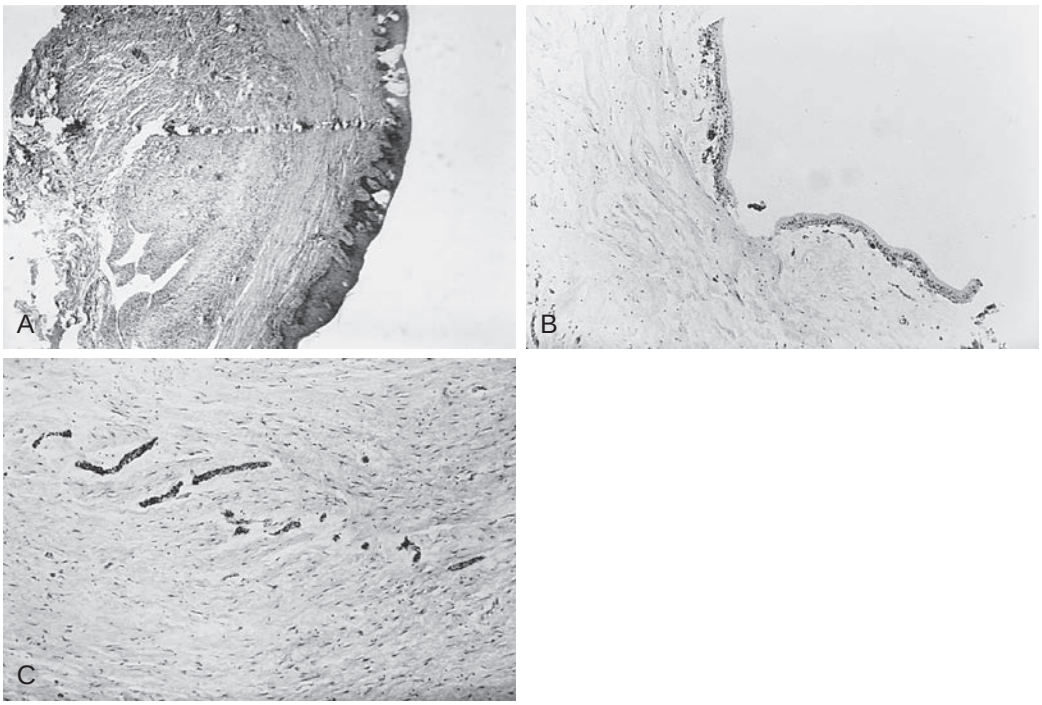


• **Figure 18-24** Central odontogenic fibroma of mandible. A 13-year-old girl was seen for a gingival enlargement and noneruption of mandibular right first and second molar teeth. **A,** Radiographs showed the two molars and the developing third molar to be displaced and enveloped by a poorly delineated soft tissue lesion. A somewhat gelatinous soft tissue mass was excised by a combination of enucleation and curettage, and the three teeth were removed. The first and second molars appeared malformed. **B**-**C,** Tissue sections revealed slightly varying morphologic characteristics of myxoid-appearing connective tissue with scattered strands of odontogenic epithelium and odontogenic epithelial rosettes, **(D)** several whorled areas of myxomatous connective tissue surrounded by denser connective tissue, and **(E)** peripherally more dense collagenous tissue containing scattered small epithelial rosettes. The lesion was not encapsulated.

Radiographically, odontogenic fibroma is generally radiolucent and multilocular, although unilocular lesions are not unusual. The lesion may have a well-defined sclerotic outline or an ill-defined nonsclerotic border that merges into surrounding bone as if infiltration is occurring. Lesions in dentate areas are frequently associated with the roots of teeth and may cause extensive root resorption or root divergence (see Figure 18-24, *A*). Several large lesions have been associated with unerupted third molars, and infrequently, radiopacities may be seen in a lesion.

The histologic composition of odontogenic fibroma varies and is perhaps a reflection of the histologic sources of the lesion. Origins in the dental papilla, follicular sac, and periodontal membrane have all been proposed and indeed may be a reasonable explanation for the different histologic patterns encountered in the lesion.

The connective tissue stroma may exhibit a whorling or interlacing dense collagen matrix and a hypocellular or fairly cellular uniform fibroblast population, or may show a somewhat loose fibrillar or myxoid background. The odontogenic epithelial component is scattered throughout the connective tissue as narrow islands, strands, or cords of cuboidal or slightly polygonal cells. Most notable is the obvious passivity of the epithelium, which lacks an ameloblastic appearance. Very occasionally an inductive-like hyalinization effect is seen in the connective tissue around some epithelial islands, and even cementum-bone-like or dentinoid-like calcification. Some lesions have a sparse odontogenic epithelial population,



• **Figure 18-25** Follicular sac. Hyperplastic myxomatous or fibromyxomatous tissue of follicular sacs may be misinterpreted occasionally as odontogenic fibroma or myxoma. Radiographs and clinical findings should be submitted to the pathologist to prevent such an occurrence. **A,** Follicular tissue and overlying mucosa excised with a rudimentary supernumerary tooth from the anterior palate of an infant. Enlarged follicular sac removed during surgical exposure of an impacted maxillary canine. **B,** Note reduced enamel epithelium that covered the canine crown, **(C)** along with larger mass of the follicular sac containing scattered odontogenic epithelial rests.

whereas others show a profuse odontogenic epithelial proliferation, to a degree that overshadows the connective tissue. The odontogenic fibroma is not encapsulated, and the intraosseous lesion either is circumscribed or merges with the surrounding bone (see Figure 18-24, *B-E*).

Peripheral Odontogenic Fibroma

The peripheral odontogenic fibroma mirrors the central lesion in histologic appearance. However, a compilation of case reports and studies[143,169-180] shows that the extraosseous lesion is found more frequently in the mandible than in the maxilla and affects males and females almost equally. There is a wide age range of occurrence from the first to the eighth decade. Most lesions are found anterior to the second premolar and measure between 1 cm and 3 cm in diameter. The lesions are always on the attached gingiva, are pedunculated or sessile, and have a normal gingival color. Large lesions may displace teeth but do not usually involve the underlying bone. Radiographs reveal calcification in the peripheral lesion more often than in the central lesion. It is probable that the gingival lesion described as *odontogenic epithelial hamartoma*[181] is an exuberant expression of peripheral odontogenic fibroma.

Differential Diagnosis

The hallmark of the odontogenic fibroma continues to be the presence of inactive odontogenic epithelium, whether sparse or profuse, in a connective tissue stroma, which varies from dense to loose. The production of a small amount of a cementum-like or dentin-like calcification does not mitigate against this diagnosis. Two thoughtful reports by Gardner,[182,183] in 1980 and 1982, sought to resolve some of the conflicting opinions regarding the histologic composition of odontogenic fibroma. He proposed that two forms of the lesion be recognized—a *simple central* or *simple peripheral type* and a WHO *central* or WHO *peripheral type.* However, most recent writers believe that these designations are unnecessary additions to the nomenclature.

Diagnostic distinction should be made between odontogenic fibroma and other central connective tissue lesions that do not contain epithelium, such as desmoplastic fibroma and myxoma, both of which are more aggressive than odontogenic fibroma. The ameloblastic fibroma does contain odontogenic epithelium in addition to an active fibromyxoid connective tissue stroma; however, the epithelium in this odontogenic mixed tumor is an active and proliferative component that histologically simulates an ameloblastic or dental lamina appearance. The ameloblastic fibroma is also more aggressive than odontogenic fibroma. The follicular sac surrounding the crown of an unerupted tooth also contains both odontogenic epithelium and connective tissue and, if hyperplastic, may be misinterpreted as an odontogenic fibroma or myxoma, a not infrequent error (Figure 18-25).

Management

Odontogenic fibroma is a benign lesion, small or extensive, and probably has finite growth potential. However, recurrences or, in most instances, regrowth of residual lesions have been reported for both central and peripheral forms.[173,180,184] It is also possible that in very rare instances, central odontogenic fibroma may exhibit marked infiltrative behavior similar to that of fibrosarcoma.[173] Thus, each lesion must be carefully assessed histologically.

Central Odontogenic Fibroma

Excision is dependent on the clinical extent and anatomic involvement of the individual lesion. Most lesions can be managed by a combination of enucleation and curettage. Rarely is a resection procedure required. If the tumor incorporates the mandibular neurovascular bundle, an attempt should be made to preserve it. Teeth in the lesional area should be removed.

Peripheral Odontogenic Fibroma

The lesion should be excised to the interface with bone and a modest perimeter of uninvolved tissue. Teeth that are obviously incorporated in the tumor should be removed.

Cementoblastoma

Cementoma is the time-honored designation for connective tissue lesions of the jaws that produce cementum-like or osteocementum-like calcifications. It has long been recognized that the term *cementoma* encompasses several pathologic entities that overlap and bear histologic similarities to each other but should be separated on clinicopathologic bases.[171,185] As often occurs, lesions that have similarities and are extensively studied and recorded over time generate a confusing array of terms until some acceptable consensus is achieved to bring order to seemingly disparate pathologic processes (e.g., cementoma, periapical cemental dysplasia, florid osseous dysplasia, multiple cemento-ossifying fibroma, gigantiform cementoma, cementifying fibroma, and chronic sclerosing osteomyelitis). Presently it is accepted by most oral and maxillofacial pathologists that such lesions

[186,187]

seen that calcifications histologically similar to cementum or osteocementum are found also in fibro-osseous lesions of the paranasal sinus area and craniofacial bones and, therefore, may originate from the endosteal connective tissue of medullary bone as well as connective tissue of the odontogenic apparatus. The fibro-osseous lesions of ossifying fibroma and cemento-osseous dysplasia are not considered here. The cementum-forming odontogenic tumor is considered.

The cementoblastoma (also called true cementoma) is an uncommon, perhaps rare, odontogenic tumor of connective tissue forming cementum-like calcification, fused to a tooth root.

Clinicopathologic Considerations

The cementoblastoma occurs with almost equal frequency in the mandible or maxilla, and always in the premolar or molar region. Most cases are found within the second decade, and without a gender predilection. The lesion tends to grow slowly by expansion and eventually produces a clinical enlargement that sometimes resorbs the lateral and medial cortical bone. Discomfort or pain is a not-uncommon clinical symptom. Palpation of the tooth involved in the lesion, or palpation of the hard lesion underlying the mucosa, is painful. Paresthesia is not present, and the affected tooth is frequently vital.[188,189] Lesions range in size from 0.5 cm to 5.5 cm in diameter and may involve the maxillary sinus and orbital floor.[190]

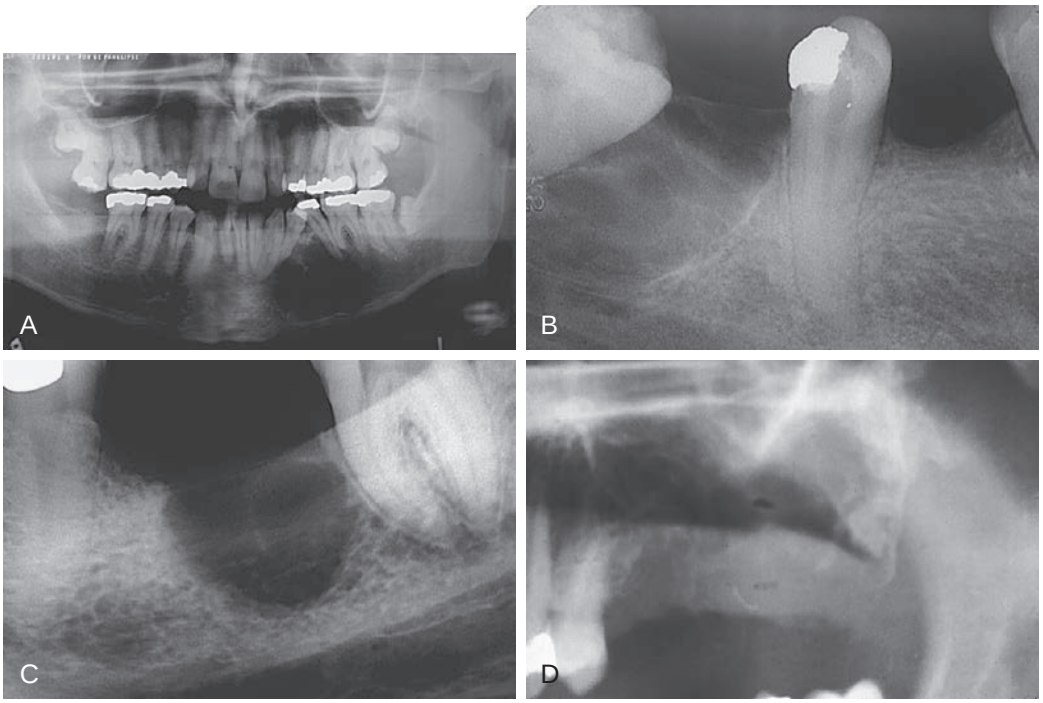
Radiographically, the cementoblastoma presents a well-defined round or oval calcified mass attached to the root of a tooth, which may show obvious resorption. The central area of the lesion may be uniformly dense or slightly mottled, and the more peripheral calcified regions may exhibit a radial distribution. The border of the lesion is usually radiolucent and sharply demarcates the lesion from the surrounding medullary bone[189,191]

Histologically, a dense cemental or osteocemental mass, with numerous reversal lines, forms a calcified mosaic pattern and occupies the central areas of the lesion. Entrapped cells are sparsely scattered within the cementum. At the edges of the dense calcified masses, an active vascular fibroblastic connective tissue stroma, with little collagen and dilated thin-walled vessels, forms large hyperchromatic cementoblasts that line the cementoid (osteoid) seams of the calcifying trabeculae; multinucleated giant cells lie in trabecular lacunae and appear to be simultaneously remodeling the trabeculae. The outermost peripheral trabeculae are not well mineralized and adjoin a narrow border of fibrous connective tissue that separates the lesion from the adjacent medullary bone. The lesional areas that fuse directly with the resorbing dentin of the root replace the periodontal ligament at the junction and may even invade the pulpal tissue[188,189,191-193]

The cementoblastoma parallels the histologic characteristics of the *osteoblastoma* and may represent the cemental analogue of that endosteal bone tumor.[194] Both lesions share an active vascular calcifying tissue and are differentiated by the radiographic and cemental appearance of the former and the obvious bone trabeculae of the latter. Differentiation between osteoblastoma and *osteoid osteoma* is based on the latter's more cortical position, small size, and histologic and radiographic features of a small central soft tissue nidus surrounded by sclerotic bone.

Management

The number of reports in the literature that strictly define the cementoblastoma according to age, site, clinical symptoms,



• **Figure 18-26** Odontogenic myxoma. **A-C,** Several radiographic patterns seen in odontogenic myxoma of the mandible and **(D)** maxilla with sinus involvement.

radiographic identification, and histologic appearance testify to its apparent slow growth and benign nature. The size of the lesion varies but is usually between 1 cm and 3 cm in diameter and is almost always separated from surrounding bone by a surgically discernible capsule-like connective tissue, permitting enucleation after exposure of the lesion. Larger lesions can be cut into segments for enucleation; however, the tooth attached to the lesion is firmly fused and in almost all instances must be or should be removed with the lesion. In one interesting report, including a 4-year follow-up period,[195a] endodontics with preservation of the tooth and excision of the lesion was successfully performed. Complete enucleation of the lesion and curettage of surrounding bone constitute sufficient treatment, and recurrence is not expected. However, a recent paper by Brannon et al[195b] reviewed a large series of cementoblastomas and the literature with emphasis on recurrence. In 35 cases for which they had follow-up data, 13 (37.1%) had recurrence. Their study showed that recurrence (regrowth of residual lesion) is a consequence of incomplete removal.

Because of the presence of areas of active osteoid (i.e., cementoid) formation by large hyperchromatic and pleomorphic cells, histologic misinterpretation of or doubt about the benign nature of the lesion is possible if all clinical and radiographic data are not appreciated. The occasional "sunburst" radiographic appearance of the lesion in an axial projection produced by the radial calcifying trabeculae may hide the defining sharp border.[189] This should not be mistaken as radiographic evidence of osteosarcoma and, conversely, should not be ignored by the surgeon if further study is warranted.

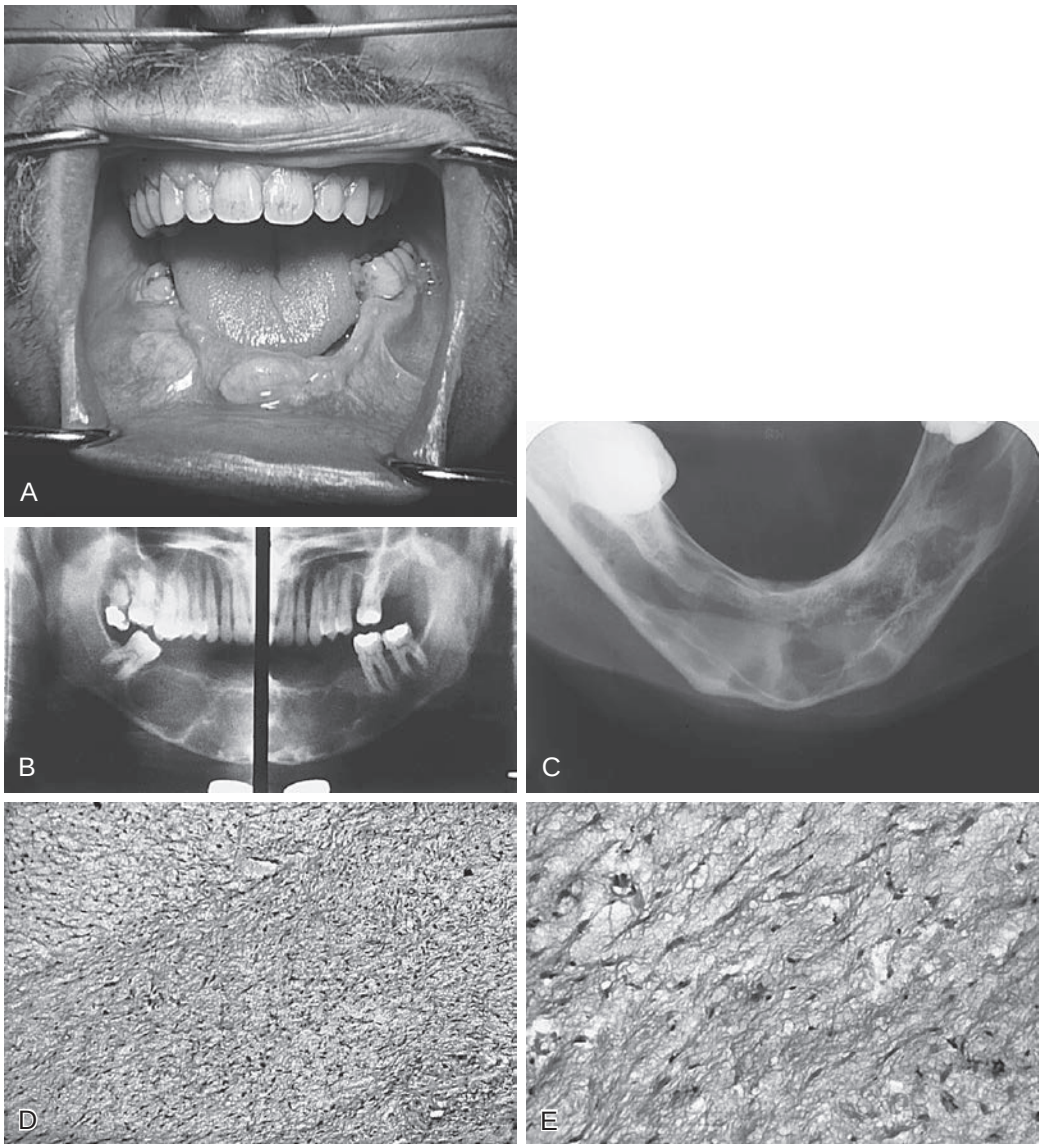
Odontogenic Myxoma

The *myxoma (odontogenic myxoma, myxofibroma) of the jaws is a benign, usually slow-growing, infiltrative tumor of connective tissue* (Figures 18-26 to 18-28). It is presumptively odontogenic in origin because almost all cases have been found in the jaws, and its histologic appearance most closely simulates that of the mesenchymal tissue of the follicular sac or dental papilla. Most authors believe the lesion is exclusively found in tooth-bearing areas of the jaws.[196] However, a few cases have been seen in nontooth areas of the jaws.[197] A report of three cases of extragnathic fibromyxomas, only one of which had accompanying photomicrographs, was not convincing.[198] Extensive literature (well over 200 reported cases) indicates that the lesion is neither common nor rare.[199]

Clinicopathologic Considerations

The lesion occurs in both the maxilla and the mandible, with a slight preponderance in the mandible. Myxoma tends to be unilateral, but lesions may extend past the midline (mandibular lesions more frequently than maxillary lesions). There is a slightly more frequent occurrence in females than in males and a very wide age range, from 11 months[200] to the seventh decade. However, most lesions are clinically detected within the second to sixth decade. The occurrence in children may be higher than previously believed.[201]

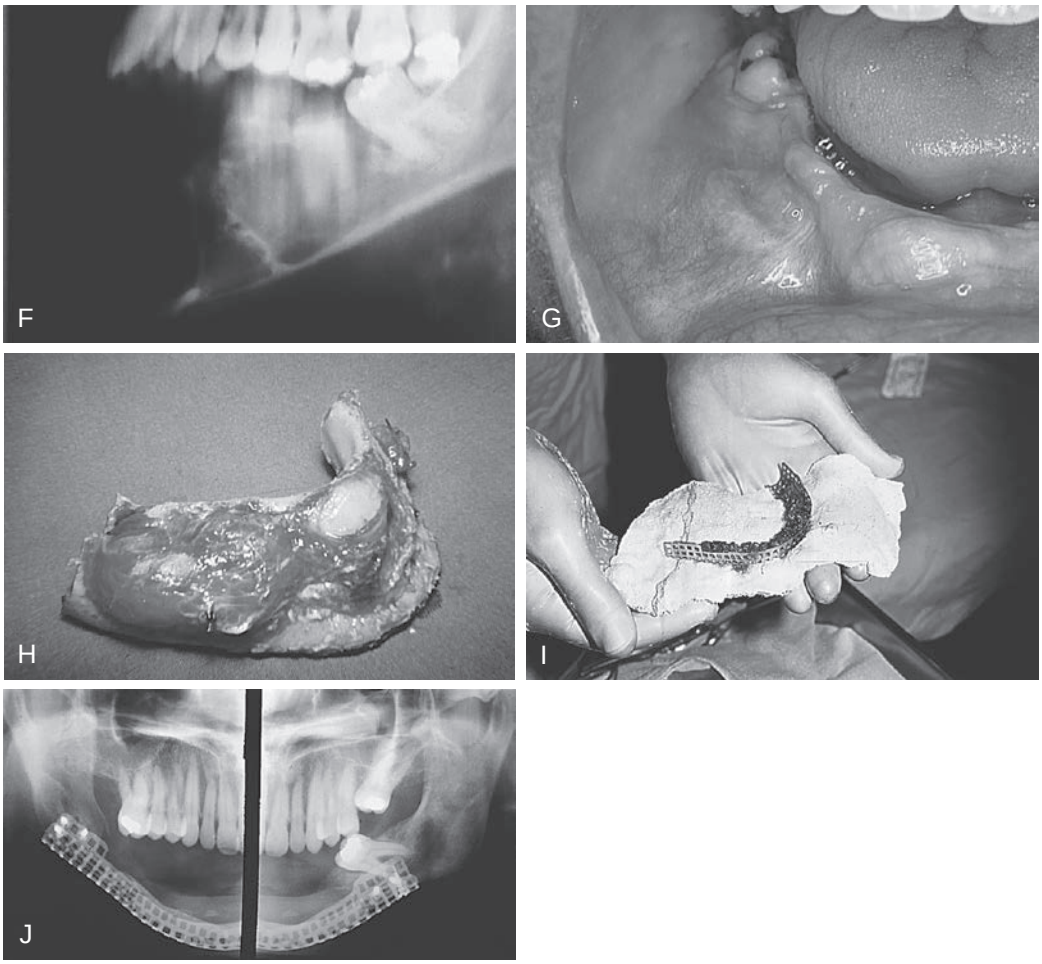
Radiographically, most lesions are multilocular, whether small or extensive; however, unilocular lesions have been reported. Some myxomas radiographically resemble dentigerous cysts if an unerupted tooth has been "trapped" within the



• **Figure 18-27** Odontogenic myxoma of mandible. **A-C,** A 44-year-old man was referred for treatment of an extensive multilocular mandibular lesion. **D-E,** The lesion had been excised 6 years earlier with a histologic diagnosis of odontogenic myxoma and was now recurrent and greatly increased in size. A repeat biopsy confirmed the diagnosis.

lesion. The myxoma may displace teeth or rarely resorb tooth roots if the lesion involves dentate areas.[202] The lesion may be entirely radiolucent or have a "soap bubble," "honeycomb," or striated appearance described as similar to that of the strings of a tennis racket. The radiographic image is not pathognomonic and may simulate a number of diverse lesions such as ameloblastoma and hemangioma, as well as others. *The radiograph may indicate a lesion-bone boundary more circumscribed than is actually present* (see Figure 18-26, *A-D*).

Histologically, myxoma is characterized by stellate, angular, or rounded mesenchymal (fibroblast-like) cells with long protoplasmic processes in a mucoid stroma, staining heavily basophilic with hematoxylin and eosin. Fibrillar strands of reticulin and occasional well-formed collagen fibers permeate the mucopolysaccharide ground substance, which histochemically consists of hyaluronic acid and chondroitin sulfate. Some myxomas produce sufficient stromal collagen to justify a histologic designation of myxofibroma. Rarely, odontogenic epithelial rests may be encountered in the lesion. Mitosis is not a feature of myxoma. Although some radiographs of the lesion may give the appearance of circumscription or well-defined margins, few lesions demonstrate histologic evidence of encapsulation,[203] and most should be regarded as not encapsulated. Small loculi of tumor infiltrate the marrow and resorb medullary bone in a three-dimensional manner in advance of the main lesional mass. Bone resorption takes place in the absence of osteoclasts, and the tumor directly abuts the bone. Large or small lesions can resorb cortical bone and penetrate periosteum (see Figure 18-28, *O*). Thus, the lesion may be directly contiguous with overlying gingiva or alveolar mucosa. There often appears to be a surgical plane between myxoma and



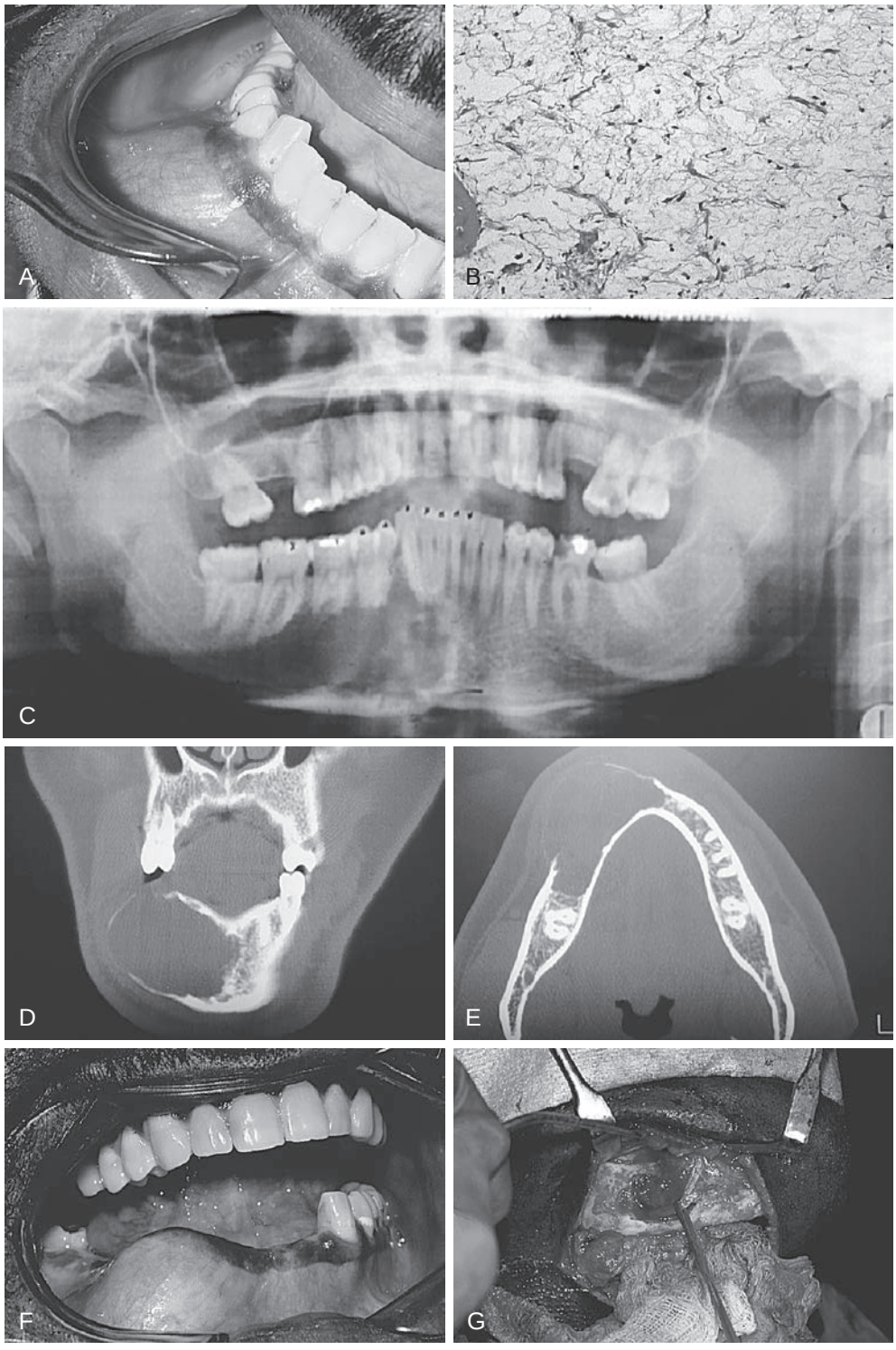
• **Figure 18-27, cont'd** **F,** A tomogram demonstrated buccal and labial cortical bone resorption. **G,** The tumor was palpable immediately beneath the gingival and vestibular mucosa; note indentation of tumor mass by maxillary teeth. **H,** A transoral resection with continuity defect from right to left third molar areas and immediate reconstruction with iliac crest bone graft was performed. The inferior alveolar nerve was sacrificed, with preservation of almost all gingival and alveolar mucosa. Within 4 days a *Pseudomonas* species infection occurred, causing loss of graft. Aggressive antibiotic and local treatment resulted in complete healing of the tumor bed and soft tissues. Mandibular spatial position was maintained by a Hall Morris appliance. **I,** Six months later, continuity was successfully established by an extraoral approach using a titanium crib filled with autogenous iliac cortical bone chips and cancellous marrow. **J,** Panograph 3 years after surgery.

adjacent soft tissue, unless inflammation and/or ulceration in the area promotes intermixing of lesion and soft tissue at the juncture (see Figures 18-27 and 18-28).

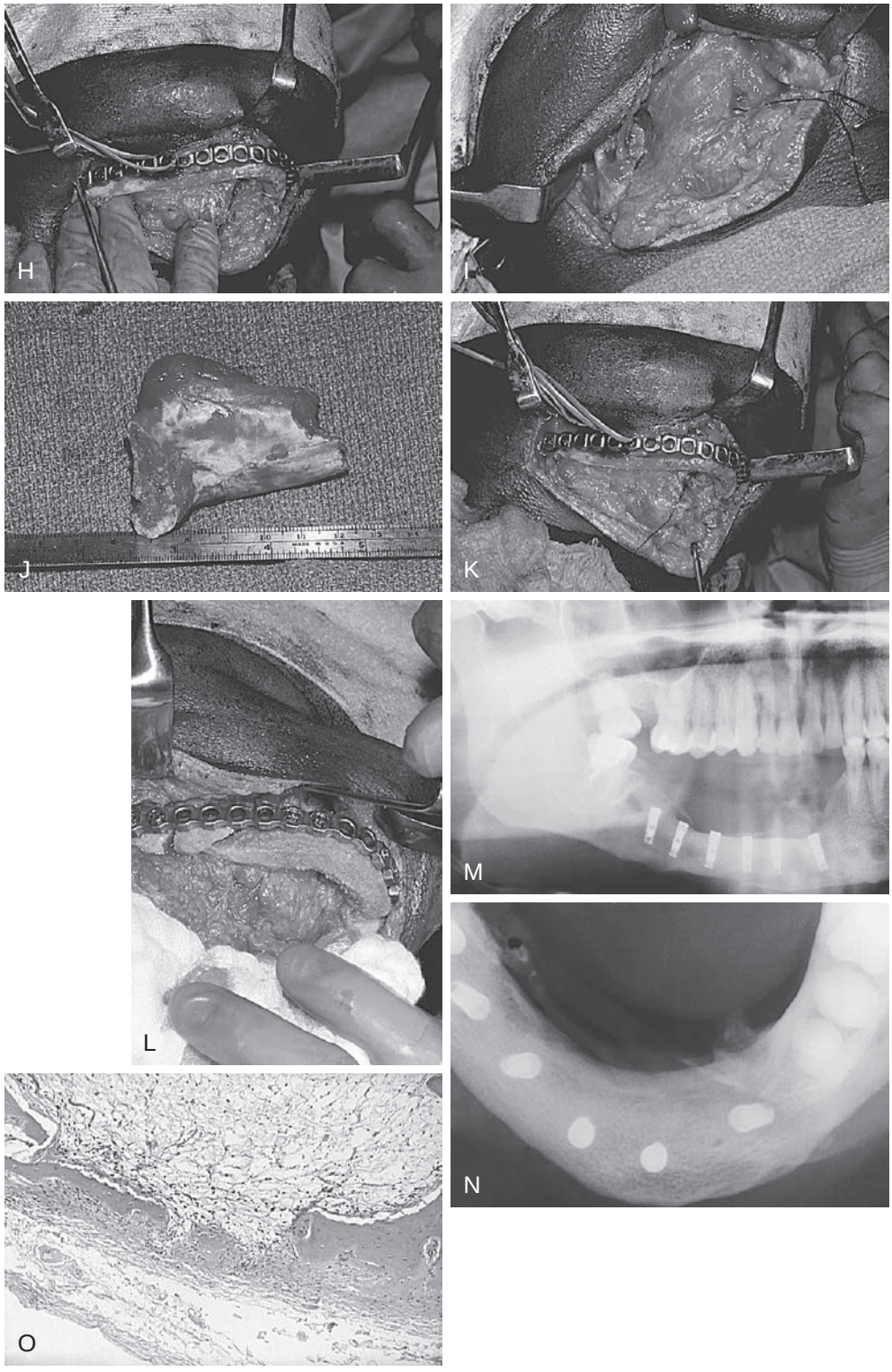
Clinically, myxoma increases in size slowly and is asymptomatic and may not be diagnosed until an extensive lesion produces swelling or the lesion is discovered in radiographs. Tooth movement is not common and does not cause patient complaint.[204] In dentate areas the lesion may extend into interradicular areas, and in edentulous areas the lesion may expand toward the occlusal surface and interfere with occlusion. Maxillary myxomas may infiltrate into and occupy the maxillary sinus and cause nasal obstruction and even exophthalmos.[199]

Differential Diagnosis

There are no means to distinguish myxoma radiographically from a host of odontogenic or nonodontogenic lesions. However, histologically, few lesions may be misinterpreted as myxoma. Those odontogenic lesions that contain a marked epithelial presence such as ameloblastoma or ameloblastic fibroma offer no challenge, and odontogenic fibroma usually contains sufficient epithelium to be readily differentiated. It is possible for myxofibroma to be so heavily collagenized or for desmoplastic fibroma or neurofibroma[205] to contain enough myxomatous areas to create diagnostic doubt, but this is highly unusual. The absence of marked mitotic activity mitigates against a sarcomatous lesion, such as malignant fibrous histiocytoma, but does not exclude the possibility. More commonly, a hyperplastic follicular sac or a pulpal "bulb" separated from the developing root of an unerupted tooth is misinterpreted as myxoma (see Figure 18-25). Soft tissue mucinosis or myxomas of oral soft tissue are not discussed here and bear no relation to central



• **Figure 18-28** Odontogenic myxoma of mandible. **A,** A 36-year-old man requested treatment for his mandibular tumor, biopsied and histologically diagnosed as odontogenic myxoma 2 years previously at another institution. Resection and bone graft reconstruction had been recommended; however, the patient, fearful of the procedure, refused. Increase in the size of the lesion prompted the patient to seek treatment. **B,** The previous tissue slides were requested, and the diagnosis was confirmed. **C**-**E,** Imaging revealed the tumor extent. Teeth proximal and distal to the lesion as well as within the lesional area were extracted to permit soft tissue healing for attempted retention of mucosal tissue. **F,** Further oral expansion of the lesion occurred during the 3½-month healing period. An extraoral approach with continuity resection and immediate bone graft was planned, as well as preservation of the inferior alveolar neurovascular bundle and mental nerve (if possible). Maxillary and mandibular fracture bars were placed. The lesion was approached from the inferior border of the mandible (the inferior border was seen to be involved by tumor). The mental nerve was seen coursing superiorly over the tumor mass and was dissected free and preserved, with sacrifice of the anterior incisive extension. **G,** The lesion was displaced superiorly and the mandibular canal was decorticated, unroofing the inferior alveolar neurovascular bundle to a point well proximal to the angle extent of the lesion; the neurovascular bundle was lifted free and protected. A reconstruction bar (plate) was sized and bent to conform to the inferior border of the symphysis and right body, and to extend past the proximal (angle area) and distal (left body) resection margins.



• **Figure 18-28, cont'd** **H,** The plate was fixed to the mandible by screws past the intended resection margins, and then unscrewed and set aside (the screw holes marked the sites of reattachment of the plate to preserve the spatial contour of the mandible). Superior dissection over the tumor mass was attempted to free the tumor from the overlying gingiva without perforation into the oral cavity; however, this proved impossible from the inferior approach, and a gingival laceration occurred. The oral cavity was entered and an extended incision was made through the gingival crest mucosa, permitting visual dissection of the lesion, freeing mucosa and isolating the tumor. **I,** The continuity resection was completed, and **(J)** the specimen was removed (viewed from lingual surface). The laceration was repaired, and the oral incision was sutured in a "watertight" fashion. Intermaxillary fixation wires were placed. **K,** The reconstruction plate was reattached with additional screws, and the detached extrinsic tongue muscles were sutured to the plate. The wound was closed in layers and a drain placed. **L,** Ten months later a full-thickness iliac crest graft was taken, sculpted, and placed through an extraoral approach. The graft consolidated in 9 months. The reconstruction plate was removed transorally, and six titanium implants were placed for a prosthesis. **M-N,** Two-year postoperative panograph reveals good bone repair and bulk. **O,** Photomicrograph of specimen: tumor interface with mandibular inferior border. Note resorption of mandibular inferior border cortex.

myxoma. Grossly, the myxoma is readily identified by its gelatinous texture and shiny appearance.

Management

Despite the voluminous literature on myxoma, accurate reports of long-term follow-up evaluation or statistical analysis of the efficacy of various treatment modalities are not available. It is generally known that recurrences (i.e., regrowth), early or late, are seen more often in lesions treated by curettage and/or enucleation than in lesions surgically resected. The key to successful treatment, and avoidance of recurrence, is appreciation of the infiltrative behavior of the myxoma. Although benign, the lesion does not exhibit limited growth potential; enlargement in all dimensions continues. The following management protocol, which is employed by the writers, is offered:

- Biopsy performed in a central area of the lesion and at the radiographic lesion-host bone interface histologically identifies the lesion, establishes the physical characteristics of the tumor (i.e., whether one is dealing with a loose gelatinous, mucoid mass or a lesion with more firm consistency), and determines the presence of a circumscribing border and, most importantly, the infiltrative characteristics at the lesion-bone interface. Entry to the lesion should be through a noninflamed, nonulcerated crestal area to prevent "contamination" of mucosal tissue subsequently required for closure in the definitive procedure.
- Attempts to excise by enucleation and curettage should be restricted to unilocular lesions of no more than 1 cm to 2 cm in diameter, accompanied by vigorous and purposeful curettage of the surrounding bone bed. Rapid histologic sections help determine, but do not necessarily prove, that the entire lesion has been removed. Hypothetically, lesions that contain more collagen than those that are predominantly mucoid have a greater probability of successful enucleation and curettage. Chemical cauterization (e.g., Carnoy solution) of the tumor bed may be of value. Teeth and alveolar processes at the edge or within the radiographic and clinical limits of the lesion should be removed. Grinding of the tumor bed by burrs does not permit histologic examination of the lesion-bone interface. Histologic evidence of tumor at the interface should initiate plans for reoperation within a 3- to 4-month period with excision of bone perimeters for further histologic analysis.
- Extensive lesions should be excised by Rs-CD or Rc-CD, including a perimeter margin of tumor-free bone. An unproven recommendation of a 1-cm margin is suggested but should be confirmed by histologic analysis of the specimen. The decision to perform an Rs-CD or Rc-CD is dependent on the anatomic extent of the lesion. If Rs-CD is likely to result in incomplete excision or pathologic fracture, Rc-CD should be performed.
- The neurovascular bundle of the mandible should not be sacrificed routinely, even in lesions that require Rc-CD. The mandibular canal may be intact, or relatively intact, providing protection for the inferior alveolar nerve. The canal can be unroofed and the neurovascular bundle exposed and examined throughout the length of the lesion. If the bundle is obviously permeated or hopelessly involved by tumor, it should be included in the resection. In the instance of a more collagenized (myxofibromatous) lesion, the bundle may be displaced rather than incorporated and, if separable from the tumor, can be preserved.
- The decision for immediate or delayed reconstruction is dependent on the clinical and/or histologic certainty of complete excision of the tumor and the tissue requirements for reconstruction (as outlined in management of ameloblastoma).

Mixed (Epithelial/Mesenchymal) Odontogenic Tumors

odontogenic epithelium and odontogenic ectomesenchyme. The lesions produced demonstrate a spectrum that includes anomalies, hamartomas, and benign and malig-

na

ha

the literature.[206-211] There is still difference of opinion regarding whether some lesions are hamartomas or neoplasms, whether some should be considered extensions of an existing

elopmen-

dontoma)

must begin as a soft tissue lesion, but it is not known whether an observed soft tissue lesion *(ameloblastic fibroma)* will progress through developmental stages *(ameloblastoma fibro-odontoma)* and mature to a harmless calcified state or whether both ameloblastic fibroma and ameloblastic fibro-odontoma will continue to expand as a hamartoma or neoplasm.

It is probable that all the possibilities may occur; however, there are no histologic means to predict the biologic behavior of a specific lesion. From the surgical perspective, although most mixed odontogenic lesions exhibit benign behavior and should be treated conservatively, management is based on the clinical circumstance of the specific lesion at the time of discovery. For the most part, and for the purposes of this discussion, the lesions are presented as traditionally defined without further regard to their probable interrelationships. However, in the discussion of *odontoameloblastoma* and *ameloblastic fibrodentinoma* some special notice is taken of the delineation of these lesions.

Odontoma

The odontoma is radiographically and histologically recognizable in two forms—*compound odontoma* and *complex*

odontoma (Figure 18-29). Both are the end products of the anomalous completion or incompletion of tooth formation by odontogenic epithelium and odontogenic ectomesenchyme. The compound odontoma usually consists of formed calcified toothlike structures or miniature teeth, and the complex odontoma is a disorderly and haphazard arrangement of calcified dental structures.

Clinicopathologic Considerations

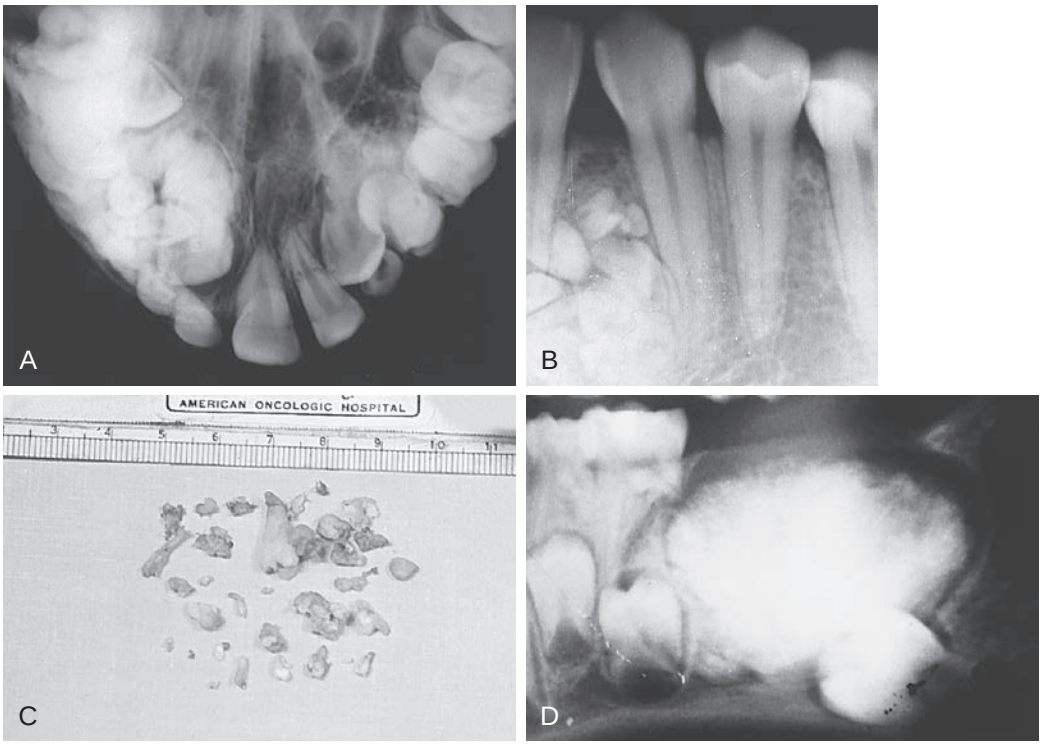
The odontoma is considered to be the most common odontogenic lesion and occurs in both jaws, with a slight prevalence difference between the complex (more common in the mandible) and the compound (more common in the maxilla).[171] Most compound odontomas are seen in the anterior jaw, whereas complex odontomas are seen most often in the posterior jaw, particularly in the third molar region.[169] There is an insignificant gender difference.

Although the age range is between the first and seventh decades, most odontomas are discovered in the first and second decades. The lesions remain asymptomatic and are clinically revealed by routine radiographs or by radiographs taken because of the persistence of a deciduous tooth, noneruption of a permanent tooth, or, in some instances, alveolar bone or jaw enlargement.

Radiographically, mature lesions are readily distinguished. A compound odontoma is seen as a packet of malformed or dwarfed teeth or toothlike forms surrounded by a narrow radiolucent zone, sometimes overlying or alongside an unerupted tooth or between the roots of a deciduous tooth, preventing eruption of the underlying permanent tooth. The complex odontoma may be a small, large, or smooth ovoid, densely radiopaque mass, frequently overlying a displaced unerupted tooth, often surrounded by a thin radiolucent zone.

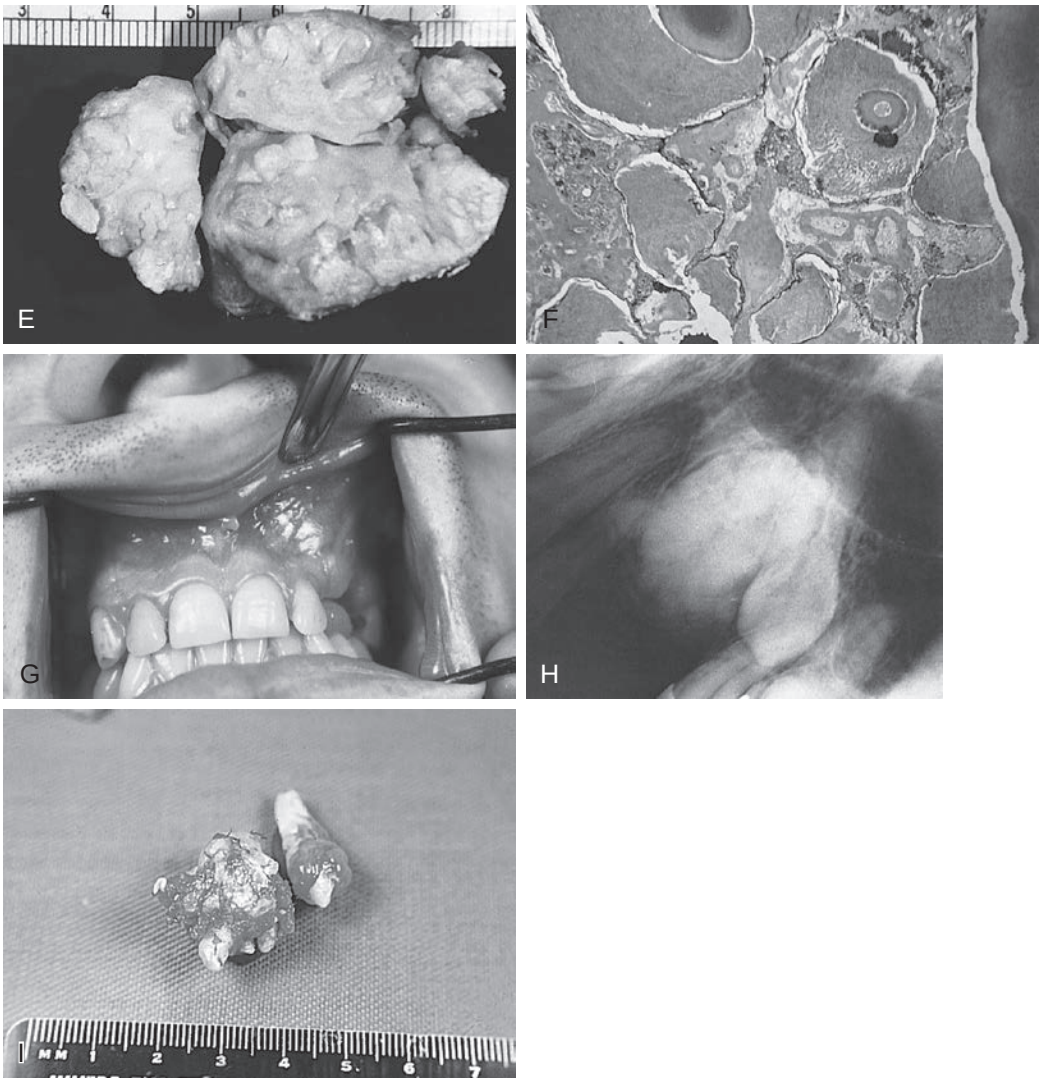
The forming odontoma radiographically reflects the stage of development at the time of discovery. Thus, complete radiolucency is possible when the lesion is initiated, extending to the later appearance of calcified structures as the odontoma "matures." Occasionally, large well-circumscribed cystlike lesions show a mixed radiolucent/radiopaque image, with irregularly shaped calcified complex odontomatous masses surrounded by radiolucent areas.

Grossly and histologically, the compound odontoma is usually found within a connective tissue capsule. The lesion is composed of anatomically distinct, small, well-formed or distorted teeth with enamel, dentin, pulp, and cementum. The complex odontoma lacks anatomic organization and consists of calcified dental tissue in bizarre combinations, often bound together in a mass of cementum, also frequently surrounded by a thin connective tissue capsule. Histologic differentiation between the two types is not always possible since combinations occur (see Figure 18-29). Occasionally, the lumen of a calcifying odontogenic cyst contains complex odontomatous masses[212,213] (Figure 18-30).



• **Figure 18-29** Compound and complex odontoma. **A-B,** Radiographs of compound odontoma demonstrate readily identified malformed and miniature teeth. **C,** Individual dwarfed teeth and toothlike forms from a specimen of a maxillary compound odontoma. **D,** Radiograph of complex odontoma shows densely radiopaque calcified mass.

Continued



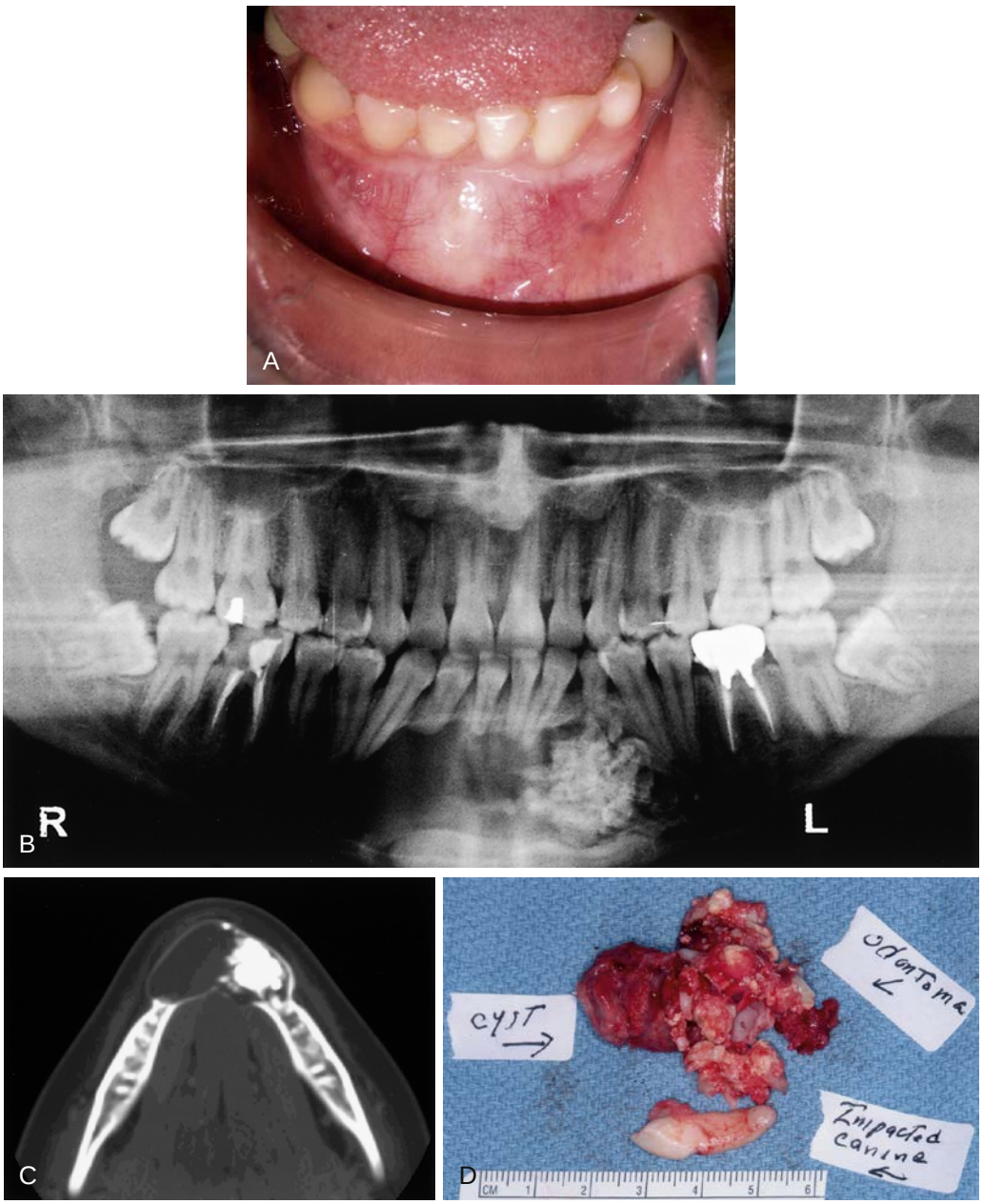
• **Figure 18-29, cont'd** **E,** Specimen photograph of a large complex odontoma reveals toothlike forms embedded in a mass of dentin and cementum. **F,** Photomicrograph of a still "maturing" complex odontoma. **G-I,** Clinical appearance and radiographic and gross specimens of a complex-compound odontoma enucleated from the anterior maxilla of an 18-year-old man.

Management

- The completely calcified complex or compound odontoma is biologically inert and need not be removed if the clinical diagnosis is secure and no useful purpose would be served by removal. However, there are several reasons for excision of a lesion: (1) because of patient concern about the diagnosis, once informed of the lesion's presence; (2) to permit the possible eruption of a tooth blocked by an odontoma, in a clinically favorable position; and (3) to establish a diagnosis between a complex odontoma and other radiographically opaque lesions such as cementoblastoma, or large lesions containing a mixture of radiolucent and radiopaque areas that might represent ossifying fibroma or an odontogenic neoplasm (e.g., CEOT, odontoameloblastoma).
- Both compound and complex odontomas are approached through intraoral mucosal incisions and adequate removal of overlying bone to expose the lesion. Compound odontomas are enucleated if the capsule is intact, or the individual tooth forms are carefully removed if the capsule is disrupted. Small complex odontomas are enucleated in the same manner. However, large or huge complex odontomas should be cut into segments for removal, in order to conserve normal bone and to prevent jaw fracture that can result if excessive elevative force is applied in areas of the lesion that lack encapsulation and may be fused to surrounding bone. The odontoma is not a recurrent lesion if calcified and completely excised; however, unnoticed remaining formative odontogenic soft tissue may continue to produce odontomatous calcified tissue.

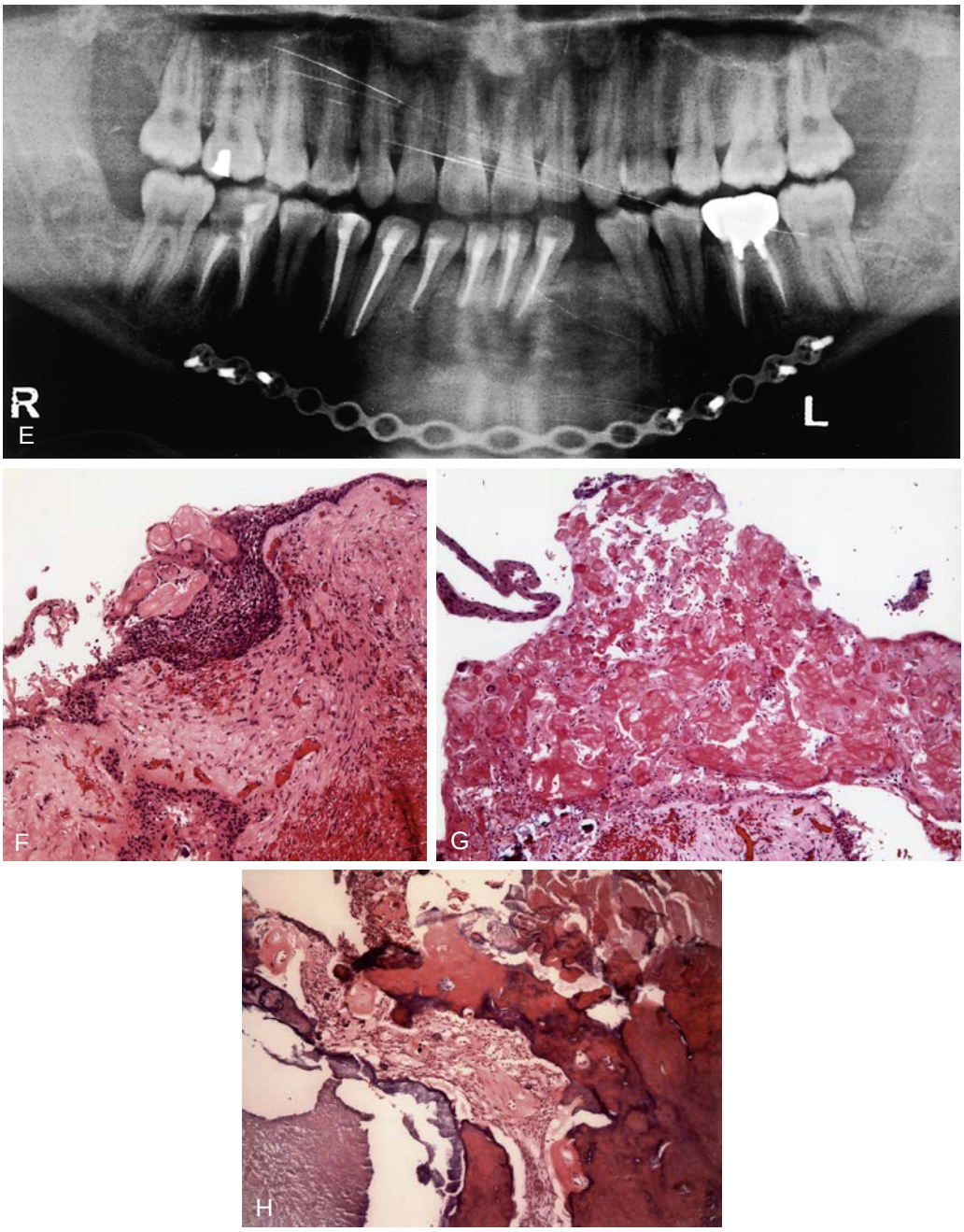
Odontoameloblastoma

The *odontoameloblastoma* (formerly called *ameloblastic odontoma*) is defined by the WHO[11] as "a very rare neoplasm,



• **Figure 18-30** Calcifying odontogenic cyst with complex odontoma. An 18-year-old woman was referred because of an enlarging anterior mandibular swelling and displaced teeth preventing mouth closure. **A,** The swelling was painless and gradually increased in size over a year. **B**-**C,** Panographic and computed tomographic radiographs revealed a 6.5 × 3.0 cm radiolucent lesion occupying the mandibular symphysis, displacing the right first premolar to the left first premolar teeth, and causing slight root-end resorption of the four anterior teeth. Lying within the extensive radiolucency was a complex odontomatous mass measuring 2.5 × 2.5 cm. The partially resorbed left deciduous canine tooth was in situ, and the permanent left canine was horizontally displaced to the inferior mandibular border. An incisional biopsy of the cyst wall was reported as calcifying odontogenic cyst (also known as keratinizing and calcifying odontogenic cyst). Before the definitive procedure, the displaced teeth were endodontically treated. The lesion was excised under general anesthesia. The cyst and odontoma were removed by enucleation and curettage. **D,** The cyst wall was both thick and thin in areas, with care taken to remove the entire cyst wall and odontoma. The mental nerve was protected and preserved. Reconstruction was immediately accomplished by adaptation of a thin reconstruction bar secured to the mandible.

Continued



• **Figure 18-30, cont'd** **E,** A mixture of iliac crest bone marrow aspirate, allogeneic bone, patient cortical bone chips, and platelet-rich plasma was implanted in the surgical defect. The wound was closed primarily. **F,** Histologic sections of the specimen showed a calcifying and keratinizing odontogenic cyst. **G,** High power of "ghost cells" in calcifying odontogenic cyst lining. **H,** Area of accompanying complex odontoma. (Case material courtesy Daniel Taub, DDS, MD, Thomas Jefferson University, Philadelphia.)

which includes odontogenic ectomesenchyme, in addition to odontogenic epithelium, that resembles an ameloblastoma both in structure and in behavior. Because of the presence of the odontogenic ectomesenchyme, inductive changes take place leading to formation of dentin and enamel in parts of the tumor" (see Figure 18-34 and comments on ameloblastic fibrodentinoma). This definition is supported by several writers, but with slightly differing connotations and emphasis. Gorlin[171] and Frissell and Shafer[214] believe the odontoameloblastoma is a "tumor in which there is simultaneous occurrence of ameloblastoma and a complex or compound odontoma within the same tumor." Regezi and Sciubba[185] state that the odontoameloblastoma is a rare variant that is essentially an ameloblastoma in which there is focal differentiation into an odontoma. However, Gorlin[171] also states that the lesion is not invasive, thus introducing a confusing contradiction regarding the ameloblastic credentials of the lesion he describes as odontoameloblastoma. Several oral

pathology texts recommend that odontoameloblastoma be treated as an ameloblastoma. However, with almost no exception, this recommendation has not been followed in the cases published under the designation of odontoameloblastoma or ameloblastic odontoma. Most such cases have been evaluated by Slootweg[209] in an extensive analysis of mixed odontogenic tumors, and in his opinion they are either ameloblastic fibro-odontomas or complex odontomas. This opinion is supported on several bases by the present writers after careful review of a number of published cases[215-224] and other cases not cited.

The published lesions, whether small, large, or extensive, are radiographically well circumscribed, appearing as radiopaque centrally, surrounded by a radiolucent zone, or containing irregular small or large radiopaque masses interspersed with radiolucent areas, and usually surrounded by a sclerotic bone margin. None appeared to give a radiographic impression of infiltration. All were conservatively excised by enucleation and/or curettage. Only a few showed recurrent growth, which could be explained by continued growth of overlooked residual lesion (as has also been described for ameloblastic fibro-odontoma). In one case, the excised regrowth demonstrated further formation of odontomatous structures.

Histologic descriptions and photomicrographs (one case did not offer a photomicrograph) of the ameloblastic elements did not describe or illustrate impressive amounts of ameloblastic tissue. All of the ameloblastomatous tissue was contained within the lesions, many of which were encapsulated. None qualified as a legitimate example of ameloblastoma that would justify aggressive treatment.

Clinicopathologic Considerations

Several cases[8,214,224] appeared to fulfill the criteria for odontoameloblastoma; however, these also did not greatly differ radiographically, or to any extent clinically, from the cases already discussed. Radiographically, they were similarly well circumscribed and contained similar opacified (calcified) odontomatous masses. The age of occurrence was mainly in the first and second decades, with a male predilection. The lesions usually occupied the posterior regions of both jaws and clinically produced expansion of the jaws. The distinguishing characteristic was that the ameloblastic elements appeared to be well-differentiated follicular or plexiform masses and islands, in more than casual amounts and distributed throughout the lesion. Only one report[217] specifically addressed an infiltrative-like quality of the lesion in one area.

Management

Almost all the acceptable cases of odontoameloblastoma described here were initially treated conservatively, including recurrences. The extensive maxillary lesion described by La Briola and colleagues[224] was initially managed by hemimaxillectomy, and the twice-recurrent lesion of Frissell and Shafer[214] was conclusively managed by Rs-CD. Conservative excision appears to be the prudent initial management selection.

- Lesions that are primarily radiopaque and circumscribed by sclerotic bone should be excised by enucleation and careful curettage.
- Lesions that contain significant areas of radiolucency, in addition to calcified odontomatous masses, should be biopsied in several areas.
  - Histologic assessment of the biopsy determines the presence or absence of a capsule and the quantity and distribution of ameloblastic elements.
  - If a capsule is present, the lesion should be excised by enucleation and careful curettage.
  - If a capsule is not present, the lesion should be excised by enucleation and careful curettage or at most Rs-CD.
- Histologic analysis of the specimen determines whether a further surgical procedure is indicated. Rarely is Rc-CD justified. However, clinical features, imaging, and anatomic involvement must be taken into account in the management of the specific lesion.

Ameloblastic Fibroma

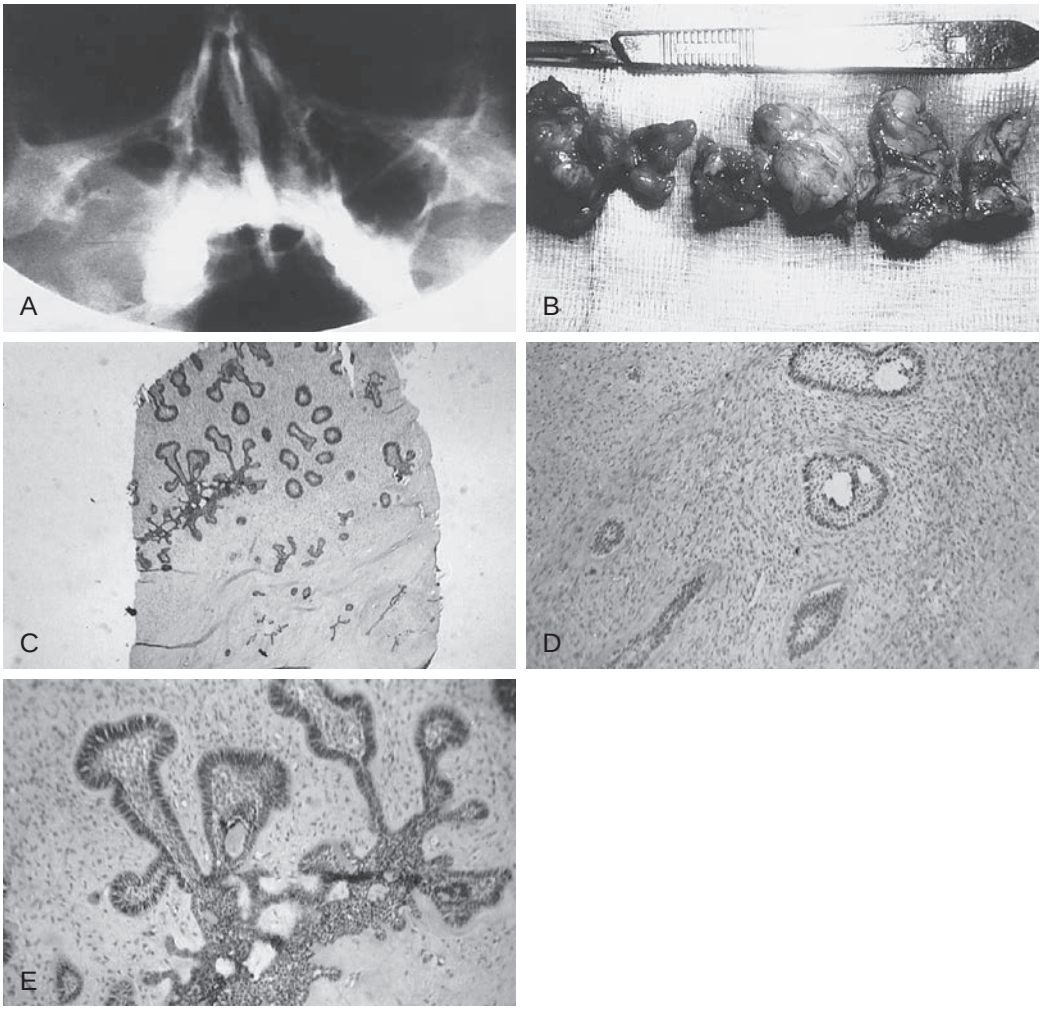
The *ameloblastic fibroma is a benign mixed odontogenic tumor in which odontogenic epithelium and odontogenic ectomesenchyme proliferate as a combined soft tissue neoplasm, without the formation of calcified tooth structures* (Figure 18-31). Although it is statistically rare, the accumulation of published cases has permitted analysis of the clinical parameters of the lesion.[209,211,225] It is probable that ameloblastic fibroma is a true neoplasm of embryonic tissue.

Clinicopathologic Considerations

The median age is 14 or 15 years, with a range of discovery up to 40 years. The youngest case thus far reported occurred in a 7-week-old infant.[226] Males and females are equally affected. The lesion occurs in both jaws; however, the mandible, particularly the third molar area, is the site of predilection.

Radiographically, ameloblastic fibroma projects a radiolucent, unilocular image, usually well delineated and frequently with a radiopaque (sclerotic) border. Ameloblastic fibroma is often associated with unerupted teeth and may resemble a dentigerous cyst. Small lesions tend to be unilocular, whereas large or extensive lesions assume a multilocular configuration, with variation in size from 1 cm to 8 cm. There are no pathognomonic radiographic clues to the lesion's identity. The only frequent clinical sign is enlargement of the affected jaw, rarely accompanied by pain. The expanding lesion may cause tooth movement, but rarely tooth root resorption.

Histologically, ameloblastic fibroma is composed of a cell-rich mesenchymal-appearing connective tissue in which odontogenic epithelium is prominently displayed and dispersed throughout the lesion. The connective tissue simulates the pattern of the dental papilla, with rounded or angulated embryonic-appearing fibroblasts. In most areas of the lesion, little or no collagen appears, and the stroma has a fibromyxoid appearance. The odontogenic epithelium is present as narrow variously shaped cords, straight or curved strands, and branching configurations of cuboidal or columnar cells. The strands frequently expand into terminal club shapes that demonstrate



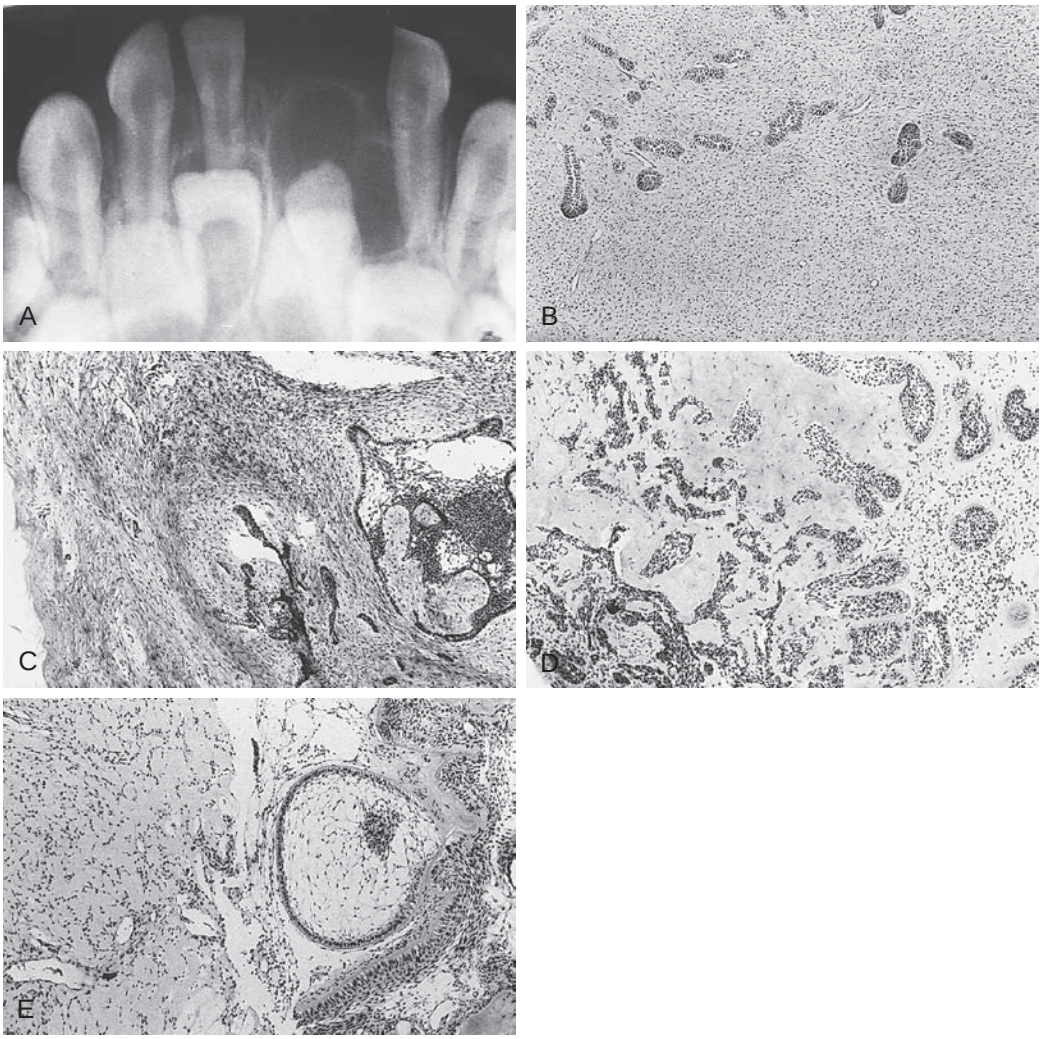
• **Figure 18-31** Ameloblastic fibroma. **A,** An extensive lesion of the right maxilla and maxillary sinus was excised by enucleation and curettage from a 27-year-old woman. **B,** The gross specimen demonstrates a lobular pattern. Tissue sections show ameloblastic configurations within a hypercellular and hypocellular fibromyxoid connective tissue. Note slight inductive effect bordering some ameloblastic strands (**C,** low power; **D**-**E,** medium power).

classic ameloblastic configuration with a central stellate reticulum appearance and peripheral columnar cells with reversed nuclear polarity. Small islands of ameloblastic cells may show a typical follicular appearance and cystic change. The microscopic patterns of odontogenic epithelium and the mesenchymal connective tissue may vary in large lesions to produce proportional differences between the two tissue components. Not infrequently, hyalinization of mesenchymal tissue is observed around the epithelial islands to indicate an inductive effect; however, induction does not proceed past this initial step. Frequently a connective tissue capsule is present.

The growth pattern of ameloblastic fibroma occurs usually by smooth expansion within the jaws, producing cortical bone thinning or occasional resorption. Several surgical descriptions, however, report that "finger-like projections of the tumor extend into the bone."[227]

Management

Ameloblastic fibroma has been traditionally managed by a conservative surgical approach, unless the extreme size of a lesion (i.e., 7 to 8 cm) has dictated the anatomic need for resection procedures (either Rs$^-$CD or Rc$^-$CD). Several case presentations[228-231] as well as Trodahl's analysis[225] report recurrences. The recurrence rate of 43.5% in Trodahl's 1972 study appears alarmingly high when compared to Zallen and co-workers' study[232] of published cases, which shows a recurrence rate of 18%. Examination of case surgical details indicates that recurrences are probably regrowth of residual tumor, not unexpected in an embryonal-type neoplasm. In Trodahl's series, 92% of the lesions were initially treated by excision (the term not further defined), enucleation, or curettage. The few recurrences reported in the literature on ameloblastic fibroma show that the recurrence exhibits the same histologic features as seen in the specimen of the initial excision, and a few demonstrated further maturation toward odontoma formation. One recurrence[229] showed acanthomatous changes in ameloblastic elements and a marked increase in collagen content. *It should be noted that a common history in the literature on ameloblastic fibrosarcoma shows that approximately 45% of the sarcomatous lesions evolve from ameloblastic fibromas that have been incompletely excised or not treated.*

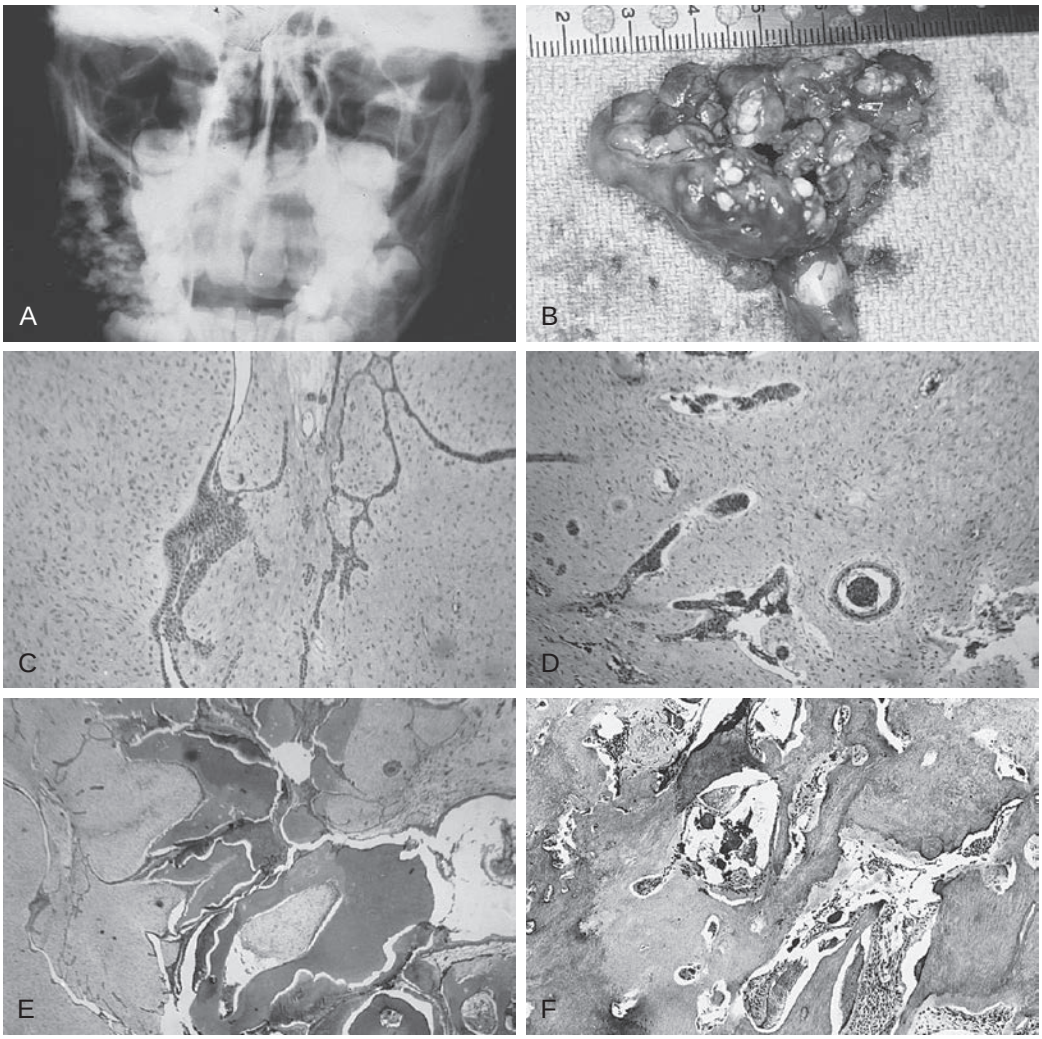


• **Figure 18-32** Ameloblastic fibro-odontoma. **A,** Periapical radiograph of lesion in the anterior mandible of a 2½-year-old child. The lesion produced a labial bulge and measured approximately 2 cm in diameter. The lesion was excised by enucleation and curettage. **B,** Photomicrographs demonstrate a soft tissue mass of cellular fibromyxoid connective tissue in which areas display ameloblastic strands and islands, some of which are surrounded by acellular zones of collagen, compatible with ameloblastic fibroma. **C,** Other areas of the lesion demonstrate hyperplastic masses of ameloblastic epithelium. **D,** However, extensive hyalinization of the connective tissue by the inductive effect of the ameloblastic-like epithelium, as well as **(E)** the presence of an enamel organ and amelogenic epithelium, presage future probable formation of an odontoma. (Case material courtesy Dr. Joseph C. Piotrowski, Toms River, NJ.)

- Most, if not all, recurrences probably result from incomplete excision; however, a conservative first approach to management is acceptable if the lesion is encapsulated.
- The presence or absence of encapsulation should be established during the first stages of the surgical procedure. Despite encapsulation, some lesions may have loculi of the tumor that escape detection and excision.
- Enucleation and curettage result in successful excision of unilocular, encapsulated lesions. Careful histologic study of multiple sections of different regions of the lesion should be carried out to detect areas of atypical change in the mesenchymal tissue.
- Extensive or multilocular lesions are more definitively managed by Rs$^-$CD or Rc$^-$CD from the outset, if surgically indicated.
- Huge lesions require Rc$^-$CD and bone graft if anatomic integrity of the jaw is so compromised that pathologic fracture may result from extirpative surgery.
- Studies of cases indicated that approximately 45% of ameloblastic fibrosarcomas evolve from untreated or incompletely treated ameloblastic fibroma (see discussion of odontogenic sarcoma).
- Long-term clinical and radiographic follow-up evaluation is required; 10 years is not an unreasonable period.

Ameloblastic Fibro-odontoma

The ameloblastic fibro-odontoma is a benign mixed odontogenic tumor that appears to be a histologic combination of ameloblastic fibroma and forming complex odontoma (Figures 18-32 and 18-33). The lesion has the expansile



• **Figure 18-33** Ameloblastic fibro-odontoma. **A,** Posteroanterior radiograph of an extensive lesion in the ramus and posterior-mid body of the right side of the mandible in an 11-year-old girl. The lesion was excised by enucleation and curettage. **B,** The specimen shows partial encapsulation with calcified dental tissues and toothlike masses embedded in the lobular soft tissue. **C-D,** Photomicrographs demonstrate regions of the lesion: Peripheral areas show ameloblastic fibroma-like proliferations, while adjoining areas demonstrate formation of malformed teeth **(E-F)** and calcifying compound and complex odontomatous masses.

growth potential of the former and the inductive capability of the latter.

Clinicopathologic Considerations

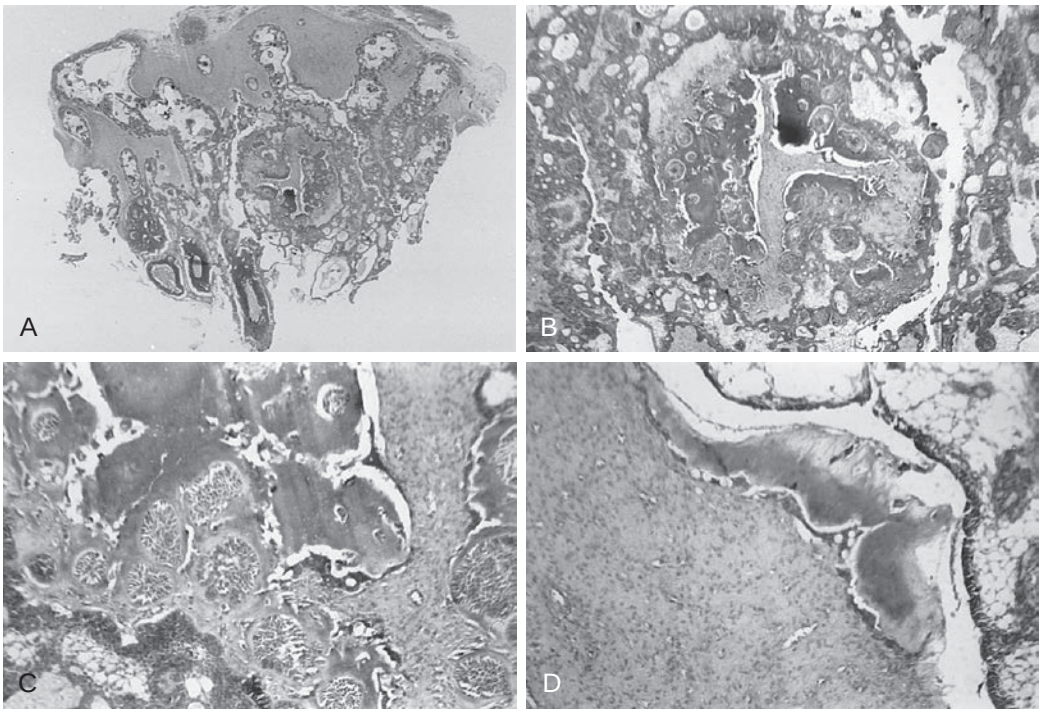
As with other mixed odontogenic tumors, the lesion is typically found in children in the first and second decades, with a male-to-female ratio of approximately 3:1. The lesion is reported to occur with equal frequency in both jaws in one series[209] and preponderantly in the mandible in another series of cases[233] with the site of predilection in the premolar-molar region. Jaw enlargement is often present without clinical symptoms.

Radiographically, the tumor is unilocular or multilocular, with well-defined sclerotic borders, and is seen as a mixed radiopaque-radiolucent large or extensive lesion. The tumor is frequently associated with unerupted teeth or in place of absent teeth. Lesions may vary in the proportion and distribution of radiolucent (soft tissue) and radiopaque (calcified) areas.

Histologically, regions of the tumor demonstrate the same composition of tissue elements as in ameloblastic fibromacords and strands of odontogenic epithelium dispersed in a cell-rich mesenchymal tissue, but also admixed with areas in which odontogenic epithelium and the mesenchymal tissue form dental papillae and enamel organs. Enamel matrix and dentin are produced in bizarre forms and combinations as in a complex or compound odontoma. The tumor is well circumscribed or surrounded by a connective tissue capsule that separates the lesion from bone.

Management

The noninvasive and expansile characteristics of ameloblastic fibro-odontoma, in addition to encapsulation or well-defined circumscription, permit conservative excision by



• **Figure 18-34** Ameloblastic fibrodentinoma. Tissue sections found in a review of archival files of the biopsy department revealed an ameloblastic fibrodentinoma, the case details of which are unknown. The histologic morphology and topography of the lesion suggest that a designation of odontoameloblastoma could also be acceptable (see text discussion). **A,** Microscopic sections had been prepared thicker than usual microtome cut. Scanning microscope demonstrates a partially encapsulated lesion whose mesenchymal connective tissue stroma contains a significant and prominent proliferation of ameloblastic epithelium in cords, strands, and islands surrounded by areas of forming dentinoid, partially calcified dentinoid, or cementoid masses and toothlike forms. **B,** The relationship of the dentinoid to the pulplike mesenchymal tissue and ameloblastic elements is seen in low power. **C,** Medium power shows mesenchymal, calcifying dentinoid, and ameloblastic elements. **D,** High power illustrates tubular dentinoid and odontoblast-like cells between mesenchyme and dentinoid, as well as ameloblastic aggregates exterior to the dentinoid.

enucleation. However, bosselated projections or lobular areas of the tumor must be carefully removed; recurrence is probable if residual lesion remains. Huge tumors[233,234] require resection (Rs-CD or Rc-CD) as indicated by the site, extent, and anatomic involvement of the lesion. It should be noted that Howell and Burkes[235] reported a case of ameloblastic fibro-odontoma that converted to ameloblastic sarcoma.

Ameloblastic Fibrodentinoma

The *ameloblastic fibrodentinoma* (AFD), formerly dentinoma, is a rare, benign odontogenic mixed tumor and is probably a variant of ameloblastic fibroma or ameloblastic fibro-odontoma, in which odontogenic mesenchyme is induced to form dentin or a dentin-like product by the odontogenic epithelium (Figure 18-34). Like ameloblastic fibro-odontoma, AFD is generally considered to be a hamartoma rather than a neoplasm; and, similar to ameloblastic fibro-odontoma, AFD can exhibit considerable growth potential. Although the designation ameloblastic fibrodentinoma is named in the index (with two page listings) of the *Tumors and Cysts of the Jaw* atlas by Sciubba and colleagues,[236] the lesion is not discussed in the text. The WHO 1992 and 2005 classification of odontogenic tumors[12,13] does list the lesion. The senior author's (L.G.) experience with the ameloblastic fibrodentinoma is limited to the discovery and study of an old archival case shown in Figure 18-34. The lesion exhibited a considerable quantity of conventional ameloblastic epithelium in relation to forming dentin, dentinoid, and several toothlike forms. I chose to call the lesion ameloblastic fibrodentinoma, but probably odontoameloblastoma or ameloblastic fibro-odontoma also would have been suitable.

The recognition of ameloblastic fibrodentinoma as an entity (and not as a taxonomic oddity) is still being examined, and despite numerous papers in the literature, the lesion may eventually be merged into ameloblastic fibro-

sen, Reichart, and Praetorius is

Clinicopathologic Considerations

A review of the literature by Ulmansky and colleagues[238] revealed 33 cases recorded between 1936 and 1993. The lesion is found more commonly in the mandible than the maxilla (3:1), and in males more often than females (2:1).

age, with the usual age below 30. Lesions in children are associated with unerupted or missing deciduous teeth and are usually found in the anterior jaw, whereas lesions in adults, involving permanent teeth, show a preference for the posterior regions of the jaw.

The lesions are asymptomatic and are clinically noted because of swelling or enlargement of the jaws. Most often failure of deciduous[239] or permanent teeth to erupt, in the presence of jaw enlargement, draws a patient to the attention of a practitioner, with subsequent discovery of a lesion in radiographic examination.

Radiographically, AFD may be small or extensive,[240] unilocular or multilocular, and most often has well-defined borders. Radiopaque material may be dispersed throughout a lesion, whereas other instances of AFD are predominantly radiolucent.[241] Unerupted deciduous or permanent teeth are often seen to be deeply situated in a lesion[242]; occasionally, heavily opacified lesions are found in edentulous areas of adults.

Histologically, AFD is seen in several configurations within a basic lesional format of ameloblastic fibroma—strands and islands of odontogenic epithelium proliferating in a mesenchymal, cellular, papilla-like connective tissue. In hematoxylin- and eosin-stained sections, the mesenchymal tissue may appear hypocellular, eosinophilic, and hyalinized in areas in which the odontogenic epithelium is embedded. Other foci may show islands of proliferating odontogenic epithelium surrounded by cell-free mesenchyme, whereas the peripheral epithelial cells of other islands take on an ameloblastic appearance and induce dentinoid matrix in the interface area with the mesenchyme. Various stages of induction of dentin may be demonstrated, resulting in lesions that display dentinoid, osteodentin, and, rarely, tubular dentin.[243] The dentin may be infrequently and poorly mineralized; however, Manning and Browne[244] have recorded an example of a large mineralized AFD.

Management

Complete excision of AFD, as recommended for ameloblastic fibroma and ameloblastic fibro-odontoma, is necessary because residual lesion has the capacity to grow. The form of excision is case dependent—enucleation if possible, with Rs-CD and Rc-CD as an option if the surgical circumstance requires or warrants.

Ameloblastic Fibrosarcoma/Ameloblastic Sarcoma

Ameloblastic fibrosarcoma (AFS) or *ameloblastic sarcoma* is "*a neoplasm with a similar structure to ameloblastic fibroma, but in which the ectomesenchymal component shows the features of sarcoma*." This definition in the WHO[11] classification has not been superseded. The WHO explanatory note further cautions that the term should be applied only to neoplasms in which mesenchymal tissue, but not the odontogenic epithelium (ameloblastic elements), appears malignant.

An AFS in which dentinoid or osteodentin is induced or an AFS in which both dentin and enamel are produced have been, respectively, termed *ameloblastic dentinosarcoma* and *ameloblastic odontosarcoma*.[245] However, several authors[246-248] believe that the variant presence of dentinoid or an odontomatous mass does not influence or alter the course of the lesion, and therefore the terms serve no useful purpose and should be discontinued.[248]

A survey of AFS in 1977 recorded 22 lesions,[235] and another survey in 1995 accounted for 51 lesions,[250] more than double the number of reported cases within 18 years. Despite the apparent rarity of AFS, numerous published case reports[235,245,246,249-253] and detailed reviews[235,247,248] have fully documented the clinical and histologic range of this neoplasm.

Clinicopathologic Considerations

Approximately 45% of AFS lesions present clinical, radiographic, and histologic evidence of origin in ameloblastic fibroma, ameloblastic fibro-odontoma, or odontoameloblastoma, thus accounting for an average age of 21 years for patients whose AFS appears to arise de novo, and an average age of 33 years for patients in whom conversion from a preexisting benign mixed odontogenic tumor (an indication of a time-related process) occurred.

There is a modest gender preference for male over female (1.5:1) and a marked predilection for the mandible over the maxilla (4:1), with most lesions appearing in the posterior areas of both jaws.

The outstanding clinical signs and symptoms were swelling and pain in almost all cases; however, paresthesia was uncommon. Mobility of teeth and an intraoral tumor mass occurred in some instances (particularly those in which massive lesions were present). Many cases exhibited a moderate growth rate over several years, succeeded by rapid growth that forced patients to seek treatment.

Radiographs demonstrate a radiolucent, multilocular appearance, with either well-defined or irregular borders. However, lesions that are very large at the time of clinical discovery show marked areas of bone destruction and indistinct margins, with thinning, expansion, or disruption of the cortex. Maxillary lesions may extend into the maxillary sinus, with destruction of the sinus walls. Root resorption and tooth displacement are inconstant features. Lesions that contain dentinoid or odontomatous tissue usually show radiopaque foci.

Histologically, as in ameloblastic fibroma, the ameloblastic cords, trabeculae, and islands in AFS do not show increased evidence of malignancy; however, the mesenchymal tissue demonstrates marked change from the dental papilla appearance and exhibits features of malignancy—hypercellularity, pleomorphism, hyperchromasia, and increased as well as abnormal mitoses.

The mesenchymal elements of the ameloblastic fibroma, per se, may present a disquieting, sometimes

chaotic appearance, but changes in size, shape, staining intensity, and mitotic activity of the cells are usually absent. Careful search of histologic sections of some ameloblastic fibromas may reveal foci of increased cellularity and changes in size and shape of mesenchymal cells. Such areas may or may not be significant in a lesion's conversion to malignancy.

In ameloblastic fibroma, many ameloblastic islands are surrounded by a clear or hyalinized zone (in which dentinoid may develop) peripheral to which is the mesenchymal stroma. In contrast to this appearance, in AFS the clear zones lessen or vanish, and the malignant stromal cells directly encircle the ameloblastic islands.

Cases that document repeated recurrences show that recurrence often is accompanied by increased cellularity and increasingly anaplastic cells, bizarre mitoses, and formation of tumor giant cells. In some recurrent lesions the ameloblastic elements notably diminished with each recurrence, and in a few cases they totally disappeared, signaling the lesion's complete conversion into fibrosarcoma. Similarly, dentinoid induced in some ameloblastic fibromas also tended to disappear completely as lesions converted to AFS. It is an interesting hypothesis that perhaps the ameloblastic epithelium and ectomesenchyme of the ameloblastic fibroma exert a reciprocal benignifying effect on each other, but when a malignant process intervenes, the ameloblastic epithelium loses not only control, but also presence.

In a study by Muller and colleagues[249] the DNA content of mesenchymal cells in AFS in comparison with ameloblastic fibroma was measured to see whether a correlation existed between histologic features and DNA ploidy. If so, DNA content could help provide an objective measurement to assess clinical behavior in addition to histologic grading. The study did not demonstrate such a correlation.

Management and Outcome

The earlier reports of AFS tended to depict the lesion in a somewhat casual manner, despite the recognition of the malignant histologic characteristics. It was mistakenly believed that local removal of the tumor was sufficient.

Leider and associates[247] in their 1972 survey found they could not correlate clinical behavior with microscopic characteristics. They believed that despite the histologic features of an anaplastic mesenchymal tumor, the lesion behaved as a low-grade fibrosarcoma. They recognized that most cases of AFS arose from malignant change in ameloblastic fibroma and that repeated recurrences led to uncontrollable disease and death. Altini and co-workers[248] in their 1985 study characterized the biologic behavior of AFS as locally aggressive rather than regionally or distantly metastatic. Both of these studies gave relatively ambiguous recommendations for "surgical excision" or "resection." Muller and colleagues[249] in their 1995 survey recommended surgical management as dictated by the clinical extent of disease. It is clear from a review of case histories that AFS has a range of biologic behavior from low-grade fibrosarcoma to high-grade fibrosarcoma.

Chemotherapy has been used in two instances in an attempt to manage recurrent extensive ameloblastic fibrosarcoma. In the first case, details of which were reported by Goldstein and associates[251] in 1976 and by Howell and Burkes[235] in 1977 (same case), a 37-year-old man had a lesion in the mandibular premolar region recognized in 1954 but treated during a 10-year period from 1960 to 1970. Initial treatments included multiple curettements over 5 years; recurrences were treated by partial resections, followed by radical resections; subsequent recurrences were treated by further resection, until massive soft tissue involvement made further surgery impossible. Chemotherapy was initiated with daily oral cyclophosphamide (Cytoxan) and weekly intravenous actinomycin D and vincristine. Clinical success with no evidence of disease for 1 year was achieved, after which a small recurrence was again treated by the chemotherapeutic regimen with a further 1-year disease free state. A small malignant melanoma was then found and excised. However, pulmonary and cerebral metastases of the melanoma occurred, and the patient died. In the second case, reported by Park and co-workers,[253] a 17-year-old boy had an exophytic intraoral lesion and a destructive lesion of the mandible and associated soft tissue. Biopsy revealed ameloblastic fibrosarcoma. Composite resection and immediate reconstruction were performed, followed by adjuvant chemotherapy with cyclophosphamide, doxorubicin (Adriamycin), and vincristine. Three months later facial recurrence was seen. Radiation was initiated without response, and the patient died. In the first case multiple diagnoses were made over the years—dentigerous cyst, ameloblastic fibro-odontoma, and finally AFS—apparently signifying a conversion; in the second case, the lesion appeared to be de novo AFS.

- Histologically, tissue analysis of ameloblastic fibroma, particularly recurrent lesions, may be difficult or lead to misdiagnosis. Multiple sections from all areas of the tumor should be studied; over- or underdiagnosis is possible.
- The potential for malignant change in ameloblastic fibroma is sufficient indication for aggressive initial resection by Rs-CD or Rc-CD. Approximately 45% of AFS is secondary to malignant change in ameloblastic fibroma.
- A total of 20% to 23% of AFS cases eventuate in death of the patient as a result of uncontrollable extension of the disease.
- Metastasis is not a usual feature of AFS behavior but has been reported.
- Early diagnosis and initial aggressive resection by Rs-CD or Rc-CD of de novo or secondary AFS is mandatory. Adjuvant chemotherapy may be indicated in massive lesions.
- Long-term clinical and radiographic follow-up evaluation of at least 10 years is necessary.

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19

Benign Non-odontogenic Lesions of the Jaws

BRIAN L. SCHMIDT

Lesions Containing Multinucleated Giant Cells

Jaw lesions that microscopically contain giant cells include the giant cell granuloma, the giant cell tumor, hyperparathyroidism, cherubism, and the aneurysmal bone cyst. All of these jaw lesions are identical histologically and must be distinguished based on clinical, radiographic, and biochemical means.

Central Giant Cell Granuloma

The central giant cell granuloma represents a benign proliferation of fibroblasts and multinucleated giant cells. Despite early references to the lesion as a "giant cell reparative granuloma," progression is likely without treatment.[1,2] The precise nature of the central giant cell granuloma remains speculative. It has been suggested that it may be an inflammatory lesion, a reactive lesion, a neoplasm, or an endocrine lesion. The proliferating cell in this lesion is the fibroblast, which is believed to produce cytokines, resulting in the recruitment of monocytes, which subsequently transform into multinucleated giant cells. Immunohistochemistry has shown the giant cells to be osteoclasts.[3] There is also debate on whether the central giant cell granuloma is unique to the jaws or whether it represents a continuum of the same disease process as giant cell tumors affecting the long bones, which are discussed later in this chapter.

Central giant cell granulomas of the jaws are most often found in children and young adults, with up to 75% of cases occurring before 30 years of age. Females are affected twice as frequently as males. The lesion most often occurs anterior to the first permanent molar teeth. The mandible is affected three times more frequently than the maxilla, and the lesion may be seen to cross the midline. There are two types of central giant cell granulomas based on biologic behavior and radiographic features. Chuong, Kaban, and colleagues formalized a classification system that also provides a guide for treatment.[4] The aggressive form has three of the following criteria: greater than 5 cm, rapid growth, root resorption, tooth displacement, cortical bone thinning, cortical bone perforation, and recurrence after curettage (Table 19-1; Figure 19-1).

A giant cell lesion that is larger than 5 cm and/or recurs after curettage is aggressive based on these characteristics alone. The nonaggressive lesion is asymptomatic, grows slowly, and does not produce cortical perforation or root resorption. Presently, there are no molecular methods of differentiating the aggressive form from the nonaggressive type, and the clinician is dependent on the history, physical examination, plain radiographs, and computed tomography with contrast. Radiographically, central giant cell granulomas may present as a unilocular or multilocular radiolucency that is usually well delineated.

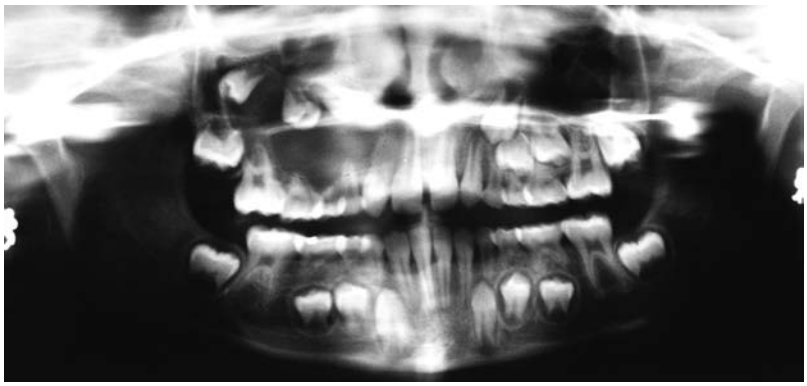
Histologically, the central giant cell granuloma contains few to many multinucleated giant cells in a background of fibroblasts with varying amounts of collagen. The multinucleated giant cells are often focally aggregated; however, they may be evenly distributed. Hemosiderin-laden macrophages and extravasated erythrocytes are commonly seen. Foci of osteoid may be seen, particularly at the periphery of the lesion. These histopathologic features are similar, if not identical, to those seen in the brown tumor of hyperparathyroidism and cherubism.

Treatment regimens have varied over the past two decades, and a single effective treatment strategy for lesions does not exist. For years surgical curettage has been the treatment of choice; however, curettage alone is associated with a 30% to 70% recurrence rate for aggressive lesions.[5] The lack of a single effective treatment is the consequence of varied biologic behavior among central giant cell granulomas. Treatment regimens should be guided by the classification of the lesion as either

TABLE 19-1 Criteria for Classifying Giant Cell Lesions of the Jaws

	Aggressive	Nonaggressive
Lesion size	≥5 cm	<5 cm
Rapid growth	Yes	No
Root resorption	Often	No
Tooth displacement	Often	No
Cortical bone perforation	Often	No
Recurrence after curettage	Yes	No

Adapted from Chuong R, Kaban LB, Kozakewich H, Perez-Atayde A: Central giant cell lesions of the jaws: a clinicopathologic study, *J Oral Maxillofac Surg* 44: 708-713, 1986.

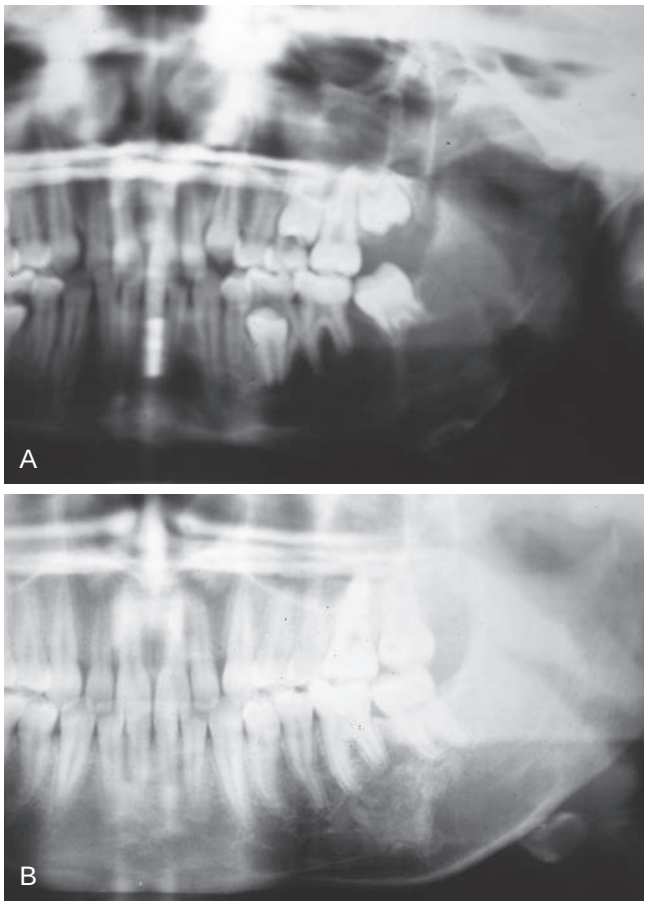


• **Figure 19-1** Central giant cell granuloma. The lesion involves the right maxilla in a 9-year-old girl with root resorption and tooth displacement.

aggressive or nonaggressive. For an aggressive giant cell lesion, resection with histologically clear margins is generally effective treatment.[4] Recurrence risk and the fact that with large lesions even conservative curettage may be associated with the loss of teeth, damage to the inferior alveolar nerve, and sinus and nasal implications has led to the development of several nonsurgical and adjuvant treatments. The first nonsurgical treatment proposed was intralesional corticosteroid injections.[6] Weekly injections of triamcinolone for 6 weeks have been shown to induce partial and in some cases complete resolution of the lesions.[6-9] The mechanism of action for steroid treatment of giant cell lesions remains unknown. In 1993, Harris reported on the management of aggressive central giant cell granulomas with subcutaneous calcitonin injections.[10] Human calcitonin 0.5 mg (100 IU) was administered subcutaneously for 1 year. Subsequent reports by Pogrel, who administered calcitonin for approximately 18 months, have confirmed the efficacy of this method (Figure 19-2).[11-13]

A double-blind placebo-controlled study evaluating the efficacy of calcitonin in the management of the central giant cell granuloma found no difference between calcitonin and placebo.[14] The mode of action of calcitonin remains speculative; however, some of the giant cells in these lesions have been shown to have calcitonin receptors.[13] Thus, the therapeutic effect of calcitonin may be mediated through inhibition of osteoclastogenesis. In 1999, Kaban and colleagues reported on the management of an aggressive giant cell lesion with interferon alpha-2a following two failed resections. Alpha-interferon given by subcutaneous injection following enucleation has clearly documented efficacy.[5,15] The lesion is enucleated with preservation of teeth and the inferior alveolar nerve. One to 2 days following enucleation, interferon alpha-2b is started at a dose of 3,000,000 units/m^2 injected subcutaneously per day. Interferon treatment is continued for 6 months or until there is evidence of complete regeneration of the defect based on a computed tomography (CT) scan. The rationale for this therapy is that the antiangiogenic action of the alpha-interferon will suppress the angiogenic component of the lesion, resulting in resolution. For aggressive giant cell lesions, two likely effective treatment regimens are resection with histologically clear margins or the combination of enucleation followed by interferon therapy. In most cases surgery is still required after the alpha-interferon treatment; however, it may be less radical, and there may be a reduced recurrence rate.

Denosumab (Xgeva, Amgen, Thousand Oaks, CA; Prolia, Bioscience Technology, Rockaway, NJ) is a human monoclonal antibody that binds receptor activator of nuclear factor-κB ligand (RANKL). Denosumab is FDA



• **Figure 19-2** Central giant cell granuloma treated with calcitonin. **A,** Left mandibular lesion in a 9 year-old. **B,** Significant resolution after 18 months of calcitonin with continued root development of the lower left second molar and eruption of the lower left second premolar. (**A** from Pogrel MA: Calcitonin therapy for central giant cell granuloma. *J Oral Maxillofac Surg* 61:651, 2003. **B** Courtesy Dr. M. Anthony Pogrel.)

approved and has been used for treatment of osteoporosis in postmenopausal women. Experience with denosumab in the management of central giant cell granuloma is limited; however, the drug shows promise in reducing lesion size.[16]

Giant Cell Tumor

The giant cell tumor normally found in long bones is an aggressive lesion that some believe is a variant of low-grade osteosarcoma. This tumor is generally believed to be an entity that is separate from the central giant cell granuloma of the jaws, although, according to some authorities it rarely occurs in the jaws. Histologically, it is very similar to the central giant cell granuloma, although the giant cells are larger with more nuclei and are more evenly distributed, the stroma is more cellular, and there may be areas of necrosis. However, in any particular case it may be difficult to make a distinction. The recurrence rate of giant cell tumors in long bones following curettage is higher than for central giant cell granulomas of the jaws, leading some authorities to advocate resection.

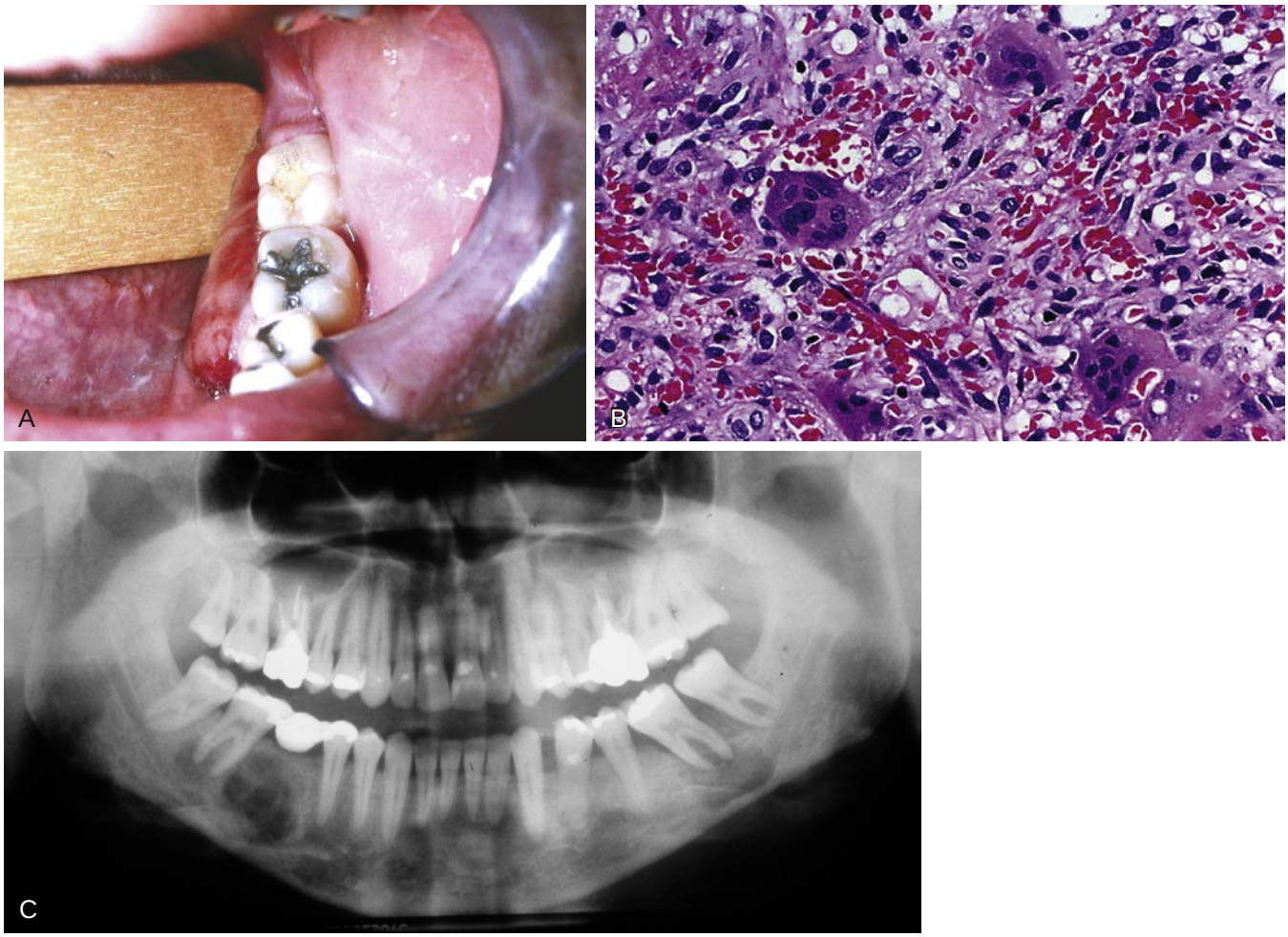
Hyperparathyroidism

Hyperparathyroidism is characterized by the overproduction of parathyroid hormone (PTH). Primary hyperparathyroidism (HPT) is the uncontrolled production of PTH as the result of a parathyroid adenoma, hyperplasia, or rarely an adenocarcinoma. Primary HPT is most commonly seen in postmenopausal women, with a female-male ratio of 3:1. Secondary hyperparathyroidism occurs in response to hypocalcemia, most often as a result of chronic renal failure. In both forms of hyperparathyroidism, excess PTH levels stimulate osteoclast-mediated bone resorption, which may produce a focal bone lesion known as a brown tumor of hyperparathyroidism. The lesion derives its name from the color of the tissue as seen on surgical exploration, which is a result of erythrocyte extravasation and hemosiderin deposition within the lesion, as well as fibrous replacement of the bone marrow.

Like the central giant cell granuloma, the brown tumor of hyperparathyroidism lesion appears radiographically as a well-defined unilocular or multilocular radiolucency. Loss of the lamina dura occurs in about 80% of patients with hyperparathyroidism who present with brown tumors and helps to distinguish jaw lesions due to hyperparathyroidism and lesions representing primary jaw tumors.[17] Loss of the radiopaque lamina dura gives a characteristic "floating teeth" appearance to dental films (Figure 19-3). The changes in bone observed with hyperparathyroidism include mild bone pain without radiologic findings, mild osteopenia, or osteitis fibrosa cystica, which is characterized by a constellation of severe changes, including diffuse subperiosteal resorption, multiple bone cysts, and brown tumors. The most common sites of brown tumors are the ribs, clavicles, pelvic girdle, and mandible. When a brown tumor occurs in the mandible, patients complain of localized jaw pain and swelling, bleeding from the gums, and loose teeth. The maxilla is an uncommon site for brown tumors.

The radiographic differential diagnosis of multiple mandibular radiolucencies includes brown tumors and other clinical entities that have distinct histologic appearances, such as Langerhans cell disease (which can also cause loss of lamina dura on dental films), primary or metastatic cancers, multiple odontogenic keratocysts as part of nevoid basal cell carcinoma syndrome, ossifying fibromas, and jaw osteomas of Gardner syndrome.

Before the advent of inexpensive assays for calcium and phosphorus in the 1950s and 1960s, brown tumors were commonly seen as the presenting symptom of hyperparathyroidism.[17] However, with current widespread screening for calcium and phosphorus abnormalities, as well as parathyroid hormone, most cases of hyperparathyroidism are detected in asymptomatic patients. Before the diagnosis of primary hyperparathyroidism is made, hyperparathyroidism secondary to renal failure should be ruled out. In the case of secondary hyperparathyroidism, appropriate laboratory values will demonstrate impaired renal function and hypocalcemia. A 24-hour urinary calcium level should be



• **Figure 19-3** Hyperparathyroidism. **A,** Left mandibular gingival lesion in a 30-year-old woman with hyperparathyroidism. The associated mandibular molars were mobile. **B,** A biopsy of the gingival lesion revealed spindle-shaped fibroblastic cells, extravasated red blood cells, and giant cells in varying shape and distribution. **C,** The panoramic radiograph demonstrated multiple radiolucencies in the mandible.

measured to rule out benign familial hypocalciuric hypercalcemia, a hereditary condition that leads to hyperparathyroidism because of low renal sensitivity to parathyroid hormone. As opposed to patients with primary hyperparathyroidism, patients with benign familial hypocalciuric hypercalcemia do not benefit from parathyroidectomy.[18] Brown tumors can be seen in primary hyperparathyroidism or in secondary hyperparathyroidism related to renal failure. Because there are a number of familial hyperparathyroidism syndromes, a family history should be elicited. Hyperparathyroidism can occur as part of a multiple endocrine syndrome (multiple endocrine neoplasia type 1 or 2A) or as the hyperparathyroidism–jaw tumor syndrome. Hyperparathyroidism–jaw tumor syndrome is an autosomal dominant disease that is characterized by either adenoma or carcinoma (in 10%-15% of patients) of the parathyroid, fibro-osseous lesions of the jaws, renal cysts, and tumors. Eighty percent of patients with the syndrome will present with hyperparathyroidism.[19] Hyperparathyroidism–jaw tumor syndrome was recently shown to be caused by a mutation in tumor-suppresser gene *HRPT2* (also known as *CDC73*).[19,20] This tumor suppressor gene encodes a protein parafibromin.[19] *CDC73* mutations have dominant germline gene behavior and variable penetration. The jaw tumors of this syndrome, interestingly, are not giant cell tumors and thus occur by a mechanism distinct from hyperparathyroidism. Forty percent of patients with the syndrome will develop jaw tumors, including ossifying fibromas, that are distinct from the brown tumors secondary to hyperparathyroidism.

Histologically, the giant cell lesions associated with hyperparathyroidism are characterized by proliferation of spindle-shaped fibroblastic cells, extravasated red blood cells from hemorrhage, hemosiderin deposits, and trabeculae of new bone formation. CD68-positive giant cells can be present in varying shape, distribution, and number and are consistent with increased osteoclast activity.

Patients with primary hyperparathyroidism will be hypercalcemic, with associated signs and symptoms including fatigue, weakness, memory loss, depression, renal symptoms (polyuria, polydipsia, renal stones), constipation, abdominal pain, and pancreatitis. In contrast, those with secondary hyperparathyroidism will be hypocalcemic and

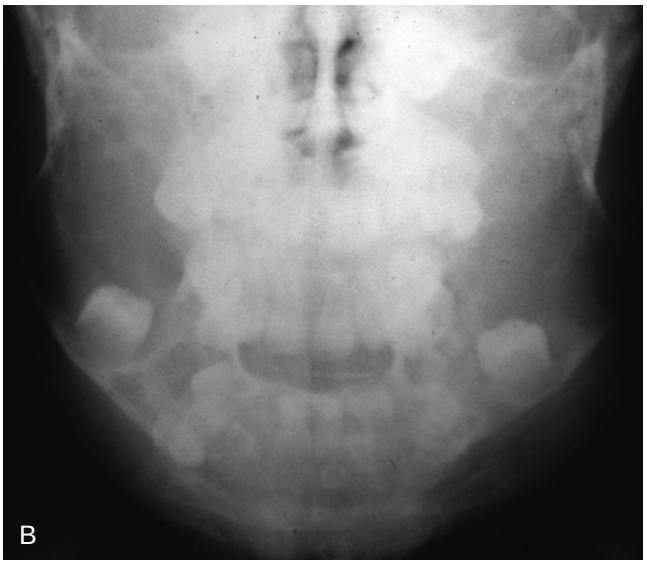
those with central giant cell granulomas will have normal serum calcium levels. Elevated serum PTH levels are associated with both forms of hyperparathyroidism. Normal PTH levels are found in association with central giant cell granulomas. Therefore, serum calcium and PTH levels should be obtained in patients with giant cell lesions in order to exclude hyperparathyroidism. If a diagnosis of hyperparathyroidism is confirmed, treatment must be aimed at the cause (parathyroidectomy). Brown tumors of primary hyperparathyroidism are treated with surgical removal of the abnormal parathyroid tissue and normalization of parathyroid hormone levels. Typically the brown tumors will regress after the hyperparathyroidism has been successfully corrected.[17,21,22] Surgical excision of the brown tumor itself is generally not recommended. Complete healing of the affected bone, however, can be delayed as much as 5 years with conservative management.[23] Thus, surgical resection of lesions that are large, symptomatic, or at risk for pathologic fracture might be indicated.

Cherubism

Cherubism is a rare hereditary condition characterized by painless, bilateral, symmetrical expansion of the embryologic mandible and maxilla. It was first described in 1933, when it was named familial multilocular cystic disease of the jaws.[24] It follows an autosomal dominant pattern of inheritance with 100% penetrance in males, 50-75% penetrance in females, and variable expressivity. There is a 2-to-1 male predominance. Sporadic cases have also been reported in up to 40% of cases. The genetic defect has been mapped to chromosome 4p16.3,[25,26] which encodes the binding protein SH3BP2.[27-29] Recently, work with murine genetic models has suggested that infection and activated macrophages might be driving development and progression of cherubism.[30]

The lesions of cherubism commonly begin to manifest as painless, bilateral, symmetric expansion of the jaws between 2 and 5 years of age (Figure 19-4), although milder forms may not be detected until a later age. The lesions are confined to the mandible and maxilla and the remaining facial bones are not involved. The regions most often affected are the mandibular angle, ascending ramus, retromolar region, and maxillary tuberosity; however, in severe cases the entire mandible and maxilla may become involved with resultant difficulties with speech and chewing. Middle conchal expansion with maxillary involvement might manifest as difficulty with nasal breathing. Most cases involve the mandible only. On palpation, the affected areas of the jaws are hard. The mandibular condyles are always spared. With involvement of the maxillary contribution to the orbital floor, the globes may be displaced upward, resulting in scleral show. With eyes that appear to be turned upward and a round face, children with a severe form of this condition appear like cherubs depicted in Renaissance paintings. Interference of the developing teeth can lead to missing, malformed, or impacted teeth.





• **Figure 19-4** Cherubism. **A,** Frontal view of a 5-year-old boy with bilateral facial expansion. **B,** Radiolucencies in the mandible bilaterally with sparing of the condyles. (Courtesy Dr. M. Anthony Pogrel.)

Radiographically, the involved bones show multilocular radiolucencies with thin and expanded cortices. There may be premature exfoliation of primary teeth as well as unerupted and displaced permanent teeth on the radiograph. The mandibular condyles will appear normal on radiographs. Histologically, the lesions resemble the central giant cell granuloma. However, some lesions will exhibit eosinophilic perivascular cuffing of collagen surrounding small capillaries throughout the lesion, allowing for differentiation between the two lesions.

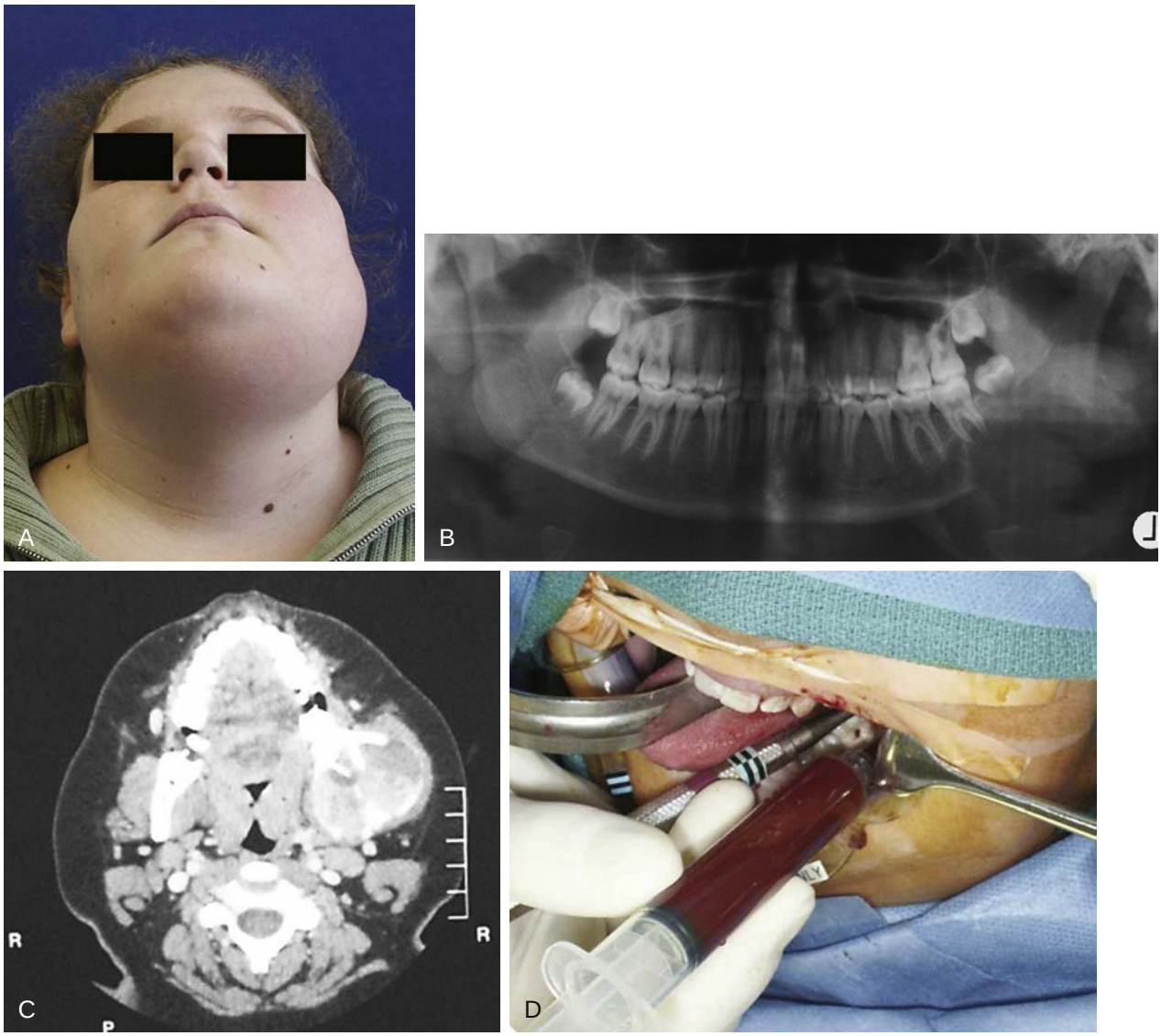
The lesions of cherubism tend to enlarge until puberty, at which time they begin to regress. In the majority of cases near-complete resolution of the facial expansion occurs by 30 years of age. Therefore, treatment is usually conservative,

allowing natural regression to occur. If surgical recontouring of expanded bone is necessary, it is best to defer it until after puberty. During childhood and early adolescence, treatment should be directed toward facilitating the eruption of teeth. Despite the histologic similarity of cherubism to central giant cell granuloma, calcitonin has no efficacy in the management of the lesions associated with cherubism.[31]

Aneurysmal Bone Cyst

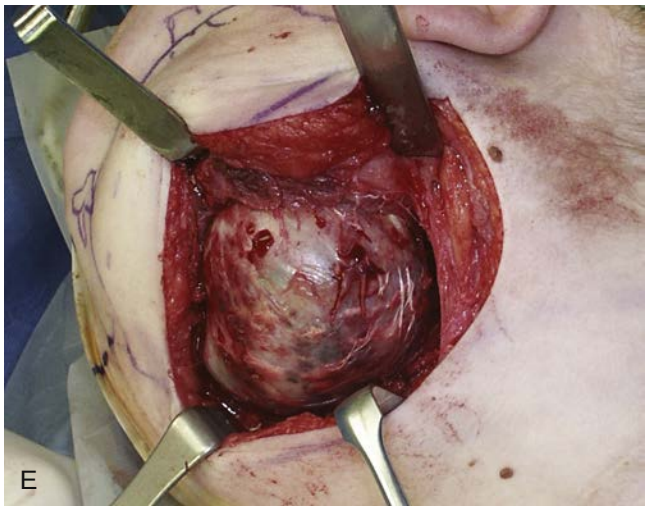
The aneurysmal bone cyst is a pseudocyst characterized by blood-filled spaces in a connective tissue stroma containing multinucleated giant cells. The lesion was first described by Jaffe and Lichtenstein in 1942.[32] Jaw involvement was first reported in 1958.[33] The lesion occurs most commonly in the long bones and vertebrae. Within the craniofacial complex, it is most common in the mandible, followed by the maxilla. The etiology and pathogenesis of the lesion remain unknown, although the lesion is generally regarded as reactive. Controversy remains over whether the lesion occurs as a primary entity or results from the development of a dilated vascular bed in a preexisting intrabony lesion. Molecular evidence now exists that supports the theory that vascular injury is important in the development of this lesion.[34] There is also controversy as to whether the aneurysmal bone cyst is a distinct entity or whether the lesion is a form of the central giant cell lesion. In the jaws, the aneurysmal bone cyst occurs with other bone disease 22% of the time.[35]

Aneurysmal bone cysts can occur at any age; however, the peak incidence occurs within the second decade of life, with most occurring prior to 30 years of age. There is a slight female predilection. Mandibular and maxillary lesions most frequently occur in the molar regions. Patients often present with facial swelling that may develop fairly rapidly and can be associated with pain; however, often the lesions are asymptomatic (Figure 19-5). The lesion usually appears radiographically as a multilocular radiolucency,



• **Figure 19-5** Aneurysmal bone cyst. **A,** A 13-year-old girl with a rapidly expanding mandibular angle mass over the course of 3 weeks. **B,** Panoramic radiograph revealed expansile, destructive lesion. **C,** Axial CT demonstrating cortical expansion and thinning. **D,** At the time of surgical resection the lesion was filled with blood.

Continued





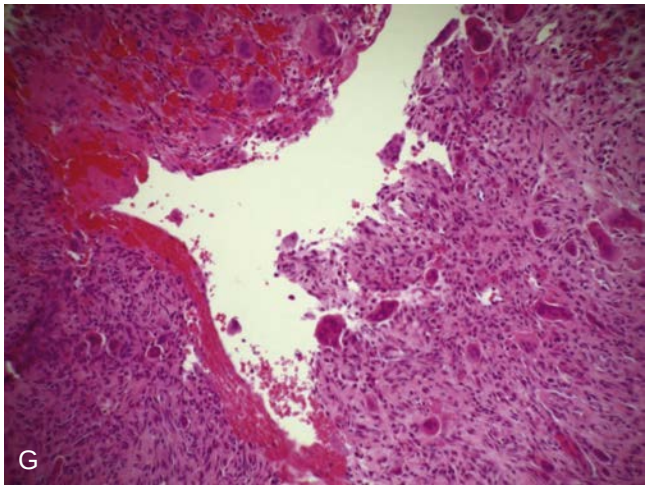


Figure 19-5, cont'd **E,** Lesion at time of resection. **F,** Resected lesion. **G,** Histology shows a cellular connective tissue stroma admixed with multinucleated giant cells and extravasated red blood cells. A prominent sinusoidal space is seen.

giving it a "soap bubble" appearance; however, lesions can appear unilocular. The cortex can be expanded, thinned, or destroyed.[36] Microscopically, sinusoidal blood-filled spaces of varying size are seen. These spaces are not lined by endothelium, but are surrounded by a fibrous connective tissue stroma with variable numbers of multinucleated giant cells that typically line the cystic spaces. The stromal cells consist of fibroblasts, myofibroblasts, osteoblasts, and histiocytes.[37] Osteoid and woven bone can often be seen within the lesion.

Treatment for aneurysmal bone cysts should be based on the biologic behavior of the lesion. Treatment options include enucleation, curettage, curettage with cryotherapy, and resection. In the long bones, curettage alone has been associated with a recurrence rate in the range of 50%.[38] The combination of curettage and cryotherapy is associated with a decreased rate of recurrence.[39,40] Although some authors feel that maxillofacial aneurysmal bone cysts are associated with a relatively high recurrence rate, curettage remains the treatment of choice. For lesions that are rapidly growing, resection is often necessary. At the time of surgery, lesional tissue appears like a "blood-soaked sponge." Although lesions are often blood-filled, significant hemorrhage is usually not encountered.

Fibro-osseous Lesions

Ossifying Fibroma (Cemento-ossifying Fibroma)

mal bone by fibrous tissue and varying amounts of newly formed bone and/or cementum-like material. Because of their histologic similarities, ossifying fibroma, fibrous dysplasia, and cemento-osseous dysplasia are classi-

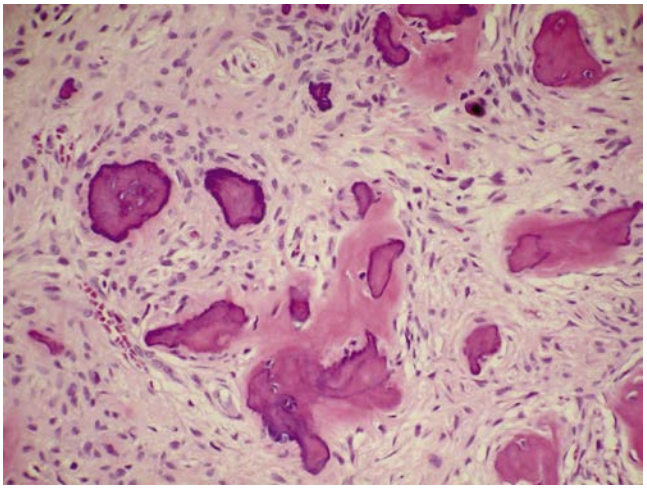
somal abnormalities have been identified in the ossifying



• **Figure 19-6** Ossifying fibroma. Panoramic radiograph demonstrating well-demarcated radiolucent-radiopaque lesion.

fibroma[42-44]; however, the molecular mechanisms that underlie the development of this tumor remain unknown. Histologically, the ossifying fibroma is characterized by spindle-shaped fibroblasts within a background of fibrous connective tissue. Bony spheroids are distributed throughout the lesion. Lesions with similar clinical presentation and clinical behavior that contain spheroidal bone have been designated cementifying fibroma or cementoossifying fibroma.

Ossifying fibromas typically present as a painless, slow-growing, and expansile lesion. Although they occur over a wide age range, most cases occur in the third and fourth decades of life. There is definite female predilection. They are felt to be confined to the jaws and craniofacial complex. The mandible, particularly the premolar-molar region, is affected more commonly than the maxilla. Rare multicentric and/or familial ossifying fibromas have been reported.[45,46]



• **Figure 19-7** Ossifying fibroma. Cellular fibroblastic tissue with areas of calcification with osteoid differentiation.

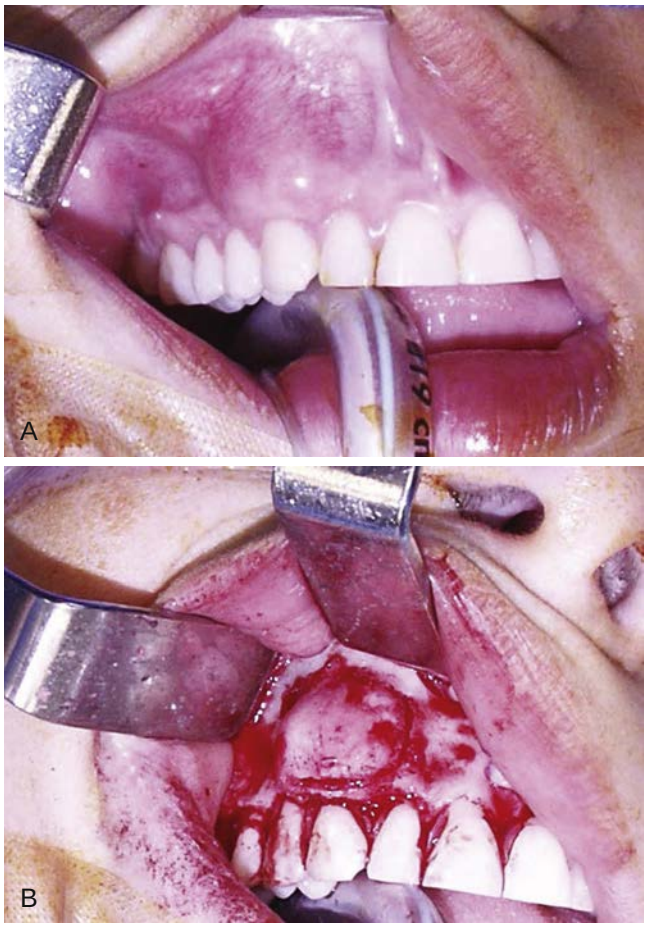
The borders are usually smooth and may be sclerotic. Root displacement and, less commonly, root resorption may be seen. Histologically, they are composed of a fibrous stroma with bony trabeculae and/or cementum-like spherules evenly distributed throughout the stroma (Figure 19-7).The microscopic appearance may be indistinguishable from fibrous dysplasia.

The recommended treatment of ossifying fibromas is complete surgical excision and will depend on the location and size of the lesion. The smaller lesions characteristically shell out from the surrounding bone with ease (Figure 19-8). Reported rates of recurrence have ranged from less than 1% to 63%.[47-55] Involved teeth with evidence of resorption should be removed with the lesion. In light of the potential for recurrence, some authors advocate more extensive surgery for larger, more aggressive lesions and lesions involving the craniofacial bones.[49,56,57] If resection is planned, it is important to consider that ossifying fibromas do not display an infiltrative pattern into bone and therefore require smaller margins (approximately 5 mm) than the 1 cm typically required for an ameloblastoma, odontogenic myxoma, or calcifying epithelial odontogenic tumor.

Juvenile Ossifying Fibroma (Juvenile Aggressive Ossifying Fibroma; Juvenile Active Ossifying Fibroma)

The juvenile ossifying fibroma is considered by many to be a unique lesion because of its reported tendency to occur in children and adolescents, its more complex histologic features, and its tendency for more aggressive growth. However, there is no general agreement among pathologists with respect to the proper terminology, histopathologic features, or criteria for separating these lesions from the conventional ossifying fibroma.[58] Histologically the lesions are typically characterized by many spindled cells with a small amount of intervening collagen and osteoid. A rearrangement of the long arm of chromosome 12 that includes the genes *MDM2* and *RASAL1* might drive juvenile ossifying fibroma and might serve as a diagnostic and predictive marker for aggressive behavior.[59]

The lesions are typically observed in patients younger than 15, rapidly increase in size, and generally do not



• **Figure 19-8** Ossifying fibroma. **A,** Well-demarcated maxillary expansion with intact mucosa. **B,** Because lesion was small and well demarcated, it was treated with enucleation. The lesion easily shelled out.

produce pain or paresthesia. In comparison to ossifying fibroma, the mandible is much less commonly involved. The maxilla, paranasal sinuses, orbit, and frontal and ethmoid bones are more commonly affected. Because of these sites of involvement, patients can present with nasal obstruction, proptosis, and exopthalmos.[60] Two variants of the juvenile ossifying fibroma have been described. These are the trabecular variant[61] and the psammomatoid variant.[62] The trabecular variant has strands of immature cellular osteoid within the lesion and usually occurs in childhood with a slight maxillary predilection. The psammomatoid variant has small spherical ossicles surrounded by osteoid rims within the lesion. It occurs over a wider age range than the trabecular variant and usually affects the orbit or paranasal sinuses.

Although considered more aggressive than the more common ossifying fibroma that generally occurs at a later age, aggressive excision is recommended for the juvenile ossifying fibroma if the lesion is recognized early, is well confined within the bone, and is accessible to meticulous technique. Recurrence rates of 20% to 58% have been reported.[58] Clinical behavior such as rapid growth might require more aggressive management including resection with 5-mm margins (Figure 19-9).

Fibrous Dysplasia

Patients with fibrous dysplasia exhibit slow, asymptomatic enlargement of either one (monostotic) or multiple bones (polyostotic). The bone enlargement is due to replacement of medullary bone with a fibrous connective tissue proliferation containing variable amounts of osseous matrix that do not mature to lamellar bone. The etiology of fibrous dysplasia is unknown; however, the presence of an activating mutation of Gs alpha gene in osteoblastic progenitor cells has been proposed to lead to increased proliferation and abnormal differentiation of bone.[63] Fibrous dysplasia can present as a component of multiple syndromes. The combination of polyostotic fibrous dysplasia, café-au-lait macules, and endocrine abnormalities including precocious sexual development, acromegaly, hyperthyroidism, hyperparathyroidism, and hyperprolactinemia is McCune-Albright syndrome. The combination of cutaneous melanotic pigmentation and multiple skeletal lesions consisting of fibrous dysplasia is known as Jaffe-Lichtenstein syndrome.

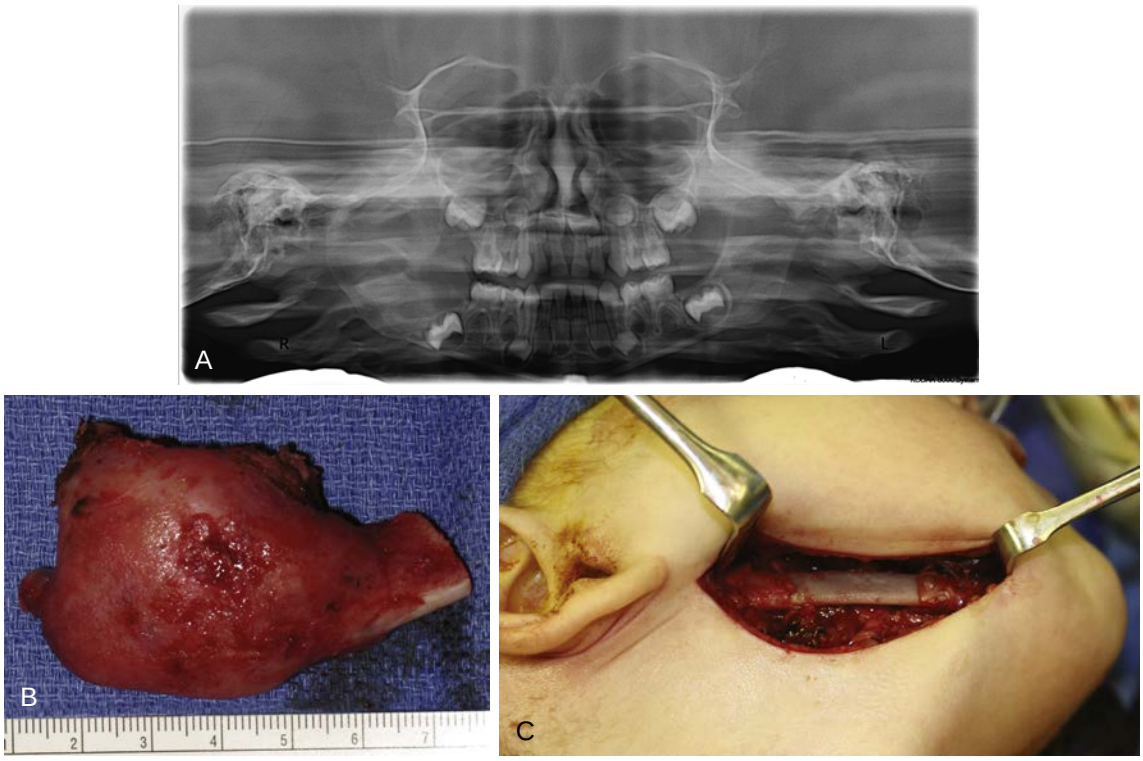
Monostotic fibrous dysplasia commonly involves the jaws, skull, long bones, pelvis, and ribs. Jaw involvement involves the maxilla more commonly than the mandible; the premolar region is most commonly involved in the former and the body region in the latter. Patients usually notice slow, asymptomatic enlargement. Whereas displacement of teeth commonly occurs, mobility of teeth is uncommon. A key clinical and radiographic feature for diagnosing fibrous dysplasia is the lack of a clear margin between the affected bone and the normal bone. The histologic features of fibrous dysplasia consist of fibroblasts within a background of collagen.

Treatment for fibrous dysplasia is necessary only when patients develop functional or cosmetic disturbances due to the bone expansion and should be delayed until adulthood if possible. Lesion expansion will typically stabilize after puberty. A skeletal survey can be used to determine whether the patient has polyostotic or monostotic fibrous dysplasia. Clinical and radiographic examination can be used to follow the extent and progression of disease. When the maxilla or mandible is affected, bone recontouring can be performed transorally. Resection has been recommended in cases where hearing or vision was threatened; however, prophylactic decompression is not recommended.[64]

Cemento-osseous Dysplasias

Periapical Cemental Dysplasia

This lesion primarily affects the anterior mandibular region of middle-aged black women. The teeth involved are vital. Patients are generally asymptomatic, and the lesions are generally discovered on routine radiographic examination. The lesions typically start as radiolucencies involving the apices



• **Figure 19-9** Juvenile ossifying fibroma. **A,** Panoramic radiograph of rapidly expanding right mandibular lesion in a 3-year-old girl. **B,** Aggressive clinical behavior dictates resection. The lesion is well demarcated with adjacent mandible grossly normal. **C,** Reconstruction with costochondral graft and resorbable mesh.

of the mandibular incisors. With time the lesions produce a radiolucent-radiopaque pattern with a progressive increase in radiopacity. Ultimately the radiolucent-radiopaque pattern stabilizes on radiographs. The diagnosis can be made based on clinical and radiographic features, and a biopsy is not required. When biopsied the tissue generally consists of cells in a background of collagen that contains a variable amount of cementum or osseous-like tissue. The amount of calcified tissue increases with time. No treatment is required for periapical cemental dysplasia.

Florid Cemento-osseous Dysplasia

Florid cemento-osseous dysplasia is similar to periapical cemental dysplasia but involves all portions of the mandible and in some cases the maxilla (Figure 19-10). Similar to periapical cemental dysplasia, this disease process typically involves middle-aged black women. Also similar to periapical cemental dysplasia, the lesions present as a mixed pattern on radiographs. The lesions are typically asymptomatic. Surgical trauma in the form of a biopsy, tooth extraction, or poorly fitting dentures can lead to a chronically draining site that does not heal and can progress to osteomyelitis. The histologic features will parallel those of periapical cemental dysplasia, except that florid cemento-osseous dysplasia often contains large sclerotic, acellular collections of cementum-like material.

The diagnosis should be made on the basis of clinical and radiographic examination. Biopsy and tooth extraction should be avoided. Development of osteomyelitis in the setting of florid osseous dysplasia should be managed in similar fashion to osteomyelitis. Debridement of symptomatic areas might be required.



• **Figure 19-10** Florid cemento-osseous dysplasia. (Courtesy Dr. M. Anthony Pogrel.)

Focal Cemento-osseous Dysplasia

Focal cemento-osseous dysplasia is a localized form of cemento-osseous dysplasia. Either the mandible or maxilla can be affected, with the posterior mandible being the most common site. Involved areas are generally less than 2 cm. Women are more commonly affected than men. Both white and black patients can be affected. Lesions are generally asymptomatic and identified on routine radiographs. Diagnosis is made on the radiographs, and biopsy is generally not required. Treatment is necessary only if symptoms require removal of the involved tooth and localized debridement. Lesions can develop in multiple sites consistent with florid osseous dysplasia.

Neurogenic Tumors

Schwannoma (Neurilemmoma)

The schwannoma is a slow-growing, benign tumor arising from Schwann cells of the nerve sheath (neurilemma). As this encapsulated tumor enlarges, it pushes the involved nerve aside without enveloping it. It most commonly occurs in the soft tissues of the head and neck, as well as the flexor surfaces of the upper and lower extremities. Intraosseous lesions are rare; however, the mandible is the most common site of occurrence for central lesions, and maxillary lesions have been reported. Lesions may occur over a wide age range but are most common in young adults. Bony lesions may be asymptomatic or produce expansion, pain, paresthesia, tooth mobility, and/or tooth displacement.

The usual radiographic appearance is that of a well-defined, unilocular radiolucency with a thin, sclerotic border. Histologically, this is an encapsulated spindle-cell tumor that consists of variable amounts of two types of tissue, Antoni A and Antoni B. Antoni A tissue consists of spindle cells organized in palisaded whorls and waves around central acellular, eosinophilic areas termed Verocay bodies. Antoni B tissue consists of spindle cells randomly arranged within a loose, myxomatous stroma. The tumor is strongly S-100 protein positive.

Intraosseous schwannomas can be treated by enucleation and curettage. When the lesion arises from an identifiable nerve, such as the inferior alveolar nerve, it can be excised from the nerve while preserving nerve integrity (Figure 19-11, *A*). Recurrences are rare.

Neurofibroma

Neurofibromas arise from a mixture of cell types, including Schwann cells and perineural fibroblasts. They may occur as solitary lesions or in association with neurofibromatosis. Solitary lesions are much more common than those associated with neurofibromatosis (Figure 19-12). Neurofibromatosis is an autosomal dominant condition in which 50% of cases result from spontaneous mutation. Two types of this genetic disorder exist, neurofibromatosis type 1 (von Recklinghausen disease of the skin) (Figure 19-13) and neurofibromatosis type 2 (central neurofibromatosis). Neurofibromatosis types 1 and 2 are genetically and clinically distinct. Of patients with neurofibromatosis type 1, 95% show autosomal dominant missense or nonsense mutations, small insertions or deletions, large-scale deletions, or chromosomal translocations affecting the *NF1* gene located on 17q11.2.[65] Type 1 neurofibromatosis has variable disease manifestations. Tissues of neural crest origin are affected.

Neurofibromatosis type 1 can be diagnosed when two or more of the following exist:

1. Six or more café-au-lait spots greater than 5 mm in diameter in prepubertal patients and greater than 15 mm in postpubertal patients
2. One plexiform neurofibroma or two or more neurofibromas of any type
3. Two or more pigmented iris hamartomas (Lisch nodules)
4. Inguinal or axillary freckling
5. Optic nerve glioma
6. A distinct osseous lesion such as dysplasia of the greater wing of the sphenoid or pseudoarthrosis
7. A first-degree relative with neurofibromatosis type 1

Type 2 can be diagnosed when one or more of the following findings are present:

1. Bilateral cranial nerve VIII schwannomas (acoustic neuromas)
2. A first-degree relative with neurofibromatosis type 2 and either a single cranial nerve VIII mass or any of the following findings: schwannoma, neurofibroma, meningioma, glioma, or juvenile posterior subcapsular lens opacity

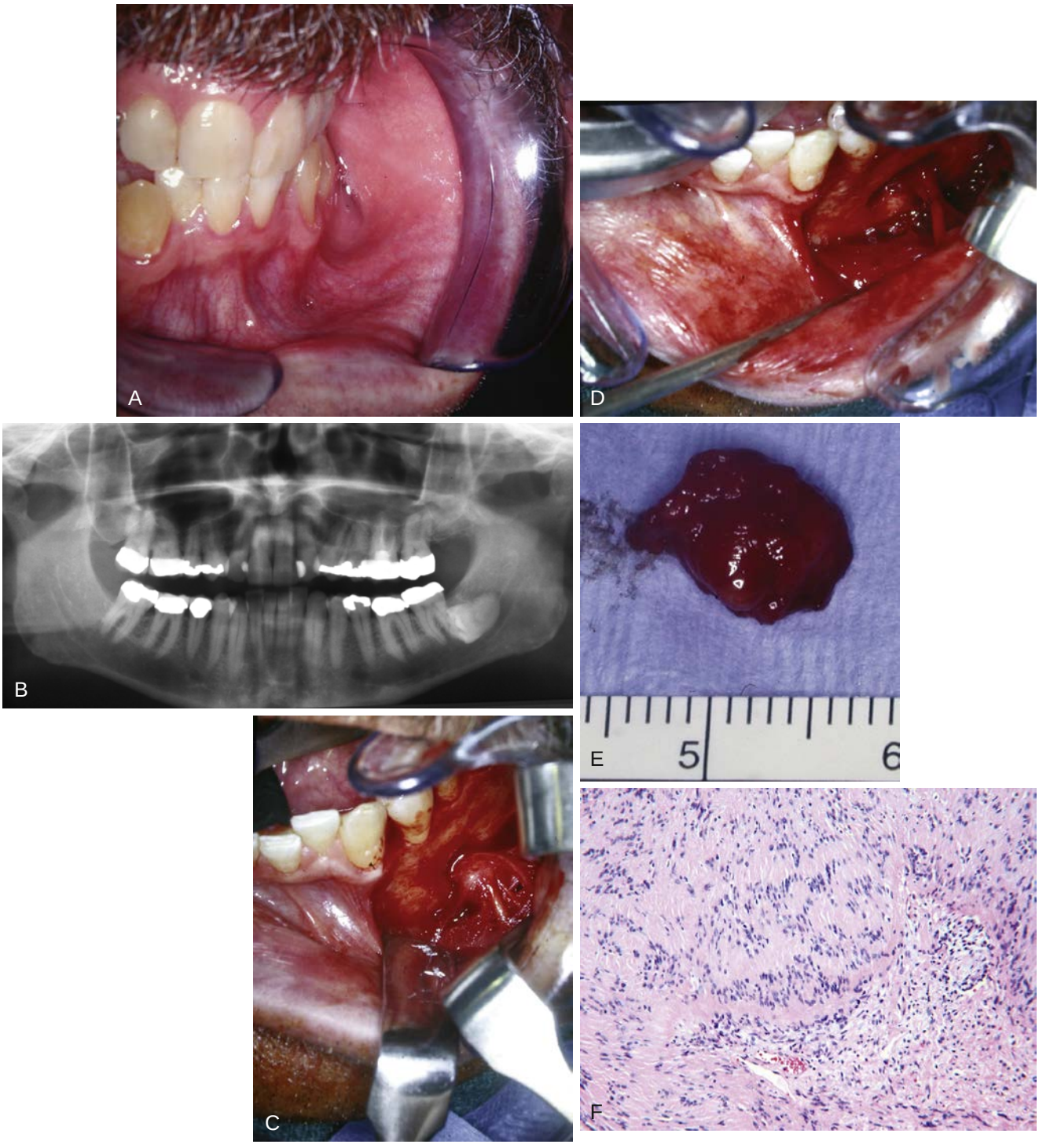
Although most commonly reported in soft tissues, neurofibromas do occur in bone and have been reported in association with the inferior alveolar nerve. Pain or paresthesia may result from lesions of the inferior alveolar nerve. Patients may also present with cortical expansion. Intraosseous lesions may produce a well-demarcated or poorly defined unilocular or multilocular radiolucency. Adjacent soft tissue neurofibromas may produce cortical erosion. Solitary neurofibromas and those found in association with neurofibromatosis share the same microscopic features. The tumor is composed of spindle-shaped cells with fusiform or wavy nuclei in a delicate connective tissue matrix. It is not encapsulated and may blend with the adjacent connective tissues. Mast cells are characteristically scattered throughout the lesion. A histologic subtype known as a plexiform neurofibroma is highly characteristic of neurofibromatosis.

The normally recommended treatment of solitary lesions following biopsy is localized excision with a 1-cm margin if possible. As opposed to the schwannoma, the involved nerve cannot be preserved because the neurofibroma arises from within the nerve. The lesions are often vascular, and extensive blood loss has been reported from surgical management of mandibular lesions; thus some authors have advocated mandibular resection. Radiation therapy is not recommended. The number of neurofibromas that can occur with neurofibromatosis type 1 makes complete surgical therapy impractical. In these cases, surgery is reserved for lesions that are large, symptomatic, and/or compromise function. Malignant transformation to neurogenic sarcoma occurs in 5% to 15% of neurofibromas associated with neurofibromatosis. Malignant transformation is felt not to occur with solitary lesions.

Other Tumors

Osteoid Osteoma

The osteoid osteoma is thought to be a benign neoplasm with unclear etiology. The osteoid osteoma and osteoblastoma are histologically identical, and the latter can be considered a larger version of the former. They are distinguished from one another primarily by size, differences in sites of occurrence, and associated symptoms. The osteoid osteoma is smaller than 2 cm; occurs most frequently in the femur, tibia, and phalanges; and presents with nocturnal pain that

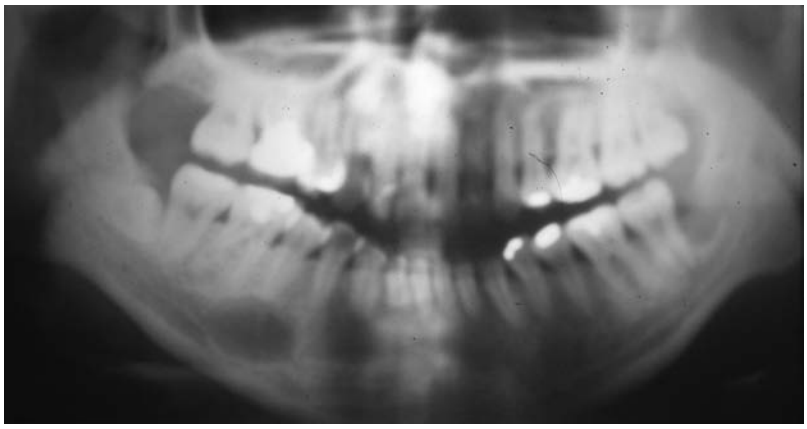


• **Figure 19-11** Schwannoma. **A,** A mass is present at the site of the mental nerve foramen between the first and second bicuspids. **B,** Panoramic radiograph revealed an expansile lesion within the inferior alveolar nerve canal. **C,** A mass associated with the mental nerve was identified on exploration. **D,** The mass was resected with preservation of the main branch of the mental nerve. Only a single branch of the mental nerve required resection, and this branch could be repaired primarily. **E,** Resected mass. **F,** Histology demonstrated palisaded Schwann cell nuclei around acellular zones forming Verocay bodies.

is alleviated by aspirin. Most cases occur in the second decade, with 85% to 90% occurring before 30 years of age. There is a 2-to-1 male predilection. The osteoid osteoma very rarely occurs in the jaws. Its characteristic radiographic feature is a zone of reactive sclerosis surrounding the lesion.

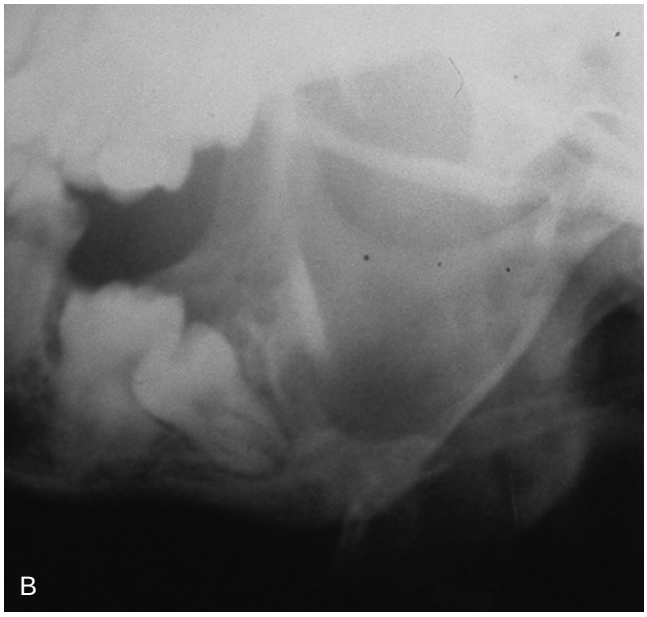
Osteoblastoma

The osteoblastoma is greater than 2 cm in diameter, occurring most frequently in the vertebrae and long bones of the extremities. The craniofacial skeleton is the site of



• **Figure 19-12** Neurofibroma. Solitary lesion involving right inferior alveolar nerve. (Courtesy Dr. M. Anthony Pogrel.)





• **Figure 19-13** Neurofibromatosis type I. Patient with combination of café-au-lait spots and neurofibroma. **A,** Multiple café-au-lait spots. **B,** Neurofibroma involving inferior alveolar nerve. (Courtesy Dr. M. Anthony Pogrel.)

involvement in 15% of osteoblastomas. The mandible is the most commonly affected site in the head and neck. Within the jaws, the posterior tooth-bearing portion is the area most often involved; however, the condyle and the coronoid process are generally spared.[66] Clinically, the osteoblastoma often develops relatively rapidly, producing swelling and pain in patients less than 30 years of age, and men are twice as commonly affected as women.[67] Osteoblastomas in younger patients can be considerably more aggressive. Paresthesia should alert the clinician to the possibility of an osteosarcoma. In contrast to osteoid osteomas, the pain is not typically nocturnal and it does not respond as well to aspirin. Enlarged lesions are typically painful on palpation.

Radiographically, these lesions are usually well defined with a mixed radiolucent-radiopaque pattern (Figure 19-14). In contrast to the osteoid osteoma where sclerotic bone surrounds the lesion, a thin radiolucent rim typically surrounds the variably calcified osteoblastoma. Slower growing osteoblastomas might demonstrate a sclerotic border on plain radiographs. Histologically, irregular trabeculae of osteoid and immature bone are seen within a cellular, richly fibrovascular stroma. The osteoid trabeculae, which exhibit varying degrees of calcification, are surrounded by prominent osteoblasts, which are large, hyperchromatic, and uniform. Osteoclasts may be adjacent to the bone, and irregular reversal lines are often present. In some cases, histologic differentiation between osteoblastoma and low-grade osteosarcoma may be difficult.

Treatment of the osteoblastoma is generally confined to conservative surgical resection with a 5-mm margin. There have been reports of some lesions regressing after incomplete excision or biopsy.[68] Recurrences are rare, but have been reported particularly when surgical access is restricted given the location. Recurrent osteoblastomas should be treated with en bloc resection.[69] Rare examples of malignant transformation have been reported.[70,71] However, because of the possible difficulty in differentiating some osteoblastomas from osteosarcomas, some of these may represent an incorrect initial diagnosis. There is no role for radiation therapy.



• **Figure 19-14** Osteoblastoma. Well-defined mixed radiolucent-radiopaque lesion involving the left posterior mandible (Booth PW, Schendel SA, Hausamen JE (editors): *Maxillofacial surgery,* Vol 1, ed 2, 2007, Churchill Livingstone.)

Osteoma

Osteomas are benign tumors composed of mature compact or cancellous bone. They are distinguished from the common palatal and mandibular tori as well as buccal exostoses despite identical histopathology. Tori and buccal exostoses are felt to be of developmental or reactive origin and not true neoplasms. Osteomas may arise from the surface of bone (periosteal osteoma), or they may be located in the medullary bone (endosteal osteoma).

Osteomas may arise in the paranasal sinuses, skull bones, and facial bones, including the maxilla and mandible. The craniofacial and jaw bones are the most commonly affected of all bones.[72] The mandible or maxilla can be involved. Periosteal osteomas are most likely to affect the angle portion of the mandible. Maxillary sinus involvement can present as ophthalmologic symptoms, headaches, or sinusitis. They most commonly develop in young adults but can be identified in any age. Osteomas are usually solitary, except in cases of Gardner syndrome. Periosteal osteomas most often present as slow-growing, painless, discrete bony masses. Endosteal osteomas are usually asymptomatic and noted on routine radiographs. Radiographically, osteomas appear as well-circumscribed, sclerotic masses. There are two histologic variants. One variant consists of normal-appearing, dense, compact bone with sparse marrow tissue. The other form consists of lamellar trabeculae of cancellous bone with fibrofatty marrow. Osteoblastic activity is often prominent.

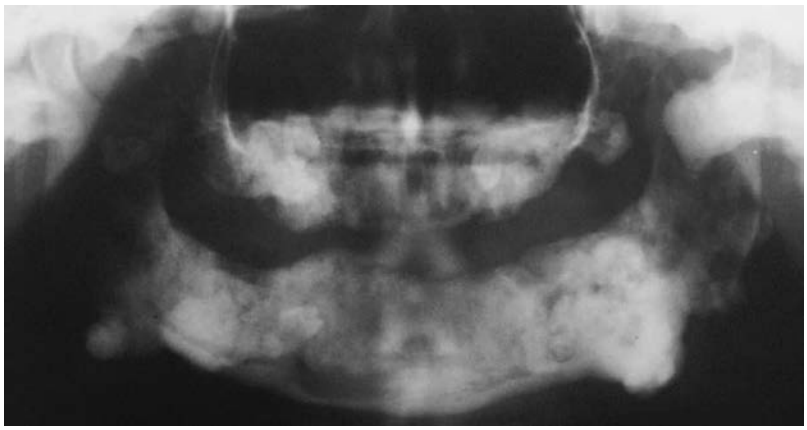
Gardner syndrome is a rare autosomal-dominant condition first reported in the early 1950s.[73] Patients with Gardner syndrome have different combinations and display a variable onset of the triad of skin and soft tissue tumors, benign osteomas, impacted permanent and supernumerary teeth, odontomas, and congenital hypertrophy of the retinal pigmented epithelium (CHRPE).[74,75] Osteomas are reported in 50% of patients. The genetic defect has been mapped to 5q21 where the familial adenomatous polyposis (APC) gene resides[76-78] The gene encodes a 2843-amino acid polypeptide.[77] The majority of patients have an incomplete manifestation of the syndrome. The most clinically important aspect of the syndrome is the high rate of malignant transformation of bowel polyps into invasive adenocarcinoma. In fact, the malignant transformation rate is 50% by age 30. As a result, patients with an established diagnosis of Gardner syndrome typically undergo a prophylactic colectomy. Patients with multiple osteomas should undergo investigation for Gardner syndrome. Osteomas in association with Gardner syndrome are frequently seen at the mandibular angles as well as other facial bones and long bones (Figure 19-15). It is important to note that the development of osteomas precedes the other manifestations of the syndrome.

Histologically osteomas can consist of mature lamellar bone or cancellous bone with abundant fibrofatty marrow between bone trabeculae. Radiographically osteomas show as well-circumscribed, densely sclerotic, and radiopaque; a sclerotic border can be present. Endosteal osteomas are generally identified on routine radiographic examination.

Osteomas can be managed based on clinical behavior. Small, asymptomatic cases may be followed clinically and radiographically. If an osteoma is deforming or causing pain, it can be treated by local excision. An endosteal osteoma can be treated with enucleation. Periosteal osteomas can often be osteotomized from the mandible along a cleavage plane. Recurrences following excision are very rare.

Chondroma

Chondromas are benign tumors composed of mature hyaline cartilage. They most commonly occur in the bones of the hands and feet, with very rare occurrences in the craniofacial complex. Within the maxillofacial region, they can involve



• **Figure 19-15** Mandibular and maxillary osteomas in patient with Gardner syndrome. (Courtesy Dr. M. Anthony Pogrel.)

the nasal septum and anterior maxilla, as well as the mandibular condyle, coronoid process, body, and symphysis.

Chondromas typically presents as a painless, slowly progressive swelling. They usually appear before 50 years of age. There is no sex predilection. Radiographically, they appear ing small chondrocytes with regular nuclei. The microscopic distinction between a benign chondroma and low-grade chondrosarcoma is very difficult. Considering the rarity with which chondromas occur in the craniofacial complex, the difficulty in differentiating between a chondroma and a low-grade chondrosarcoma, and the aggressive nature of chondrosarcomas, one should question the diagnosis of a benign chondroma in the jaws.

In order to avoid the potential risk of undertreating a malignancy, some authors consider chondromas of the jaws as potentially malignant and manage them accordingly.[79] These authors recommend wide surgical resection with 1-cm margins. If the lesion recurs following more conservative surgical treatment, the lesion should certainly be considered a low-grade chondrosarcoma and treated with wide surgical resection.

Osteochondroma

Osteochondroma is the most common benign tumor of bone, but rarely affects the oral and maxillofacial region.[80] It represents a hamartomatous process affecting endochondral bones and is cartilage-capped bony protrusion on the external surface of bone. The lesion represents an osteocartilaginous exostosis and can affect the mandibular condyle and coronoid process, as well as the posterior maxilla, maxillary sinus, and zygomatic arch. The etiology is unclear. Stress in the region of tendinous insertion might affect cells with cartilaginous potential. Such stress could lead to the formation of these tumors at the insertion of the temporalis muscle into the coronoid process and at the insertion of the lateral pterygoid muscle into the condyle.[81] Men are twice as commonly affected as women and are usually in their 20s at the time of diagnosis; however, patients with craniofacial osteochondromas are slightly older. Because the osteochondroma often produces an exophytic growth from the mandibular condyle, symptoms can consist of difficulty with jaw opening, unilateral posterior open bite, chin deviation, and facial asymmetry.

On radiographs the osteochondroma shows up as a well-defined radiopacity with a cortical outline and a central trabecular pattern. The cartilaginous portion might not be visible on radiographs. Osteochondromas of the condyle generally extend anterior from the condyle and follow the course of the lateral pterygoid muscle. Lesions affecting the coronoid project superiorly along the course of the temporalis muscle. The histologic features demonstrate both cartilaginous and bone features. The surface portion consists of hyaline cartilage and associated perichondrium. The region adjacent to bone demonstrates endochondral ossification. Deep to the area of endochondral ossification, there is medullary bone that blends with the underlying normal medullary bone.

Treatment of the osteochondroma is generally based on the patient's symptoms. Involvement of the condyle and surrounding muscles can produce difficulty opening, jaw deviation, and pain. In such cases, condylar resection with immediate costochondral reconstruction is recommended. Conservative condylar resection with articular disc repositioning has been described.[81] Involvement of the coronoid process can be addressed with coronoid process resection.

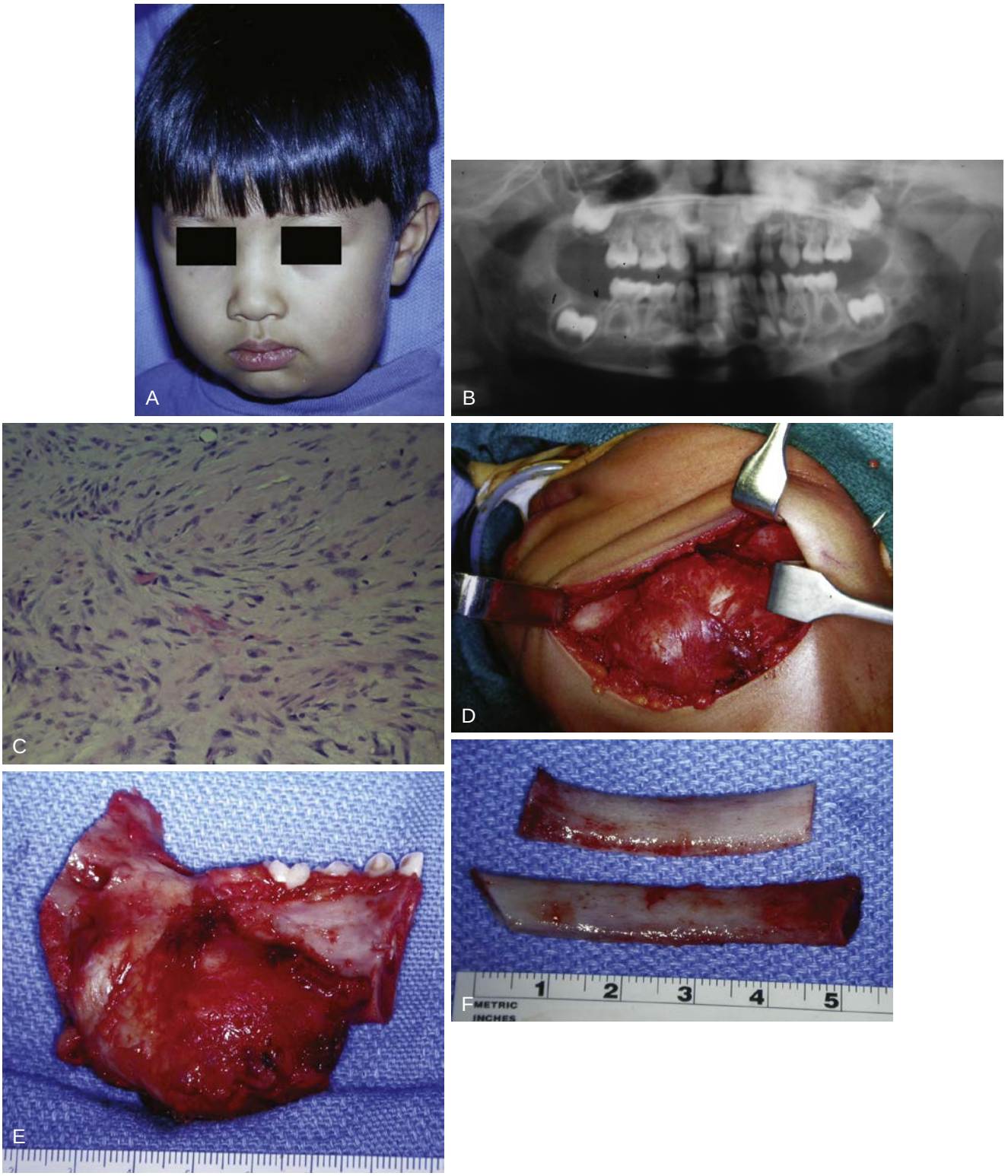
Desmoplastic Fibroma

The desmoplastic fibroma is a rare, benign, locally aggressive tumor of bone that is considered to be the osseous counterpart of soft tissue fibromatosis.[82] The etiology and pathogenesis of this lesion remain unknown, although genetic, endocrine, and traumatic factors have been suggested. The tumor affects extracranial bones including the long bone and the pelvis; however, the mandible has been considered the most common site of involvement.

The lesion usually occurs in children and young adults, with over 80% being discovered before 30 years of age.

Within the jaws, the posterior mandible body-angle-ramus is the area most frequently involved. Patients most often present with a painless, slow-growing, firm swelling of the affected jaw (Figure 19-16).[83,84] Rapid growth can occur with invasion into adjacent soft tissues.

Radiographically, the lesion typically produces a large radiolucency, which may be unilocular or multilocular. The margins may be well or poorly defined. Cortical perforation and root resorption may be seen. Microscopically, the lesion is composed of interlacing bundles and whorled aggregates of



• **Figure 19-16** Desmoplastic fibroma. **A,** A 4-year-old boy with a rapidly expanding left mandibular angle mass. **B,** Panoramic radiograph revealed destructive, expansile lesion. **C,** A haphazard arrangement of spindle-shaped fibroblasts in a collagenous stroma. **D,** Aggressive clinical behavior dictated resection. Expansile, destructive mass at angle of mandible pushing into adjacent soft tissue. **E,** Resected mass. **F,** Costochondral grafts for immediate reconstruction.

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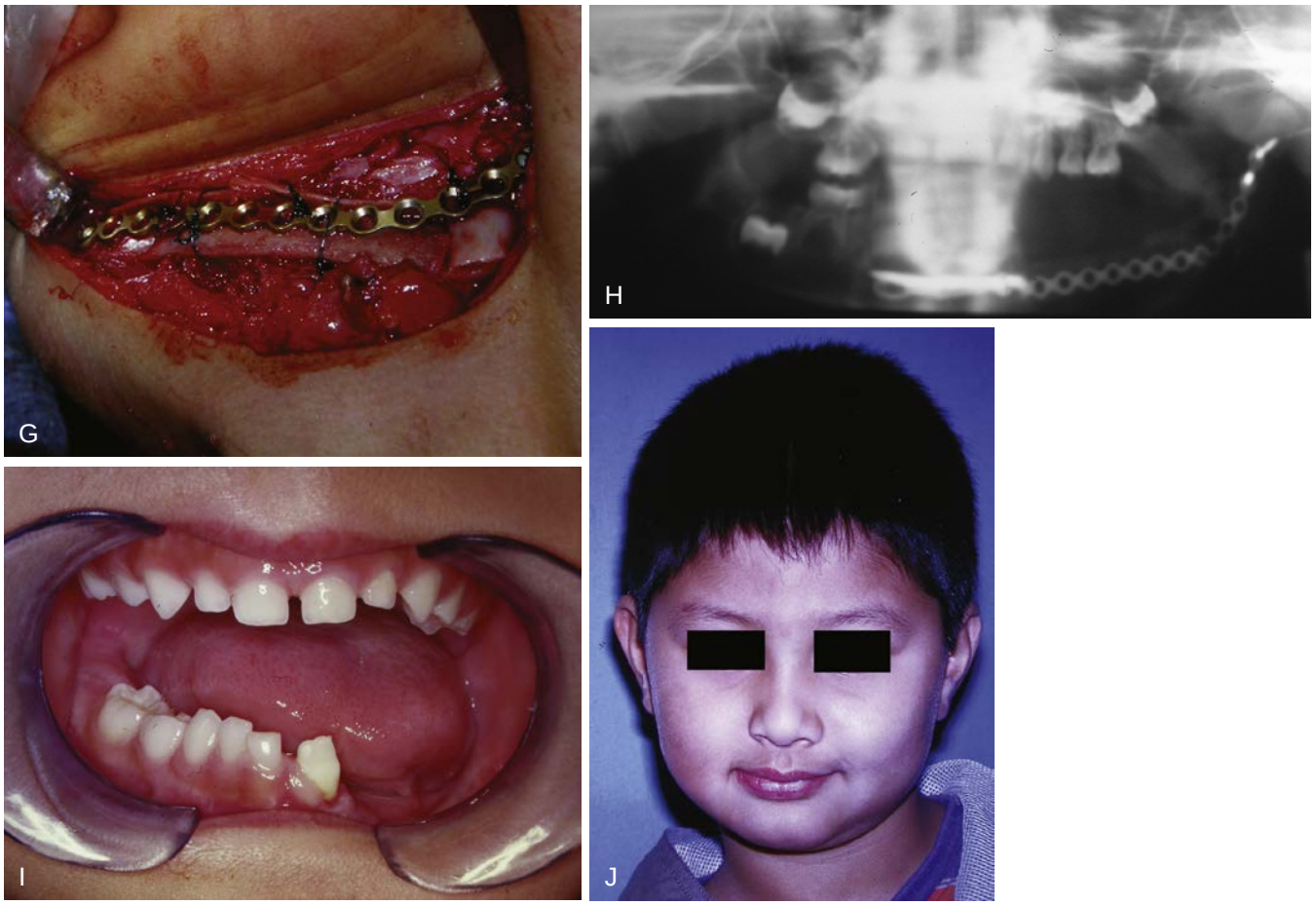


Figure 19-16, cont'd **G,** Reconstructed mandible with two ribs. **H,** Panoramic radiograph 4 years later. **I,** Symmetric mandibular opening. **J,** Normal facial contour with no evidence of recurrence. (Courtesy Dr. M. Anthony Pogrel.)

densely collagenous tissue with spindled and elongated fibroblasts. The degree of cellularity may vary from one area of the lesion to another. Cellular atypia, anaplasia, and mitotic figures are not seen. This lesion does not produce bone.

Recurrence rates following conservative surgical treatment, such as curettage and local excision, are high, whereas lesions treated by resection with wide margins do not tend to recur.[85,86] Recurrence is more commonly seen with lesions that erode bone and invade adjacent tissues.[82] Thus, despite a benign histology, the desmoplastic fibroma should be treated aggressively with resection. Radiation[87] and chemotherapy[88,89] have been recommended for lesions involving vital structures and those located in areas where resection would be debilitating; however, surgical resection is the treatment of choice in terms of tumor control and minimizing disruption of normal growth.

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20

Salivary Gland Disease

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Introduction

The salivary glands in humans are divided into the paired major glands (parotid, submandibular, and sublingual) and 750 to 900 minor salivary glands. These glands function to produce saliva, which serves as a lubricant aiding in swallowing, an emulgent aiding in the enzymatic breakdown of food, a taste mediator, and a manufacturer of hormones and hormone-like substances. It also assists in immunologic function by assisting in the excretion of endogenous and exogenous antibodies, assists in bacterial defense, and has cleansing properties.[1-4] Saliva is composed of a mixture of electrolytes and macromolecules, and its secretion is tightly modulated by the autonomic nervous system, humoral factors, and disease states. A variety of disease processes that and may include systemic diseases that involve the salivary glands.

Salivary Gland Physiology

The three basic subunits of salivary gland tissue include the acinus, the secretory duct (which is composed of intercalated and striated ducts), and the collecting duct with the acinus and proximal secretory duct comprising the "secretory end piece." The parotid and submandibular glands have a single elongated large caliber collecting duct with a few branching interlobular ducts, which are in turn connected to several lar gland is mixed between serous and mucous, and the sublingual and minor salivary glands are mostly mucous-type acini (Table 20-1).[5]

Saliva is formed via active transport in the secretory unit (acinus and secretory duct) and is under the control of complex neuronal and hormonal signals. The acinus is responsible for fluid generation. The secretion then transverses the ductal system, which is impermeable to water. Sodium (Na^+) and chloride (Cl^-) is reabsorbed, and potassium (K^+) and bicarbonate (HCO_3^-) is secreted. When entering the mouth, saliva is hypotonic (approximately 25 mEq/L NaCl). Fluid transport in salivary glands is primarily osmotic and responds to transepithelial salt gradients. Three mechanisms of primary fluid secretion have been proposed but are beyond the scope of this chapter.[6,7] Macromolecules are added to saliva by secretory granules of the acinar and ductal cells, which are under autonomic nervous system stimulation—primarily the salivary center of the medulla.[8] The rate of flow of saliva is highly variable and usually stabilizes by the age of 15 years. However, it is affected by systemic and iatrogenic processes such as radiation therapy.[9,10] Normal unstimulated and stimulated salivary flow is approximately 0.1 to 0.3 mL/min and 0.2 to 7 mL/min, respectively, with stimulated saliva flow comprising approximately 80% to 90% of daily average saliva production.[5,11] In the unstimulated state, the submandibular gland account for 71% of saliva production, whereas the parotid and sublingual glands produce 25% and 3% to 4%, respectively. In the stimulated state, the parotid gland supplies two thirds of salivary production.[12]

Acidic and sour-tasting foods increase saliva flow, whereas sweet foods decrease flow.[13,14] Other stimulants of salivary flow include chewing, gustatory, and olfactory stimuli. Increase in saliva flow in response to mastication is thought to be regulated by receptors in the mucosa, muscles of mastication, and temporomandibular joint.[15] Other factors that regulate salivary flow include circadian rhythm, mood, medications, and systemic disease.[16]

Imaging of the Salivary Glands

Not all disorders of the salivary gland require imaging as part of their workup. The purpose of imaging should be to aid in pathologic diagnosis, fine-needle aspiration, localizing a lesion, and staging. Modalities for salivary gland imaging include magnetic resonance imaging (MRI), computed tomography (CT), ultrasound (US), and sialography. Fine-needle aspiration (FNA) may be performed under US guidance to aid in diagnosis. Whereas the quality of MRI, US, magnetic resonance (MR) sialography, and CT has

TABLE 20-1 Acini Type and Saliva Viscosities by Salivary Gland Type

Salivary Gland	Acinar Type	Viscosity	Whole Unstimulated Daily Saliva (%)
Parotid	Serous	Watery	25
Submandibular	Mixed	Semiviscous	71
Sublingual	Mucous	Viscous	3 to 4
Minor	Mucous	Viscous	Trace

From Mandel ID: Sialochemistry in diseases and clinical situations affecting salivary glands, *Crit Rev Clin Lab Sci* 12:321, 1980.

increased significantly, there has been minimal advancement in conventional sialography.

Cross-sectional imaging techniques such as CT and MRI have the additional benefit of evaluating surrounding tissue planes, the extent of salivary gland tumors, and associated lymphadenopathy, vascular spread, neural spread, and bony invasion. Diseases such as sialolithiasis should usually be evaluated via CT to identify calcification associated with an obstructive stone. The chance of malignancy increases as the size of the salivary gland decreases, with 50% to 80%, 40% to 60%, and 30% to 40% of minor salivary, submandibular gland, and parotid gland tumors being malignant, respectively. Of benign lesions, 80% will be pleomorphic adenoma. Whereas lesions with smooth borders are likely benign, lesions with less demarcated borders and those that infiltrate adjacent structures are likely malignant. In general, CT should be used to evaluate inflammatory disease, whereas MRI should be used to evaluated neoplastic processes. The use of nuclear medicine imaging for salivary gland disease is not discussed here.

Computed Tomography

CT is most useful when evaluating calcific lesions and inflammatory conditions of the salivary glands.[17] This is preferred when evaluating calcifications and bony anatomy. The use of intravenous iodinated contrast increases the sensitivity for evaluating salivary soft tissue pathology, and also its extent and spread, by delineating the fat planes of the neck, which aids in differential diagnosis. Though the sensitivity of CT for detecting head and neck lesions approaches 100%, its drawbacks are that it is often poor at distinguishing benign and malignant lesions. In addition, CT may be poor at discriminating between spread to adjacent tissue and at identifying early-onset Sjögren syndrome and benign lymphoepithelial lesions associated with acquired immunodeficiency syndrome (AIDS). MRI may be better at identifying these lesions.

Magnetic Resonance Imaging

MRI is the modality of choice for identifying salivary gland neoplasms because of its ability to finely delineate various soft tissues in a high-quality manner. Most lesions will be identifiable on T1-weighted images. Benign lesions will be well defined. Pleomorphic adenomas, the most common salivary gland tumor, will have low T1 and high T2 signal intensities and solid enhancement on fat, as well as suppressed T1-weighted images after intravenous (IV) gadolinium. Warthin tumors will be seen in the lower portion of the parotid gland and as a heterogeneous signal on T2-weighted images, with bright T2 signals in the areas of cyst formation. The presence of multiple lesions is suggestive of Warthin tumor. The nodularity of the cyst will help differentiate from other cystic lesions. In addition, up to 10% of patients will present with bilateral Warthin tumors.[18] The addition of post-contrast imaging on fat-saturated sequences makes salivary lesions and their adjacent soft tissues more easily identifiable. Following fat saturation, structures that were previously hyperintense on T1-weighted images become hypointense, making the soft tissue mass well delineated within the gland. IV gadolinium contrast may further define salivary lesions, and enhancement about the meninges, within the foramina of the skull base, or within the marrow of the mandible or maxilla would all suggest spread of tumor along these structures. MRI is also best for delineating spread a long the pterygopalatine fossa, stylomastoid foramen and cranial nerve V2, foramen ovale and CN V3, foramen rotundum and CN V2, and the vidian canal and associated nerve. A possible malignant result or irregular borders on FNA should be further evaluated with MRI, as should all submandibular and sublingual gland tumors given the high incidence of malignancy and perineural spread associated with these structures. Malignant neoplasms will usually display a low to intermediate signal on T1WI and T2WI and ill-defined or irregular borders. Mucoepidermoid carcinoma may look like pleomorphic adenoma when small because of its smooth wall. It may contain calcifications and mucinous cysts that appear with high signal on T1- and T2-weighted images. Adenoid cystic carcinoma is the second most common malignancy overall and the most common one found in the submandibular and sublingual glands, with the solid form appearing low in signal on T2-weighted images and the cribriform or tubular subtype appearing high in signal on T2-weighted images. Because of the high incidence of perineural spread with this tumor, the cranial nerves and skull base must be evaluated.

Ultrasound

Ultrasound for salivary gland tumors is used with much more frequency in Europe than in North America.[19] It works in the absence of ionizing radiation and is especially useful in children. For an experienced ultrasonographer, US may identify and characterize a lesion's location. Normal salivary tissue appears homogenous and hyperechoic compared to adjacent muscles. Higher fat content increases the echogenicity and suppresses US waves, limiting the assessment of deep anatomic structures. Malignant lymph nodes will appear as lacking a fatty hilum, more round, and with

an abnormal peripheral vascularity on Doppler US. Benign

eneous inter-

Fine-Needle Aspiration

FNA is a procedure that often relies on US guidance. However, for lesions such as mobile and superficial palpable masses of the parotid gland, US may not be necessary. CT guidance may also be helpful for deeper lesions. The use of US guidance has been shown to increase diagnostic accuracy when compared to FNA without guidance.[20] In addition to making FNA more accurate, US allows the clinician to evaluate the characteristics of a lesion, such as borders and invasion to adjacent anatomic structures. With a cytopathologist present to confirm that enough material is obtained, aspiration with a 22-gauge needle is often adequate for

[21]

and positive predictive value of 90% for differentiating benign from malignant parotid lesions.[22]

Sialography

Sialography is used to visualize the intraglandular ductal system of the major salivary glands. MR sialography is very useful in evaluating the intra- and extraglandular ductal systems in conditions such as postradiation xerostomia, ductal stenosis, and Sjögren syndrome.[23] However, with the advent of serum markers such as SS-A and SS-B for Sjögren syndrome and the advances in CT and MRI, conventional sialography has become an inferior imaging modality. Sialography is contraindicated in patients with iodine contrast allergies or acute sialadenitis. To perform sialography, a blunt-tipped sialographic cannula attached to tubing is used to access the duct. Lacrimal duct dilators may be necessary to cannulate and dilate the papilla. Diatrizoate meglumine, a water-soluble contrast agent, provides excellent contrast opacification of the ductal architecture with no reported adverse effects with duct perforation. MR sialography was first reported by Lomas and colleagues in 1996[24] and produces high-resolution images of the major salivary glands displaying obstructions and duct caliber changes. MR sialography may be used in patients with contrast allergies.

Cystic Conditions

Minor Salivary Glands

The mucocele is the most common cystic lesion of the minor salivary glands. The vast majority represent extravasation phenomena and have no epithelial lining. The most common site is the lower lip in young people, and the etiology is usually minor trauma. Up to 20% of these lesions may represent true retention cysts secondary to obstruction or microliths.[25] These occur in older patients and may affect any site where minor salivary glands occur.

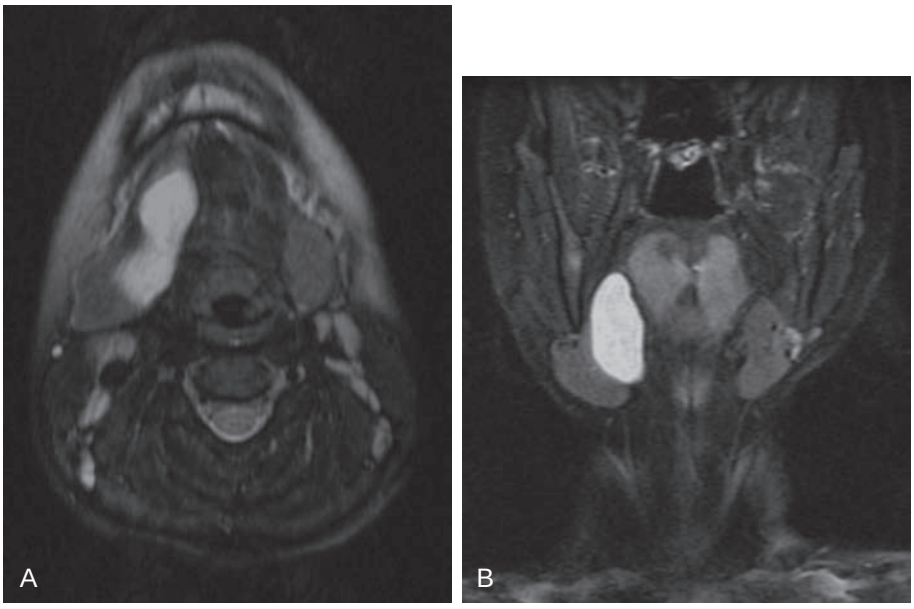
Treatment of this condition is directed toward the underlying gland. Although the mucocele may spontaneously rupture or be "drained" by the patient (occasionally leading to complete resolution following scarring) simple removal of the "cyst" leads to recurrence of the mucocele. A vertical incision over the lesion with removal of the underlying minor salivary gland is almost always curative. A critical aspect is to remove the underlying salivary glands associated with the "cyst." In cases in which recurrence has been a problem, a CO_2 laser can be used to cauterize the surgical bed and any underlying salivary tissue. The wound is left open to heal by secondary epithelialization.

Sublingual Gland

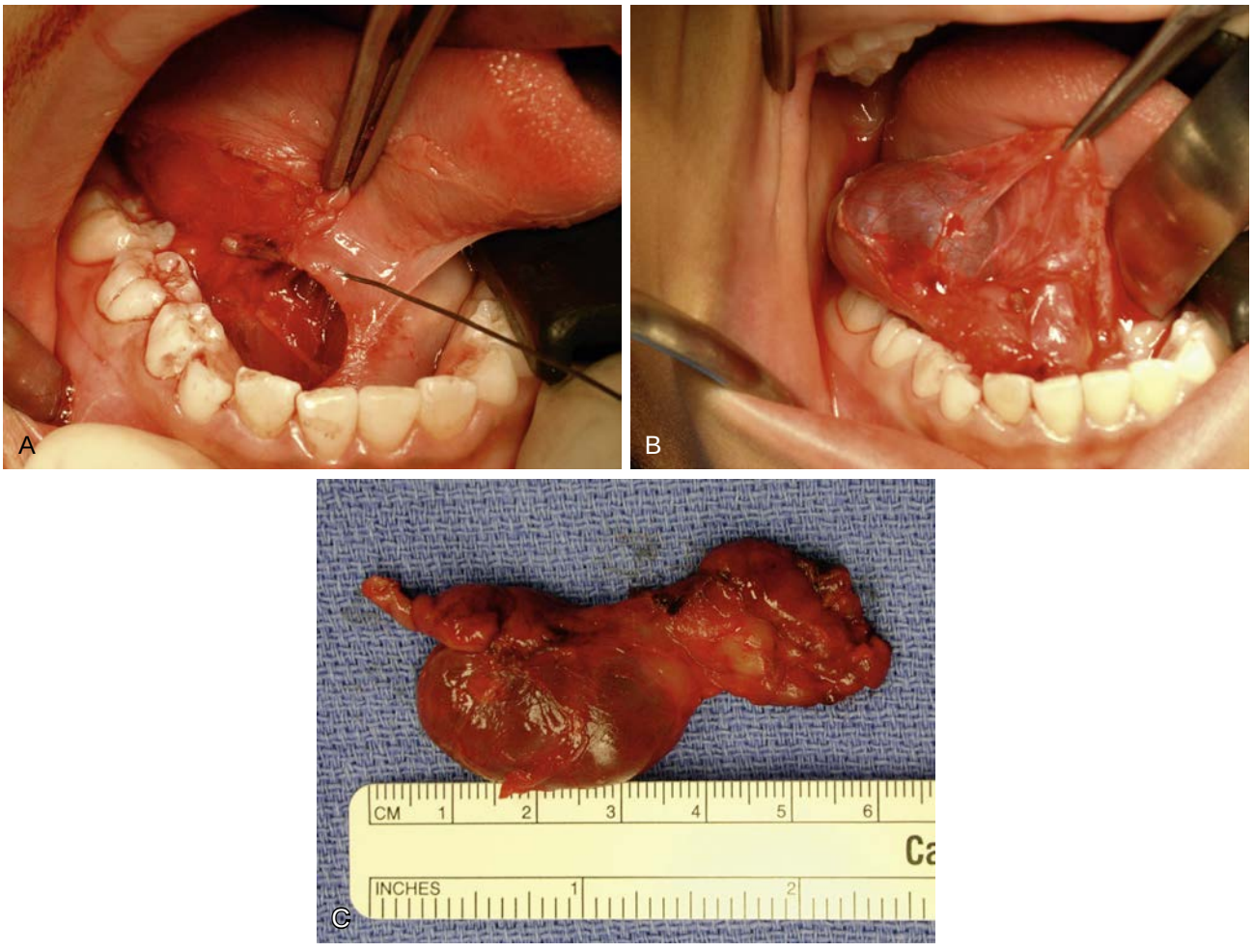
Ranulas are essentially mucoceles that arise from the floor of the mouth secondary to obstruction of the salivary ducts of the sublingual glands and, like simple mucoceles, are caused by traumatic injury to the sublingual gland or its ducts.[26] The ranula is so named for its resemblance to a frog's belly (*rana* and *ranula* mean "frog" and "little frog," respectively, in Latin). This appearance is due to the accumulation of saliva beneath the thin mucous membrane of the floor of the mouth. The majority of these lesions result from extravasation of saliva secondary to trauma. However, their occurrence in young children may indicate dysgenetic development of the sublingual gland duct system. Penetration through a dehiscence of the mylohyoid can allow the lesion to occur in the upper neck as a "plunging" ranula[27] (Figure 20-1). Management of the lesion has been the subject of controversy and can be performed in a variety of ways, which is thoroughly discussed in a definitive paper by Catone.[28] Treatment may be delayed for up to 6 months, because some may resolve spontaneously.[26] Management options include simple excision of the ranula with or without the associated sublingual gland via an intraoral approach, transcervical excision, marsupialization, laser therapy, robotic surgery, and sclerotherapy, versus injection of material into the ranula and excision.[29-34] Imaging is not

ranulas, though they may appear like well-circumscribed low attenuated masses, similar to dermoid cysts—another common neck mass in children.

However, it is our belief that the only satisfactory method of treatment is excision of the sublingual gland. Initially, Wharton's duct is cannulated so that it can be identified and protected during the dissection (Figure 20-2). Although lacrimal probes are traditionally used, cannulation may be difficult in the presence of swelling. The use of endodontic



• **Figure 20-1** Axial **(A)** and coronal views **(B)** of magnetic resonance imaging scan of a young boy with a plunging ranula; note the extension of the ranula through the mylohyoid muscle to reach the neck.



• **Figure 20-2** Cannulation of Wharton's duct to facilitate the identification of the duct during dissection. Mucosal retention sutures may be used to aid in retraction and exposure **(A).** The sublingual gland and associated ranula are then dissected and exposed, **(B)** and removed **(C).**

gutta-percha points may facilitate initial identification and dilation of the duct. An incision is made in the mucosa overlying the duct and along the floor of the mouth, leaving enough tissue for easy closure. The gland is dissected from anterior to posterior, protecting the submandibular duct and obtaining hemostasis as the dissection proceeds. At the posterior edge of the gland, care is taken to identify and preserve the lingual nerve as it passes under Wharton's duct. The posterior border of the sublingual gland may be intimately associated with the oral extension of the submandibular gland, and sharp dissection may be required to separate the two glands—often this border is not discernible. Hemostasis should be ensured before closure. For plunging ranulas, either an intraoral or a transcervical approach may be used, depending on their size, with a transcervical approach being reserved for recurrences and those with a large pseudocyst where dependent drain placement is advantageous.[30-34]

Submandibular Gland

True cysts of the submandibular gland are extremely rare and will not be discussed.

Parotid Gland

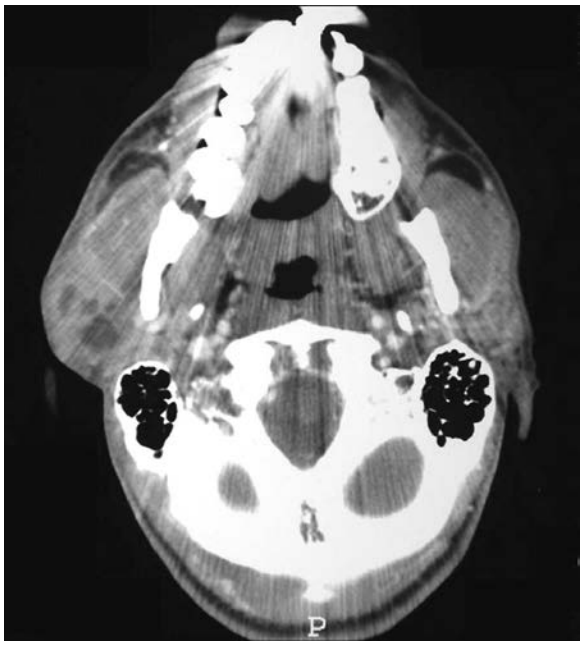
There are a number of true cystic lesions that affect the parotid gland, including hereditary polycystic disease,[35] parotid duct cysts, retention cysts, and lymphoepithelial cysts.[36] The lymphoepithelial cyst is the only common entity.

Lymphoepithelial cysts occur as solitary masses within the parotid gland that are clinically indistinguishable from parotid tumors. Also known as branchial cleft cysts, they are usually developmental in nature and histologically are composed of a squamous or pseudostratified epithelial lining surrounded by lymphoid tissue. Even when imaging reveals a cystic lesion, a cystic tumor, such as a pleomorphic adenoma, mucoepidermoid carcinoma, or Warthin tumor, cannot be excluded. The parotid lymphoepithelial cyst resembles the branchiogenic cyst histologically, but its histogenesis is thought to be due to inflammation causing proliferation of epithelial remnants within parotid lymph nodes.[37] This theory has received additional support in recent years by the recognition of multiple bilateral lymphoepithelial cysts of the parotid gland as a manifestation of acquired immunodeficiency syndrome (AIDS)[38] (Figure 20-3).

In the case of a solitary lesion of the lateral lobe of the parotid gland, superficial parotidectomy with preservation of the facial nerve is recommended. Patients infected with human immunodeficiency virus (HIV) may have bilateral occurrence of multiple lymphoepithelial cysts—bilateral parotidectomy may be beneficial for cosmetic reasons.

Inflammatory/Reactive Conditions

The salivary glands can be affected by a variety of infectious processes, either bacterial or viral. In many cases of chronic

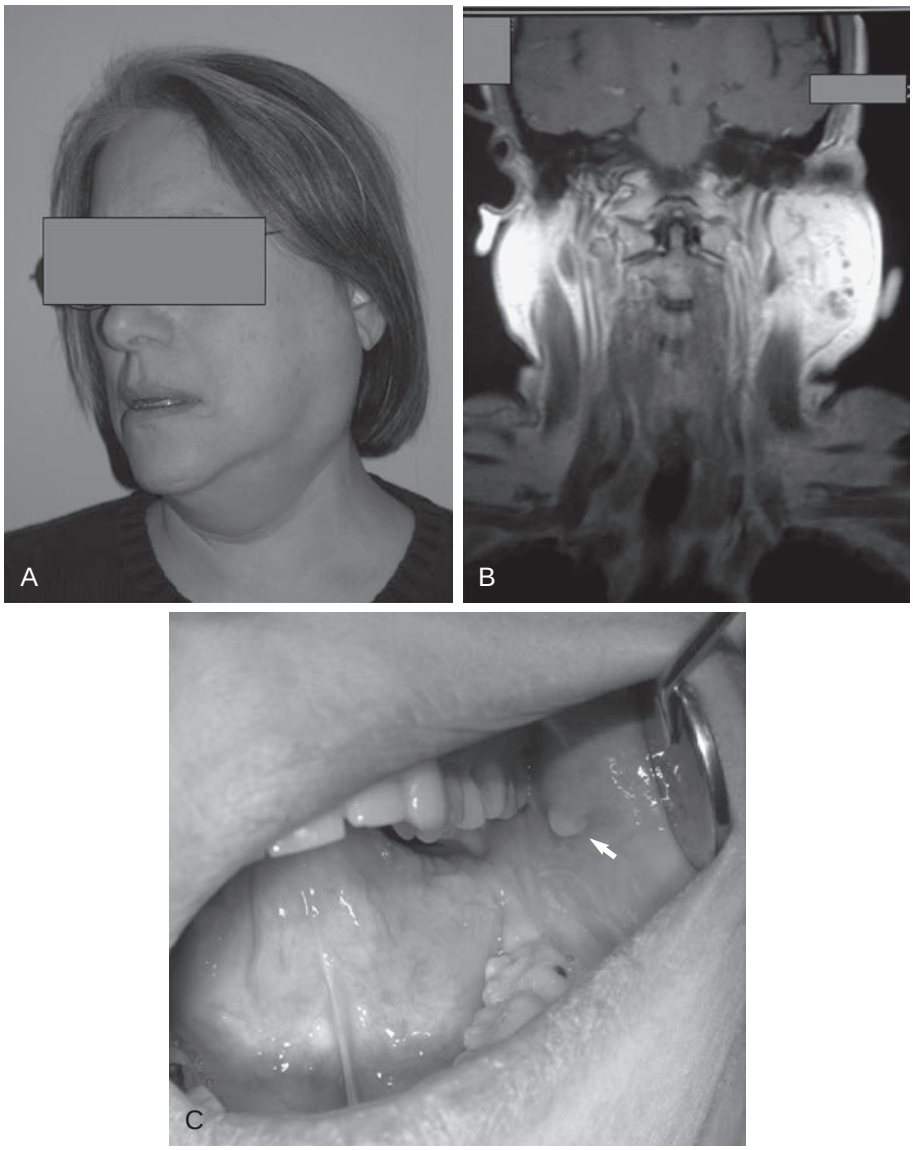


• **Figure 20-3** Patient with bilateral lymphoepithelial cyst of the parotid gland. Right greater than left.

and recurrent infections, underlying problems, such as sialoliths or ductal abnormalities, are major etiologic factors. These conditions are reviewed in the section on obstructive diseases. This section is restricted to acute infection of the salivary glands. The parotid gland is most often affected by these conditions when compared to the other major salivary glands. Radioiodine-induced sialadenitis is not discussed in this chapter.

Acute Suppurative Parotitis

Of the major salivary glands, the parotid gland is by far the most susceptible to infection. This is likely because it is mostly serous in nature, and serous saliva, when compared with mucinous saliva, lacks immunoglobulin A antibodies, lysosomes, and sialic acid—which have antimicrobial properties. In addition, saliva from the submandibular and sublingual glands contains high-molecular-weight glycoproteins that competitively inhibit bacterial attachment to the epithelial cells of the salivary ducts. A patient with acute suppurative parotitis may have symptoms and clinical findings of painful peri–parotid gland swelling, fever, redness, and purulent discharge from Stensen's duct (Figure 20-4). The condition is usually associated with an ascending infection from the oral cavity, with the causative organism being usually being *Staphylococcus aureus* and anaerobic bacteria.[39] Predominant anaerobes include anaerobic gram-negative bacilli (i.e., pigmented *Prevotella* and *Porphyromonas*); *Fusobacterium* spp.; and *Peptostreptococcus* spp. In addition to these, *Streptococcus* spp. and aerobic and facultative gram-negative bacilli (including *Escherichia coli*) have been reported. Organisms less frequently seen include *Haemophilus influenzae, Treponema pallidum, Bartonella henselae,* and *Eikenella corrodens. Mycobacterium tuberculosis* and atypical



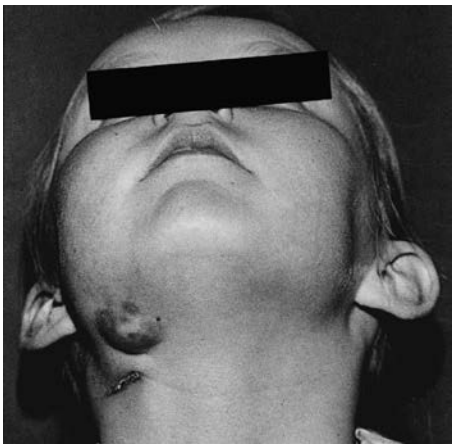
• **Figure 20-4** **A,** Patient with sudden onset of painful parotid gland swelling. **B,** Magnetic resonance imaging of the parotid glands reveals diffuse left parotid gland swelling. **C,** Purulent discharge at Stensen's duct is noted after massage of the parotid gland *(arrow)*.

mycobacteria are rare causes of infection. The choice of antibiotics should be guided by identification of the etiologic agent—which again is usually *S. aureus* in nature. In hospitalized and immunocompromised patients, aerobic and facultative gram-negative bacilli are increasingly seen.[40] Most cases are associated with systemic disease-causing cachexia or dehydration (e.g., uremia, diabetes, liver failure, or hypothyroidism). In the past, the condition was a more common postoperative complication, probably as a result of poor milking the gland when possible, and appropriate antibiotics that are well absorbed by salivary glands are prescribed. Supportive measures (e.g., fluid replacement and analgesics) should be instituted as well as sugar-free sour "candy" to encourage drainage.[13,14] If acute abscess formation occurs (Figure 20-5), surgical drainage is required. Incisions should be placed parallel to facial nerve branches to prevent injury. A preauricular incision with blunt dissection into the abscess using a small hemostat results in a more cosmetic scar and prevents facial nerve damage.

In infants and children, abscesses in the parotid region are usually due to hematogenous spread of bacteria to parotid lymph nodes. Subsequent suppuration and breakdown of nodes cause an abscess that requires drainage. Tuberculosis is another rare cause of parotitis. The infection may be confined to the parotid lymph nodes or may affect the salivary gland parenchyma. Staphylococci is the leading etiologic agent in adult and neonatal suppurative parotitis and usually resistant to penicillin but responsive to aminoglycosides or a third-generation cephalosporin.[41] Intravenous ampicillin/sulbactam or clindamycin are advised while awaiting cultures and sensitivities in order to cover for the



• **Figure 20-5** Computed tomography scan showing parotid abscess with peripheral ring enhancement.



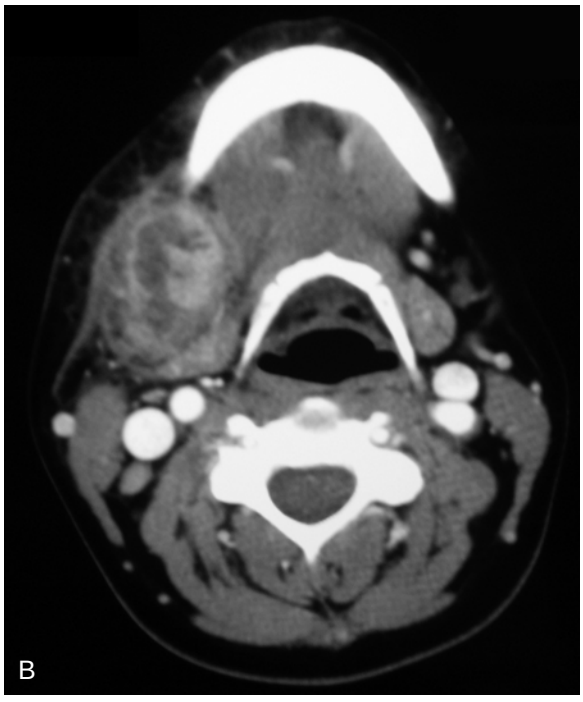
• **Figure 20-6** Ten-year-old girl with *Mycobacterium avium-intracellulare* infection of the parotid nodes, which were removed by a superficial parotidectomy. Swelling now involves the submandibular nodes.

most common pathogens.[42] However, when methicillin-resistant *Staphylococcus aureus* is identified as the causative bacterium, unless sensitive to clindamycin, intravenous vancomycin or linezolid are advised. In pediatric patients, cervical lymphadenitis associated with atypical mycobacteria may rarely affect the parotid lymph nodes[43] (Figure 20-6).

Acute Suppurative Sialadenitis of the Submandibular Gland

Acute suppurative infection of the submandibular gland occurs less often than that of the parotid gland and is usually associated with sialolithiasis within Wharton's duct. Management, however, is the same as for the parotid gland, with caution not to confuse this presentation with that of submandibular space infection from an odontogenic source, which is much more common (Figure 20-7).





• **Figure 20-7** **A,** Young female patient with a large right submandibular swelling, malaise, fever, and leukocytosis. **B,** Computed tomography scan reveals ring enhancement and diffuse swelling of the submandibular gland.

Viral Infections of the Parotid Gland

Mumps

Before the institution of routine immunization with measles-mumps-rubella (MMR) vaccine, mumps was extremely prevalent in children aged 2 to 14 years and was also known as epidemic parotitis. True mumps is caused by the mumps paramyxovirus, but a similar clinical disease can also occur with Coxsackie virus A and echovirus. The virus is spread by droplet infection and in 75% of cases affects both parotid glands. Painful parotid gland swelling may last 2 weeks. Other organs (e.g., testes, ovaries, breasts, and pancreas)

may be affected, and in adult men, orchitis may lead to sterility. Meningoencephalitis can also occur, which may damage the auditory nerve. Management focuses on the relief of symptoms with analgesics, supportive intravenous fluid therapy, and appropriate consultation for possible encephalitis, meningitis, nephritis, myocarditis, and pancreatitis. [44]

HIV

As previously mentioned, 3% to 6% of patients with AIDS may exhibit bilateral lymphoepithelial cysts, which often may be the first indicator of HIV infection.[36] In addition, in children with AIDS, bilateral parotid gland swelling as a result of lymphocytic infiltration is often seen. In the long term, lymphoma involving the parotid gland may develop in HIV patients (see the section on tumors).[36,45]

Cytomegalovirus

This systemic viral illness is particularly frequent in immunosuppressed patients (e.g., those with bone marrow transplants, on chemotherapy, or with HIV).[46] When cytomegalovirus is suspected, the patient should be isolated from pregnant women to prevent fetal infection with teratogenic effects.[47] Cytomegalovirus infection may occur in an identical fashion to infectious mononucleosis, and interestingly, viral parotitis may also occur in Epstein-Barr viral infections. Other causes of salivary gland infection include granulomatous infections (tuberculous mycobacterial disease vs. nontuberculous mycobacterial disease vs. actinomycosis), cat-scratch disease, toxoplasmosis, and parasitic infections. Other non-infectious inflammatory diseases of the salivary glands include Sjögren syndrome, sarcoidosis, Kimura disease, and Rosai-Dorfman disease.[48]

Obstructive Disease

Although the major condition considered under the heading of obstructive disease is sialolithiasis, mucous plugs, strictures, and duct ectasia may also cause obstruction and give rise to chronic sialoadenitis. Obstructive disease is clinically most relevant in the submandibular and parotid glands. The mechanism for salivary stone formation is related to the same three factors that cause cholelithiasis and renolithiasis: stasis, infection, and alteration of the duct constituents. Desquamated epithelial cells, microorganisms, and salivary duct–derived lysosomes and mitochondria-like structures may be the matrix that forms prior to calcium in the duct.[49] Furthermore, the submandibular gland is the most common gland for sialolithiasis. This is thought to be due to the alkaline pH and high mucin and calcium content of saliva in Wharton's duct, as well as the anatomic characteristics of this duct, which include a long ascending trajectory that circumvents the posterior border of the mylohyoid muscle, possibly contributing to salivary gravitational flow stasis and, perhaps, to calcium precipitation. Decreased salivary flow is further diminished after sialolith formation and salivary gland infection leading to the formation of intraductal sludge and recurrent salivary gland infections and/or recurrent sialolith formation usually necessitating sialadenectomy.

Sialolithiasis

Minor Salivary Glands

Although this is an unusual condition, it is well reported in the literature.[50] The microliths usually are of no clinical significance.

Sublingual Gland

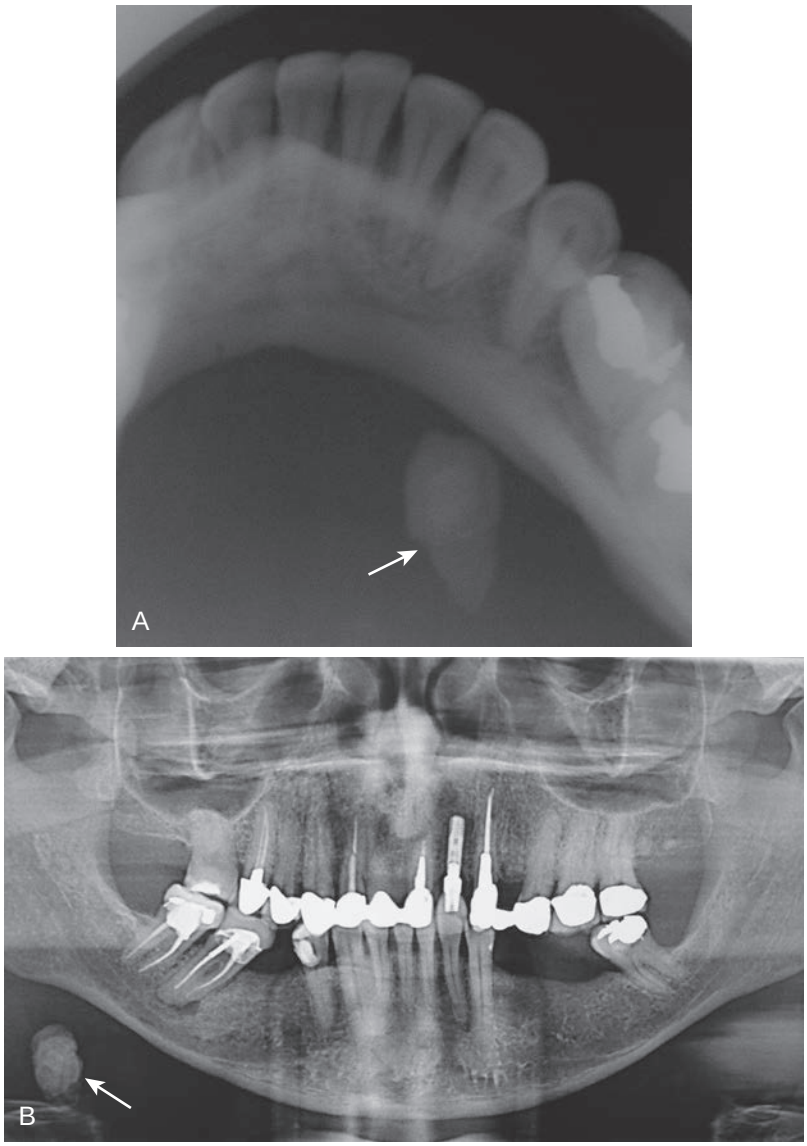
According to Rauch's extensive review of 1200 cases of salivary calculi in the German literature, 7% of salivary stones are found in the sublingual gland.[51] These may cause obstruction of the sublingual gland or problems in Wharton's duct.

Submandibular Gland

As mentioned previously the majority of sialoliths (approximately 85%) occur in the submandibular gland, probably as a result of mucous saliva produced by this gland.[52] These stones usually occur in adults and may be asymptomatic. However, when they reach a suitable size to obstruct the duct lumen, patients experience pain and swelling of the gland, particularly in relation to meals. Secondary infection often supervenes with fever, redness, and purulent discharge from the duct. Eighty-five percent of submandibular stones are radiopaque and can be well visualized on plain films. Approximately 50% of stones will be found in the duct distal to the edge of the mylohyoid muscle and are best seen in an occlusal radiograph. The remaining 50% are found below the mylohyoid or at the hilum of the gland and can be seen on lateral oblique or panoramic radiographs (Figure 20-8). Occasionally, stones are radiolucent and can be visualized only as filling defects on sialography.

Although some stones pass spontaneously or following duct dilation, most require surgical removal. The classic reports by Seward[53-55] describe the principles of surgical management. Stones, particularly those at the orifice or in the distal half of this duct, are removed transorally via sialodochoplasty (Figure 20-9). A suture is passed around the duct posterior to the stone and is used as a traction suture to occlude the duct and prevent the stone from being displaced posteriorly during surgery. A vertical incision is made over the stone, and the duct is opened to allow the stone to be delivered. The duct is irrigated to remove microliths, and the duct edges are sutured to the oral mucosa to form a new orifice. Opening the duct in a vertical manner allows marsupialization of the orifice and prevents stricture.

The further posteriorly the stone occurs, the more technically difficult it is to remove it from a transoral approach because the duct lies deeper and access to it is poor. Once the stone is at the level of the edge of the mylohyoid, removal of the submandibular gland is safer and more certain. An incision is made in a skin crease approximately two finger-widths below the inferior border of the mandible. A dissection taken is taken in the subplatysmal plane, and the inferior border of the gland is identified. An intracapsular



• **Figure 20-8** **A,** Occlusal radiograph shows a large right submandibular sialolith in the distal end of Wharton's duct *(arrow)*. **B,** Panoramic radiograph revealing a large right submandibular sialolith at a level below the mylohyoid, near the hilum of the gland *(arrow)*.

dissection is performed, staying close to the surface of the gland, mobilizing the overlying fascia and capsule of the gland superiorly to protect the marginal mandibular branch of the facial nerve. The inferior and posterior borders of the gland are mobilized rapidly with a combination of blunt and sharp dissection. The inferior border of the gland is followed anteriorly to allow the anterior pole of the gland to be mobilized from the mylohyoid muscle. In cases of chronic recurrent obstruction and sialoadenitis, scarring and adhesions may make dissection more difficult. Once the anterior pole is free, the gland can be retracted posteriorly to expose the posterior edge of the mylohyoid muscle. The muscle is retracted to visualize the lingual nerve and Wharton's duct. The nerve connection from the lingual nerve to the gland is cut, and the duct is carefully dissected from the nerve. While using traction on the gland, the duct is dissected as far forward into the floor of the mouth as possible and then ligated and sectioned to prevent leaving any residual stones (Figure 20-10).[49] The facial artery or vein may be ligated during dissection, but this is often not necessary with careful intracapsular dissection unless the vessel passes directly through the gland. Coagulation or ligation of branches from these vessels to the gland should be meticulous, and care should be taken to ensure complete hemostasis before closure. A suction drain is routinely used overnight.

Although as much of the submandibular duct as possible is removed, a small remnant remains because it is often difficult to distinguish between the submandibular and sublingual glands. Because of the secretions from the sublingual gland entering Wharton's duct, further calculi may form in this remnant, and some authors advocate removing the entire duct by dissecting and freeing the anterior third when the submandibular gland and its proximal duct are removed (as previously described).[49] However, this allows



• **Figure 20-9** **A,** Transoral surgical removal of a stone in the distal portion of Wharton's duct. **B,** Specimen.

communication between the mouth and the neck, and the surgery is no longer considered to be a "clean" case. In addition, sectioning of the sublingual ducts may lead to subsequent ranula formation.

catheters (Fogarty catheters) are passed beyond the stone, the balloon is inflated, and the catheter is removed, retrieving the stone. Miniature endoscopes allow direct visualization of stones and their removal with forceps or baskets.[13,58] Although lithotripsy has been used extensively for renal calculi, its use for salivary stones is less well reported. Extracorporeal lithotripsy has been reported to leave residual lithiasis in 40% to 50% of cases.[59] For this reason, endoscopic lithotripsy has been advocated to give improved results. With a combination of laser or pneumoblastic fragmentation and forceps extraction, 15 of 18 patients (83%) were successfully treated. However, 12 of 39 patients (31%) were unable to have successful endoscopic cannulation.[59]

Parotid Gland

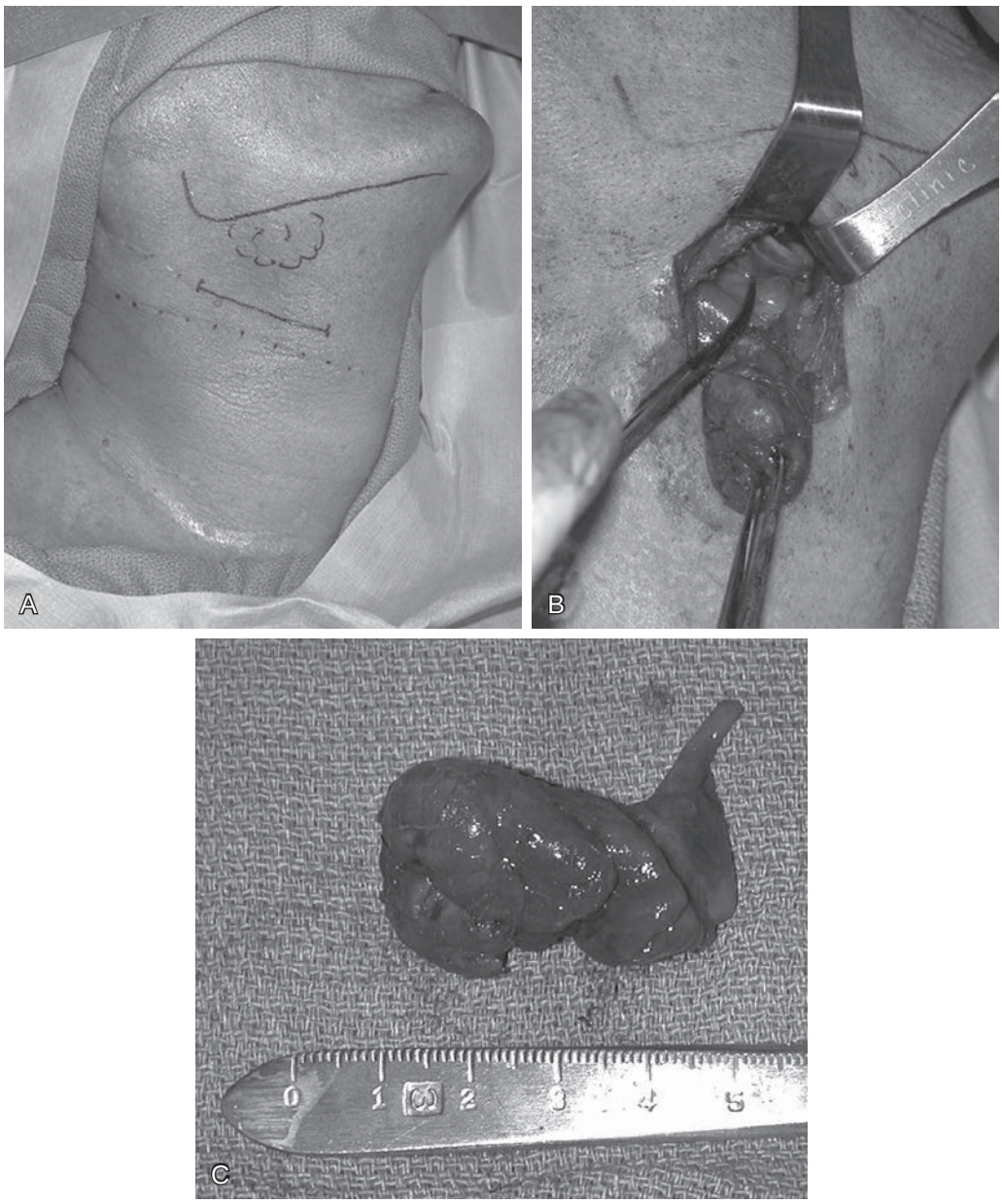
Parotid stones account for 10% of salivary stones, and the majority (85% to 90%) are radiolucent.[60] Most of these are mucous plugs, which are covered in the section on chronic obstructive sialoadenitis. True calcified stones are unusual, and virtually all are found in the duct, rather than the hilum or the gland. Their presentation is similar to that of submandibular stones, with symptoms of pain and swelling, particularly while eating. Dental radiographs held in the cheek may be useful for the diagnosis of calcified stones,[61] and sialograms are beneficial for the diagnosis of radiolucent stones.

Stones at the distal end of the duct or at Stensen's papilla are dealt with as described for submandibular stones occurring at the duct orifice. Once the stone is located posterior to the point where Stensen's duct turns around the masseter, it is no longer accessible from a transoral approach (Figure 20-11). In these cases, an extraoral approach may be chosen. Although some authors advocate an incision that is parallel to the branches of the facial nerve, this runs perpendicular to the relaxed skin tension lines. Alternatively, an incision can be made in the line of a skin crease (through skin *only*), with subsequent dissection parallel to the facial nerve branches.[62] Once the stones are removed, the duct is repaired over a plastic cannula, which is left in place for 6 weeks to act as a stent. An alternative approach to stones in the proximal duct at the hilum of the gland is a parotidectomy incision, raising a skin flap superficial to the parotid capsule and identifying the duct anteriorly as it leaves the gland. This approach results in excellent cosmesis and allows direct visualization of branches of the facial nerve.

Chronic Obstructive Sialoadenitis

Submandibular Gland

In the submandibular gland, obstruction is virtually always secondary to stone formation. If removal of the stone does not cure the condition, the gland should be excised as described earlier.

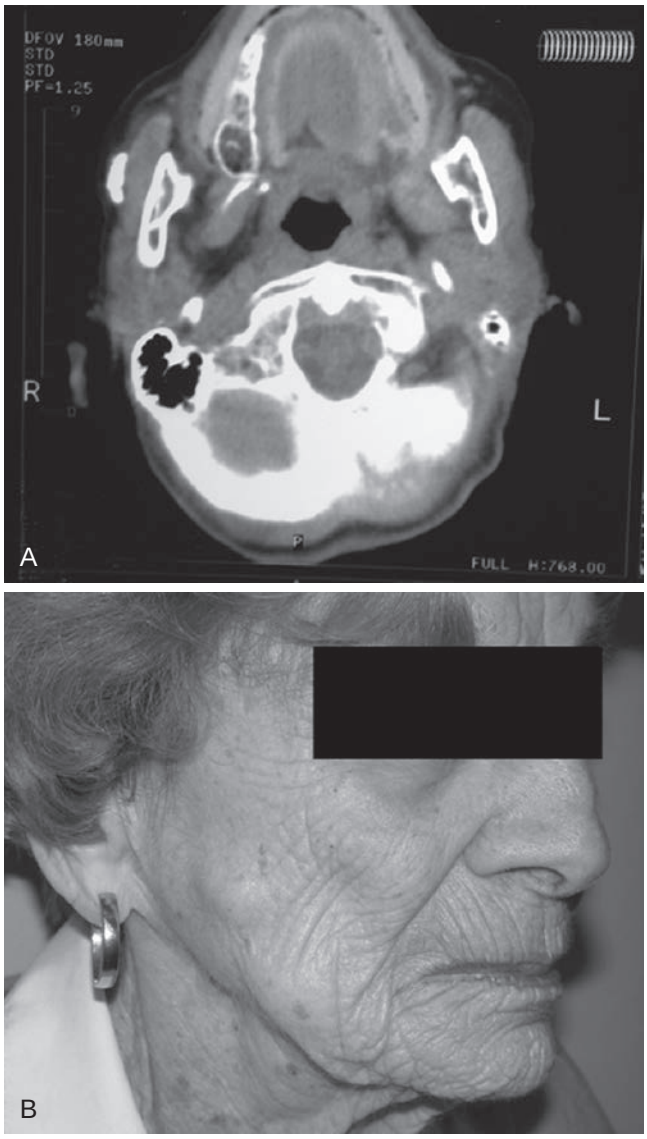


• **Figure 20-10** **A,** Marking for submandibular gland excision. The authors prefer to hide the incision within a neck crease whenever possible while staying two fingerbreadths below the inferior border of the mandible. **B,** With the dissection completed, the only remaining attachment is the duct. **C,** The specimen is removed. Note the extension of the duct.

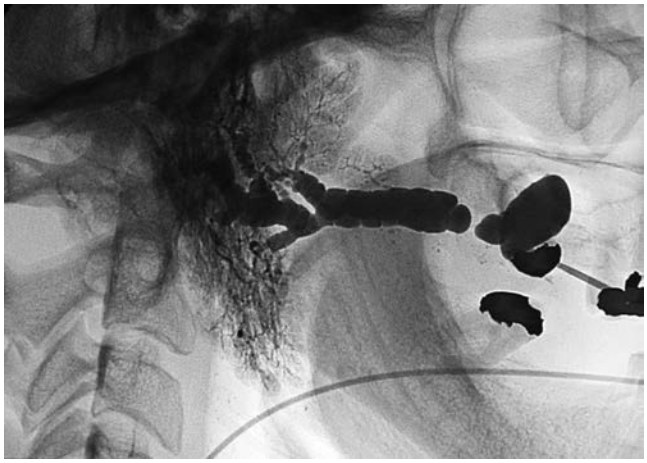
Parotid Gland

In the parotid gland, recurrent swelling, pain, and purulent discharge are the most common symptoms. Most cases occur in adults. The history is recurrent unilateral parotid gland swelling, often present for many years. The swelling is not always painful and may be accompanied by a salty taste. Initial treatment after history and examination is conservative. The patient is instructed to massage the swollen gland to "milk" out saliva and is placed on antibiotics, particularly when the saliva is purulent or "snowstorm" in appearance.

A sialogram is essential in all cases as both a diagnostic and a therapeutic tool. If a stone or mucous plug is identified, this can be treated as suggested previously.[63] Likewise, a stricture (usually as a result of trauma or a stone that has been passed) can be treated by dilation or repair of the duct. In most cases, the changes seen within the duct are nonspecific inflammation, then sialectasis, followed by dilation and segmentation of the duct. This proceeds to increased dilation of the duct with gross destruction of the salivary gland structure and the branching duct system (Figure 20-12). Most patients, even at relatively late stages, are helped by sialography, which probably relieves obstructive symptoms by its mechanical irrigation and dilation



• **Figure 20-11** **A,** Computed tomography scan of a large right parotid duct stone. **B,** Clinical image showing the elevation of the skin caused by the stone.



• **Figure 20-12** Parotid sialogram showing significant dilation of the duct in a long-standing sialoadenitis.

of the ducts. In many cases, symptomatic treatment with massage, antibiotics, and duct dilation is sufficient. Those patients who are improved by sialography and then relapse can have their ducts cannulated and irrigated with antibiotic solution or steroids. A minority of patients (less than 10%) will continue to complain of symptoms and will require parotidectomy. This operation is technically challenging because of scarring and fibrosis, which make facial nerve dissection difficult. The senior author undertakes superficial parotidectomy with the removal of Stensen's duct and the accessory gland. The deep lobe is usually not removed, although some authorities advocate total parotidectomy.

The senior author does not agree with ligating Stensen's duct for this condition. This leads to cystic dilation of the distal portion of the duct and makes subsequent parotidectomy very demanding. Another treatment that has been advocated is the sectioning of the tympanic nerve (nerve of Jacobson), a branch of the glossopharyngeal nerve in the middle ear. Although this prevents parotid secretion, the effect is only temporary. The complete pathogenesis of this condition is unknown and probably represents a combination of infection, inflammation, obstruction, and possible congenital duct abnormalities.

In children, the sialogram normally shows punctate sialectasis. However, the disease usually does not progress as it does in adults. Conservative therapy is essential because virtually all children obtain resolution of their symptoms after puberty.[64]

Tumors

All the salivary glands may be involved by tumors arising from salivary acinar or ductal cells. Two predominant theories have been proposed with regards to salivary gland neoplasms: (1) the multicellular theory, which suggests that each type of neoplasm originates from a distinctive cell type—that is, Warthin and oncocytic cell tumors arise from acinar cells, and mixed tumors arise from intercalated duct and myoepithelial cells[65,66]; and (2) the bicellular reserve cell theory, which suggests that the origin of the various types of salivary neoplasms can be traced to the basal cells of either the excretory or the intercalated duct, and either of these two types of cells can act as a reserve cell with the potential for differentiation into a variety of epithelial cells.[67] Radiation[68] and viral exposure,[69] as well as genetics, have been shown to be associated with benign salivary gland neoplasms. [70]

The most common neoplasm of the salivary glands is the pleomorphic adenoma (Table 20-2).[71] The majority of tumors (70%) occur in the parotid gland; 22% arise in the minor glands, 8% stem from the submandibular glands, and 1% in the sublingual glands. Although three-fourths of parotid and over half of submandibular neoplasms are benign, 85% of minor salivary gland tumors are malignant. This is based on data on 2807 subjects from Memorial Sloan-Kettering over a 35-year period. In total, benign neoplasms constituted 55% (1529) of all salivary gland neoplasms,

with the pleomorphic adenoma constituting 45% (n = 1280) of all salivary neoplasms, and 84% of all benign neoplasms. A study by Eveson and Cawson found that of 2410 salivary gland tumors,[72] 73% occurred in the parotid gland, with 15% of those being malignant; however, 14% occurred in minor salivary glands, with 46% being malignant. Eleven percent were submandibular gland tumors with 37% being malignant, whereas sublingual gland tumors made up 0.3% of all salivary gland tumors with 86% being malignant. Warthin tumor was the second most common benign tumor with a 12% incidence. In addition, tumors arising from nonsalivary tissue and the lymph nodes are found in the parotid glands. Malignant neoplasms of the salivary glands represent approximately 3% of all head and neck cancers. [71] Less than 5% of all salivary gland tumors occur in children; however, when they do, they are mostly malignant. [73]

TABLE 20-2 Distribution of 2807 Salivary Neoplasms

Histology	No. of Patients	%
Pleomorphic adenoma	1274	45.4
Warthin tumor	183	6.5
Benign cyst	29	1.0
Lymphoepithelial lesion	17	0.6
Oncocytoma	20	0.7
Monomorphic adenoma	6	0.2
Mucoepidermoid carcinoma	439	15.7
Adenoid cystic carcinoma	281	10.0
Adenocarcinoma	225	8.0
Malignant mixed tumor	161	5.7
Acinic cell carcinoma	84	3.0
Epidermoid carcinoma	53	1.9
Other (anaplastic)	35	1.3
Total	2807	100.0

From Spiro RH: Salivary neoplasms: overview of a 35-year experience with 2807 patients, *Head Neck Surg* 8:177-184, 1986.

The most common salivary gland malignancy is mucoepidermoid carcinoma, comprising approximately 34% of salivary gland malignancies, followed by adenoid cystic carcinoma, adenocarcinoma, malignant mixed tumor, acinic cell carcinoma, and squamous cell (epidermoid) carcinoma, making up 22%, 18%, 13%, 7%, and 4%, respectively.[71-74] When a tumor is present, the ratio of malignant to benign tumors increases from parotid, submandibular, minor and sublingual glands, respectively (Table 20-3). Salivary gland malignancies should be staged appropriately (Table 20-4).

Parotid Gland

The majority of parotid tumors are benign and occur in the superficial lobe. Parotid tumors may also occur in the accessory gland. An accessory parotid gland occurs in approximately 21% of human subjects. It is located anterior to the main parotid gland, usually just above Stensen's duct and connected by its own duct to the latter. Any lesions that can occur in the main parotid gland can also arise in an accessory parotid gland[75] (Figure 20-13).

Most benign and malignant salivary gland tumors are slow growing and are frequently present for months or even years before a patient seeks treatment. They can reach a considerable size. The usual clinical presentation is a painless ovoid mass in the parotid region that is discrete and not fixed to either skin or deep structures. Pain is usually associated with malignancy. Signs that are associated with malignancy include facial nerve palsy, skin ulceration, and cervical lymphadenopathy. However, less than a third of malignant lesions display any of these signs, and clinical differentiation between benign and malignant lesions is usually impossible. Patients should be asked about a history of skin cancer, because melanoma can metastasize to the parotid gland. Although sialography classically shows the "ball in hand" sign for parotid masses, it is no longer used for identifying tumors. CT scanning and MRI are the modalities of choice, although they are of little help for superficial lobe tumors. Both imaging modalities are useful for deep lobe tumors, particularly to demonstrate involvement of the lateral pharyngeal space by the 1% to 2% of deep lobe tumors that "dumbbell" through the stylomandibular canal formed by the membrane between the mandible and stylomandibular

TABLE 20-3 Relationship between Site of Primary Tumor and Malignancy

Site	Numbers	% Frequency	% Malignancy
Parotid	1756	72.9	14.7
Submandibular	257	10.7	37
Sublingual	7	0.3	85.7
Minor glands	336	14	46.4
Unknown	54	2.2	NA

From Eveson JW, Cawson RA: Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution, *J Pathol* 146:51-58, 1985.

TABLE 20-4 Stages of Salivary Gland Malignancies

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

From AJCC: Major salivary glands (parotid, submandibular, and sublingual). In Edge SB, Byrd DR, Compton CC, et al, editors: *AJCC cancer staging manual*, ed 7, New York, 2010, Springer, pp 79-86.

ligament. These tumors may originate from the deep or superficial lobe; however, in either case they may extend to the parapharyngeal space, displacing the oropharyngeal wall medially.

Furthermore, the parapharyngeal space can be divided into pre-styloid (anterolateral) and post-styloid (posteromedial) compartments by a fascial layer that extends from the styloid process to the tensor veli palatini. Deep-lobe parotid tumors involving the pre-styloid compartment of the parapharyngeal space may present as a submucosal bulging mass in the oropharynx and/or nasopharynx that distorts the soft palate or obstructs the eustachian tube. Tumors of the post-styloid compartment may show disability of cranial nerves IX and X (decreased gag reflex, aspiration); cranial nerve X alone, which would manifest as asymmetric palate elevation, hoarseness, and dysphagia; and cranial nerve XI, which would manifest as weakness of the trapezius muscle. An affected cranial nerve XII would manifest as atrophy and paresis of the tongue.

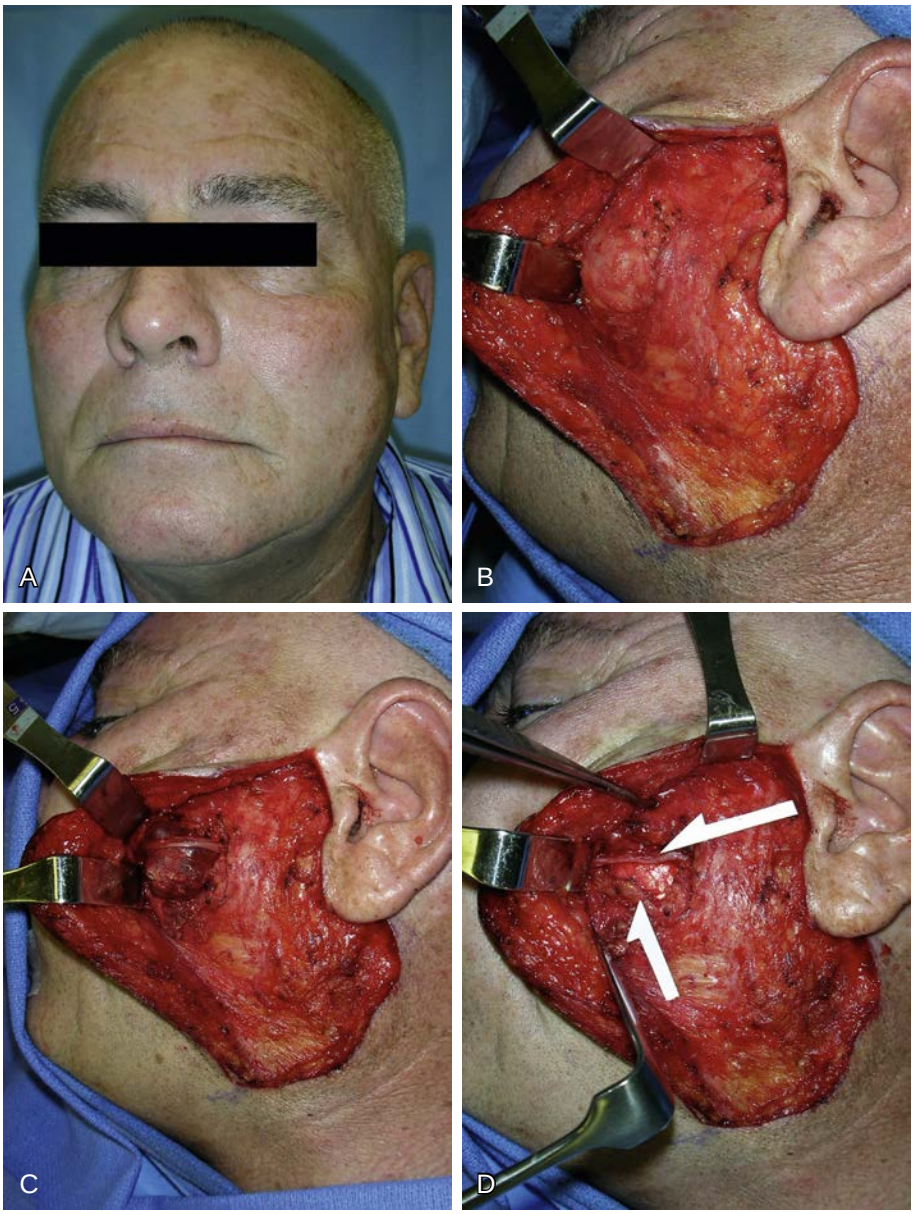
In addition, MRI studies have claimed to distinguish pleomorphic adenomas from malignant tumors on the basis of T1 and T2 characteristics. Because 80% of tumors are benign and 80% of these are pleomorphic adenomas, parotid tumors without signs of malignancy are initially approached as if they were pleomorphic adenomas. The pleomorphic adenoma has a false capsule, and if this is ruptured, the spilled tumor cells can seed and lead to recurrence. Therefore an open biopsy of parotid tumors is contraindicated. Fine-needle aspiration biopsy (FNAB) may be used for preoperative diagnosis. However, the surgeon's confidence in the diagnosis will depend on the competence of the cytologist, because the diagnosis of salivary tumors can be extremely confusing. At the time of surgery, frozen sections carry the same risk of seeding as an open biopsy, and they are notoriously unreliable in the diagnosis of malignant salivary tumors. The most common malignant tumor of the parotid gland is the mucoepidermoid carcinoma.

Benign Tumors

Pleomorphic adenoma is the most common tumor found

logic characteristics of both epithelia and mesenchymal components. Approximately 90% of pleomorphic adenomas arise superficial to the facial nerve. The nature of its false capsule with "buds" of tumor growing into it makes enucleation an illogical operation. The surgical approach adopted should remove the tumor in its entirety with a surrounding cuff of normal tissue. These surgical principles should also be applied to other benign tumors of the parotid gland. In a superficial lobe tumor, this is best achieved with a superficial parotidectomy (lateral lobectomy), which remains the basic operation in parotid surgery (Figure 20-14). The facial nerve is preserved. In deep lobe tumors, a total parotidectomy is required. This is a more technically demanding operation because of the confined space between the mandible and mastoid, the presence of the external carotid artery, and the need to protect the facial nerve. Following a superficial parotidectomy in which the superficial lobe is pedicled inferiorly to the deep lobe, the tumor is delivered inferiorly after the facial nerve is lifted away. It is rarely possible to obtain a good cuff of normal tissue around deep lobe tumors. In some cases of retromandibular tumors lying deep to the mandible, anterior dislocation of the mandible or osteotomy of the vertical ramus may be required. In large lateral pharyngeal space tumors, blind enucleation should be avoided, and various mandibular osteotomies have been described to access these neoplasms.[76] In the past, the senior author performed the double mandibular osteotomy described by Attia and colleagues.[77] However, we have recently changed our approach to a non–lip-splitting double mandibular osteotomy to preserve cosmesis, while still obtaining excellent exposure of the tumor (Figure 20-15).

Recurrent pleomorphic adenomas may be unifocal or multifocal, but in general they are rare. Multifocal lesions may involve the skin, muscle, and facial nerve and require en-bloc resection as for a malignant tumor. Recent publications suggest a limited role for radiation therapy in multifocal recurrence.[78] True malignant change is rare and usually occurs in a long-standing benign pleomorphic adenoma. The prognosis and treatment depend on the type of malignancy present and whether the tumor has extracapsular

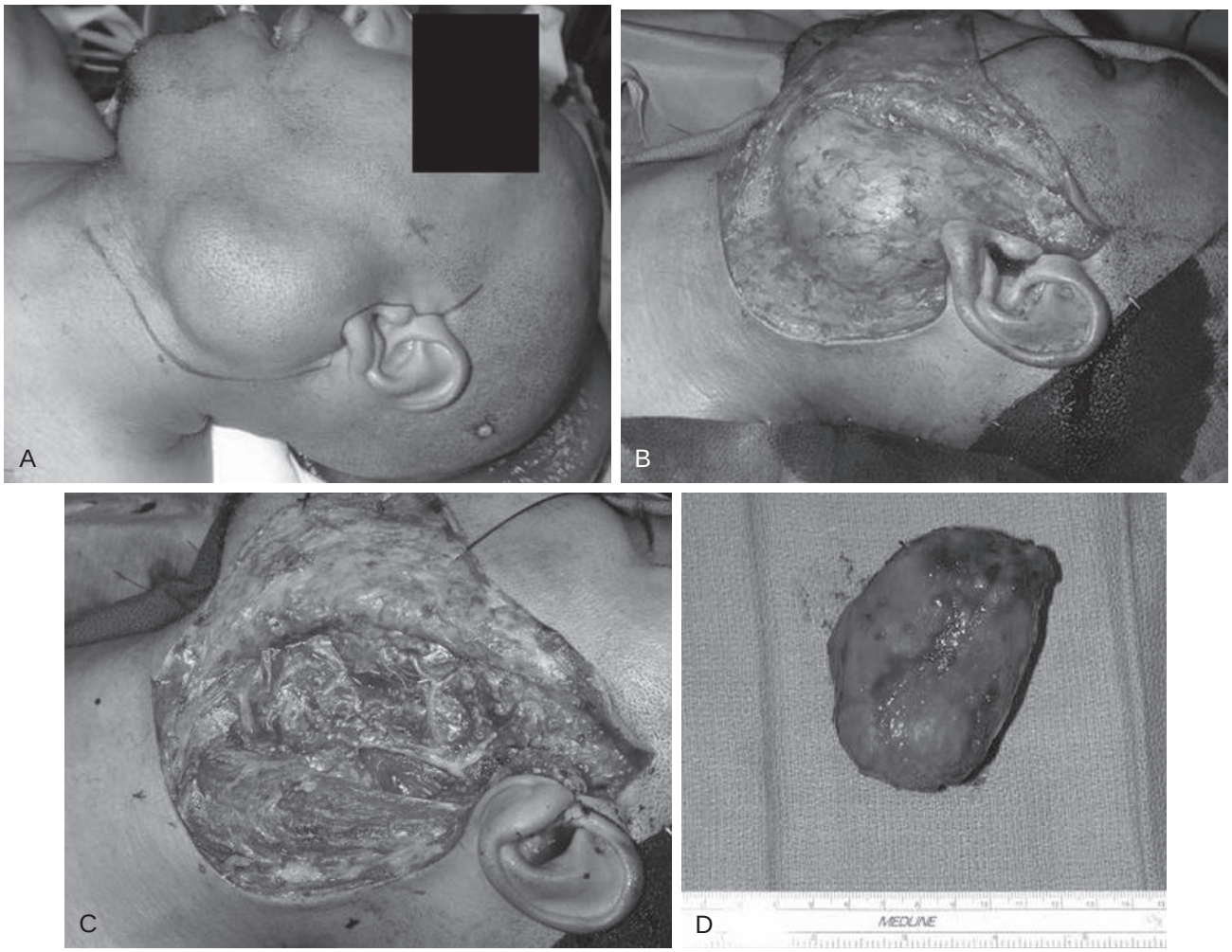


• **Figure 20-13** **A,** Patient with enlarging cheek mass over past 2 years; preoperative image revealed an anterior parotid mass, and fine-needle aspiration was consistent with a pleomorphic adenoma of the accessory parotid gland. **B,** Flap elevated to reveal the lesion. **C,** Further dissection and exposure of the buccal branch of the facial nerve traveling directly over the tumor. **D,** Completed dissection. Note the position of the nerve *(superior arrow)* in relation to the duct *(inferior arrow)*.

spread. Congenital tumors include the hemangioma, vascular and lymphatic malformations, and sialoblastoma.

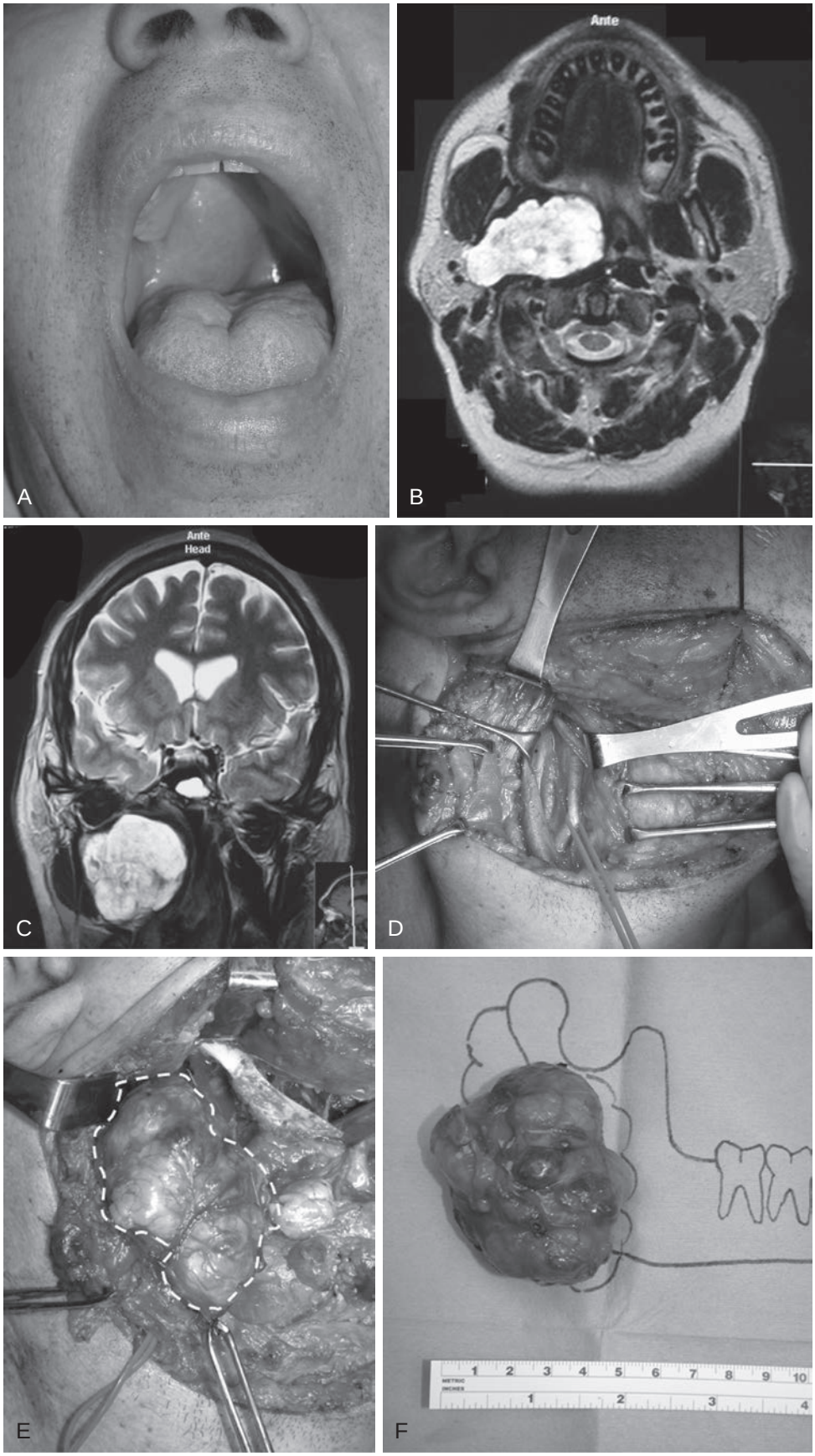
Warthin tumor is the other common benign parotid tumor and the second most common benign salivary gland neoplasm, which can be multiple and bilateral.[79] Warthin tumor is also known as papillary cystadenoma lymphomatosum or adenolymphoma. Bilateral Warthin tumors occur in 10% of cases and may be simultaneous, have a male preponderance, and are associated with cigarette smoking.[80] These "tumors" may just be reactive proliferation of salivary duct tissue in lymph nodes, and some authorities advocate no surgery if the diagnosis can be made definitively by FNAB. Other less common benign neoplasms include myoepithelioma, basal cell adenoma, sclerosing polycystic adenosis, and keratocystoma.

Briefly, for parotidectomy, a skin incision is placed in the preauricular crease, then extended to the root of the helix and inferiorly around the lobule of the ear over the mastoid tip, then slightly forward into natural skin crease of the neck (modified Blair). Alternatively, a facelift incision may be used starting just on or inside the tragus, with a posterior hairline extension versus the cervical extension of the modified Blair. A skin flap is then elevated superior to the parotid fascia in the preauricular region, and in the subplatysmal plane once in the neck. The great auricular nerve and external jugular vein are identified just over



• **Figure 20-14** **A,** A modified Blair incision is marked. Care is made not to extend the incision too far posterior to the lobule of the ear, especially in smokers, so as to prevent ischemia of the flap. **B,** Flap is elevated up, exposing the tumor. **C,** Completed superficial parotidectomy. Note the facial nerve. **D**, Excised specimen.

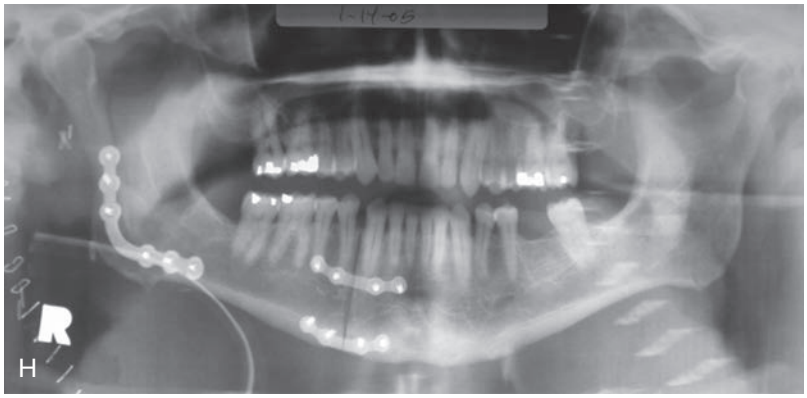
the sternocleidomastoid (SCM) muscle—these are usually divided to free the tail of the parotid off the SCM. The posterior belly of the digastric muscle is exposed proximal to its attachment to the mastoid bone. The fascia between the parotid gland and the cartilaginous external auditory canal is carefully dissected while retracting the parotid gland anteriorly. Key landmarks to identify the main trunk of the facial nerve are the tragal pointer and attachment of the posterior belly of the digastric muscle to the mastoid bone. The nerve will usually be found between these two landmarks. Usually the nerve can be found approximately 1 to 1.5 cm deep and inferior to the tragal pointer. The third landmark is the tympanomastoid suture, which can be found medial to the main trunk of the nerve. The main trunk of the facial nerve is usually 6 to 8 mm deep to the tympanomastoid suture line. If tumor lies over the main trunk of the nerve, one or more peripheral branches can be identified distally and traced back proximally to the main trunk. [81] The marginal mandibular branch may be identified below the lower border of the mandible, as it crosses the superficial branch to the facial vessels just beneath the deep cervical fascia, or the buccal branch may be identified just beneath the parotidomasseteric fascia, coursing parallel to the parotid duct. In a cadaver study by Rea and colleagues, the main trunk of the facial nerve was found 5.5 ± 2.1mm from the posterior belly of the digastric muscle, 6.9 ± 1.8 mm from the tragal pointer, 10.9 ± 1.7 mm from the junction between the bony and cartilaginous ear canal and 2.5 ± 0.4 mm from the tympanomastoid suture, making the tympanomastoid suture the most reliable landmark.[82] Once the facial nerve is identified, the overlying tissue is carefully dissected and elevated from the upper and lower divisions and off their divisions (branching at the pes anserinus). When total parotidectomy is indicated, the facial nerve and its branches are carefully dissected from the deep parotid tissue. The deep lobe is then delivered carefully and atraumatically. The nerve may need to be sacrificed when involved. Excision of parapharyngeal space salivary gland tumors is usually done as an external approach. When tumors are located in the superior aspect of the parapharyngeal space approaching the eustachian tube and skull base, a mandibulotomy is often needed for access.



• **Figure 20-15** **A,** Patient with complaints of difficulty swallowing secondary to increasing mass on the right lateral pharyngeal region. **B,** Axial magnetic resonance image of lateral pharyngeal space pleomorphic adenoma. **C,** Coronal view of same lesion. **D,** Exposure of the great vessels and placement of vessel loops for control of bleeding in case of hemorrhage during tumor dissection. **E,** Outline of the tumor as it is being delivered. The approach is facilitated by performing a double mandibular swing osteotomy. One osteotomy is performed at the subsigmoid area as a vertical subsigmoid osteotomy, and the other is performed anterior to the mental foramen. In performing this double osteotomy, the lip innervation is preserved while maintaining aesthetics by not performing a lip split. **F,** Delivered specimen.

Continued





• **Figure 20-15, cont'd** **G,** Closure of the neck after excision of the lateral pharyngeal tumor. Note that the incision is kept well below the chin, and a lip-splitting incision is avoided. **H,** Postoperative panoramic radiograph of the double mandibular osteotomy.

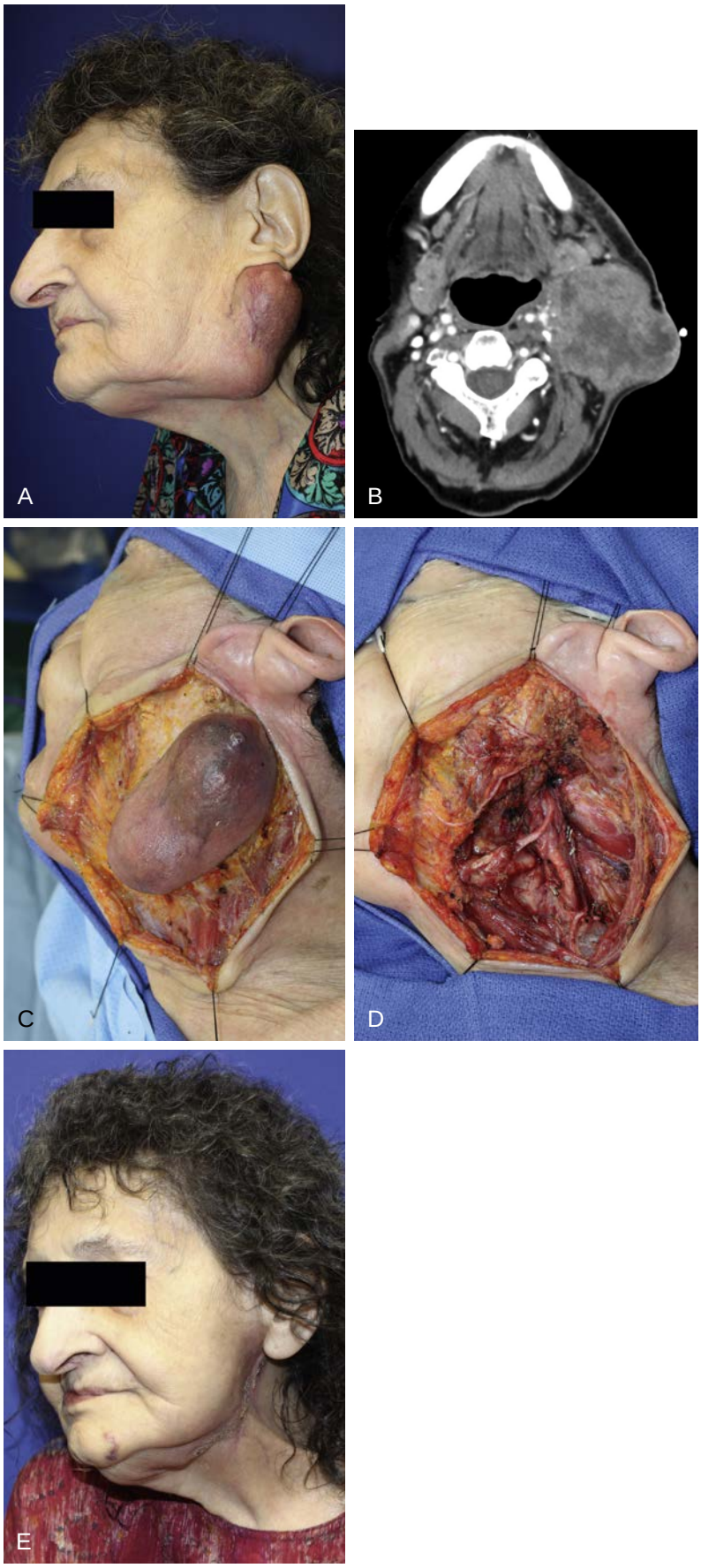
Low-Grade Malignant Tumors

The two most common low-grade malignancies are acinic cell carcinoma and low-grade mucoepidermoid carcinoma. Acinic cell carcinoma can be bilateral in 8% of cases. Mucoepidermoid carcinoma is the most common salivary cancer in children. Both of these tumors rarely metastasize to cervical nodes but are prone to local recurrence. Unless the facial nerve is involved, they should be treated similarly to a pleomorphic adenoma.

High-Grade Malignant Tumors

Adenoid cystic carcinoma is slow growing, but as a result of its infiltrative nature, perineural spread, and hematogenous metastasis, it behaves like a high-grade tumor over a long period. Five-year survival is less important than 10- or 15-year survival. Cervical metastases are found in only 20% of cases, so elective neck dissection is not advocated for the neck with no positive nodes. Wide local excision with parotidectomy, sacrificing skin, muscle, facial nerve, and bone when indicated, is the treatment of choice. Most authorities advocate adjuvant wide-field radiation therapy.

Squamous carcinoma, high-grade mucoepidermoid carcinoma, and the high-grade adenocarcinomas (e.g., comedo ductal adenocarcinoma) are aggressive cancers with a poor prognosis. These neoplasms require excision with wide margins and in-continuity neck dissection. Depending on the involvement of other sites, skin, muscle, bone, and the facial nerve may require sacrifice. A recent publication advocates preserving the facial nerve, even in high-grade malignant tumors, unless the nerve is directly involved[83] (Figure 20-16). Adjuvant radiation therapy is indicated for all these tumors. The prognosis depends on the stage at presentation, involvement of the nerve, and histologic diagnosis. There is some evidence that fast neutron radiation therapy may be more effective against salivary cancers than photon therapy.



• **Figure 20-16** **A,** Patient with squamous cell carcinoma of the parotid gland and involvement of the overlying skin. **B,** Axial view of contrast computed tomography of the neck, with contrast demonstrating a large tumor involving the deep parotid lobe and lateral pharyngeal space. **C,** Elevation of skin flap to incorporate a selective neck dissection with the parotidectomy and overlying compromised skin. **D,** Completed neck dissection and parotidectomy. **E,** Oblique view of the patient 3 months after surgery.

Nonsalivary Tumors

Tumors in the parotid gland may have a nonsalivary origin or arise from lymph nodes within the parotid gland. Tumors of nonsalivary origin are particularly common in children, with vascular malformations, particularly those of venous and lymphatic vessels, constituting 50% to 90% of all parotid tumors in the pediatric population. Treatment depends on their size and composition and whether they are high or low flow. Many require no active therapy, but surgery with or without embolization, compression, and multiple hemostatic sutures has been used. In rapidly growing hemangiomas, steroid therapy or interferon-α may be helpful. Another common parotid lesion in children and adults is the plexiform neurofibroma.

Lymph nodes within the parotid gland may be involved by metastatic skin cancer, particularly squamous cell carcinoma or melanoma. The scalp, eyelids, and neck should always be examined in a patient with a parotid mass.

Lymphomas are not uncommon in the parotid region. These may involve the lymph nodes or the substance of the gland. There is an increased incidence in patients with AIDS and also in patients with Sjögren syndrome. A sudden increase in the size of the parotid gland in a patient with Sjögren syndrome should always be regarded as a possible lymphomatous change.

Submandibular Gland

Fifty percent of tumors of the submandibular gland are malignant. A pleomorphic adenoma is the most common benign tumor, and adenoid cystic carcinoma is the most common malignant tumor of the submandibular gland. Clinically, these lesions appear as a submandibular mass that can be palpated bimanually in the submandibular triangle, which distinguishes the mass from a cervical node. Skin tethering, cervical lymphadenopathy, fixation to the mandible, and involvement of facial, lingual, or hypoglossal nerves are signs of malignancy. CT and MRI are helpful, and FNAB may give a histologic diagnosis. Other submandibular gland entities acting like tumor include chronic sclerosing sialadenitis (Kuttner tumor).

Benign tumors may be excised with extracapsular dissection and excision of the submandibular gland (Figure 20-17). The most common malignant tumor of the submandibular gland is the adenoid cystic carcinoma. Malignant tumors have a poor prognosis because of late diagnosis and early involvement of the marginal mandibular branch of the facial nerve, which would manifest as weakness of the lower lip, or change in sensation of the tongue from involvement of the lingual nerve. Frequently the mass is diagnosed as inflammatory and excised without a proper oncologic approach. Neck dissection is usually carried out with en-bloc excision of the submandibular triangle, including the mandible if it is involved. The neck dissection may be selective or a modified radical, depending on the stage of nodal disease. Radiation therapy is usually required postoperatively for malignant tumors.

Sublingual Gland

Tumors of the sublingual gland are rare (1% to 2% of all salivary gland tumors), but 90% of these tumors are malignant. The authors have yet to see a benign tumor in this region. The lesions usually occur as a hard, painless mass of the sublingual gland. Pain is indicative of perineural spread. These tumors can rapidly involve the lingual nerve, the body of the mandible, and the musculature of the tongue. Prognosis depends on the stage and microscopic diagnosis of the tumor. CT scanning or MRI is helpful in the workup, and a transoral biopsy is indicated. To obtain adequate margins, mandibulotomy and lip split are usually required, so a supraomohyoid neck dissection is undertaken in most cases. Obviously, involvement of the mandible or the lingual nerve or the presence of metastatic nodes dictates a composite resection with possible radical neck dissection or a modified radical neck dissection and postoperative radiation therapy.

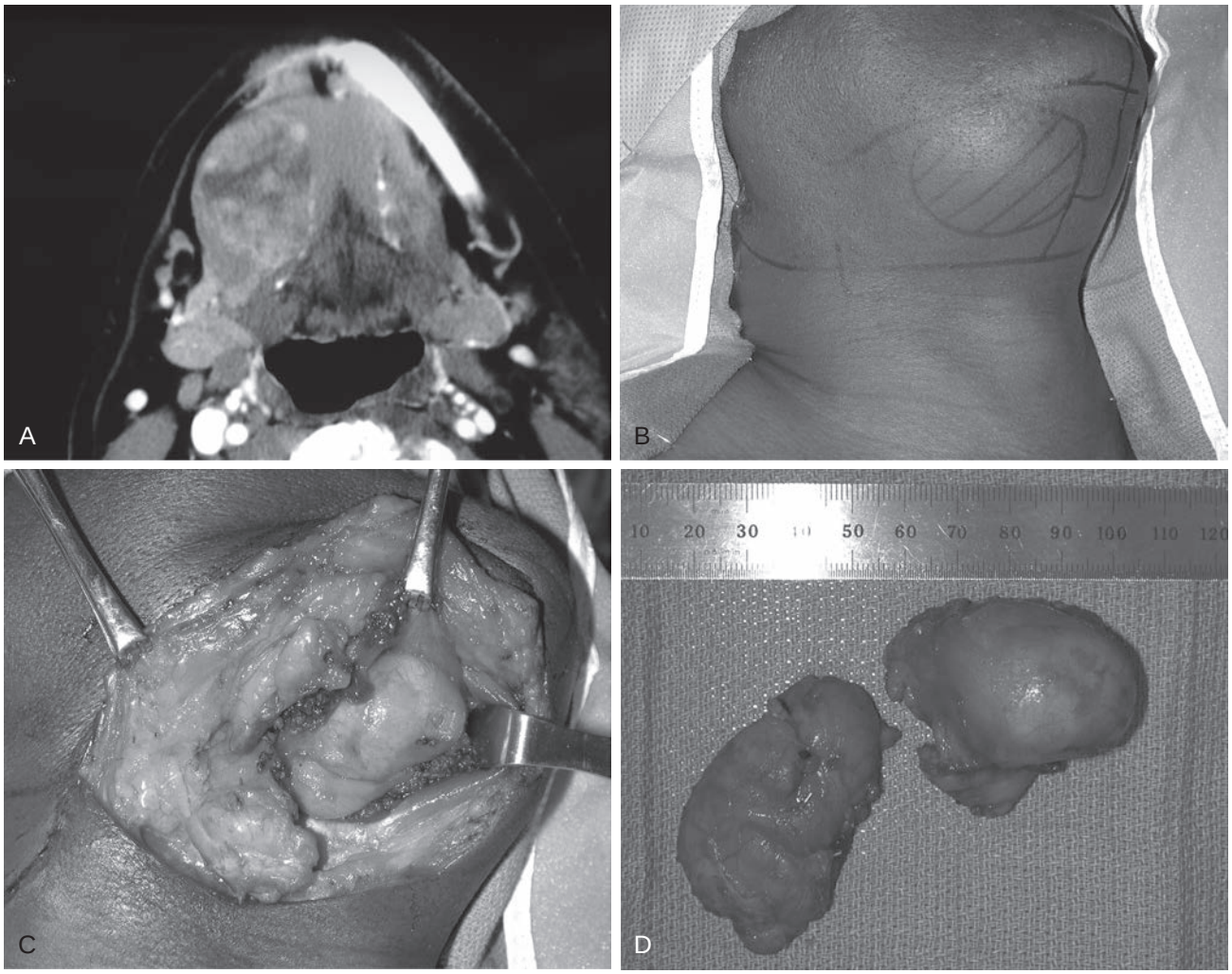
Minor Salivary Glands

Approximately 750 minor salivary glands are found in the oral cavity, nasal cavity, paranasal sinuses, and pharynx. Pleomorphic adenomas may arise from minor salivary glands, with the most common site being the palate, followed by the upper lip. Pleomorphic adenoma of the lower lip is uncommon,[84] whereas it is the most common benign tumor of the lacrimal gland.[85] The majority of these glands are found at the junction of the hard and soft palate, which is the most common site for minor salivary gland tumors. In the palate, 50% of these tumors are malignant, whereas 85% to 90% are malignant in the tongue, and only 20% are malignant in the upper lip.[83] Other benign tumors of the upper lip minor salivary glands include the canalicular adenoma and lipoadenoma.

Lipoadenoma

The diagnostic workup is similar to that for salivary tumors at other sites. CT scanning is best for bony involvement in palatal lesions, and MRI is better to display soft tissue invasion or perineural spread. A transoral biopsy should be undertaken at the center of the tumor and should include overlying mucosa. The most common benign tumor is a pleomorphic adenoma. Malignant tumors are divided into low-grade and high-grade lesions. A pleomorphic adenoma is treated by local excision with 0.5- to 1-cm margins. Enucleation will lead to recurrence. Except in the case of larger neglected tumors, reconstruction may be by primary or secondary healing or include the use of local flaps. Bony excision is usually not required because a pleomorphic adenoma does not invade bone, although it may cause pressure resorption (Figure 20-18).

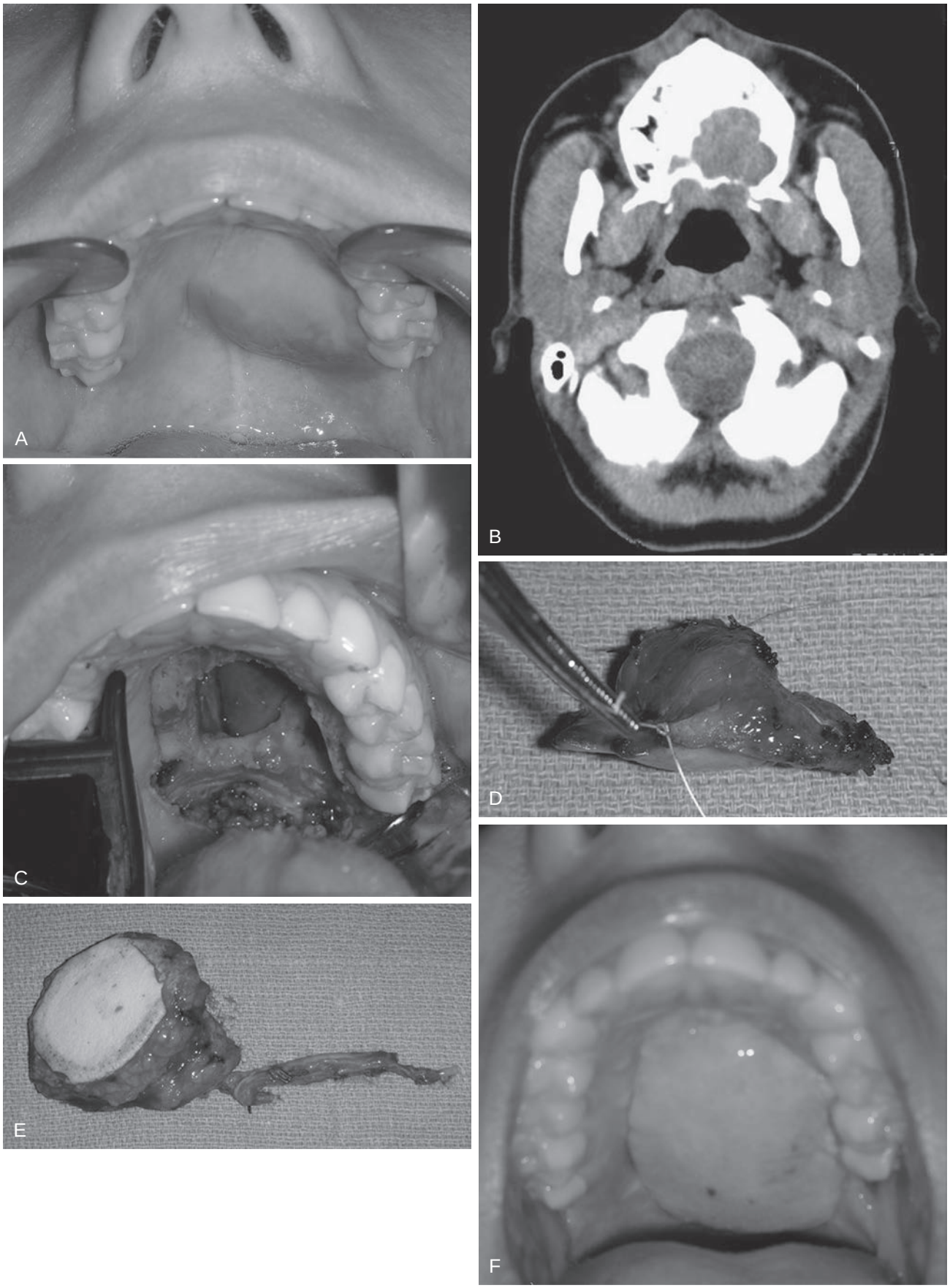
The most common malignant tumor of the minor salivary glands is the adenoid cystic carcinoma, except those



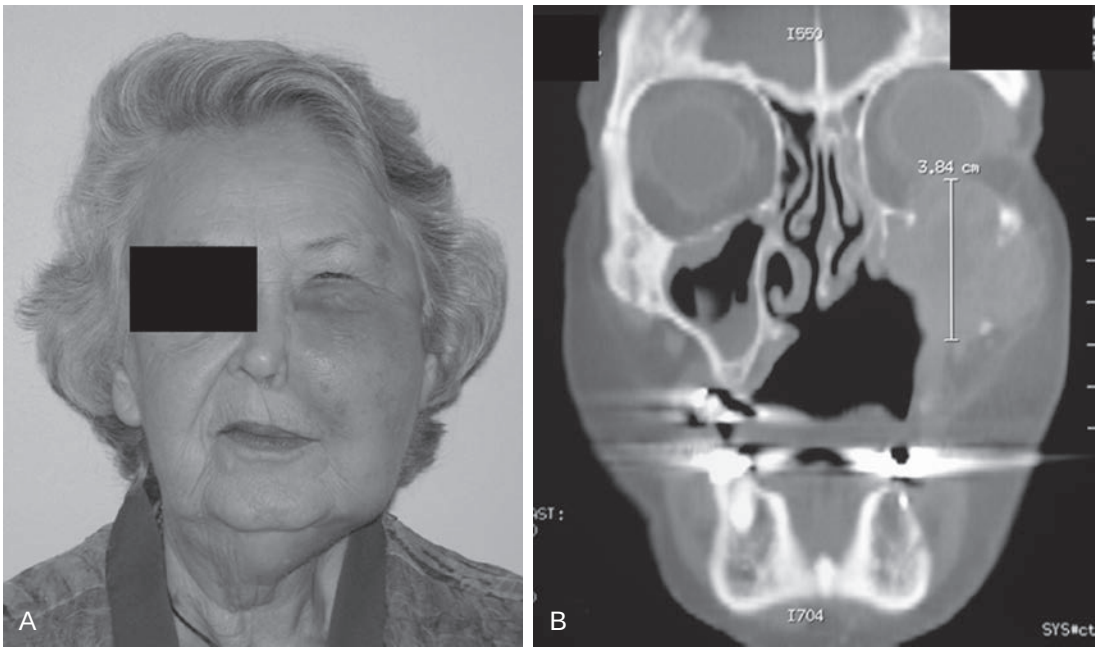
• **Figure 20-17** **A,** Computed tomography scan of a patient with pleomorphic adenoma of the submandibular gland proven by fine-needle aspiration biopsy. **B,** Intraoperative markings. Note the clearly apparent right submandibular swelling. **C,** Intraoperative dissection and exposure of the tumor. **D,** Resected specimen.

that arise in the nasal cavity and paranasal sinuses, in which case adenocarcinoma was the most common type. Low-grade malignant tumors include low-grade mucoepidermoid carcinoma, polymorphous low-grade adenocarcinoma (PLGA), and clear cell carcinoma. The first two tumors are particularly common. These lesions are all characterized by local invasion and infiltration; however, cervical node metastasis or distant metastasis is very rare. Surgery should involve wide local excision with clear margins because local recurrence is the major problem (Figure 20-19). Low-grade mucoepidermoid carcinoma is the most common malignant minor salivary gland tumor in the senior author's series, although older series report adenoid cystic carcinoma as the most prevalent. Low-grade mucoepidermoid carcinoma is frequently cystic because of its many mucous cells and has a propensity for involving the retromolar trigone. It may also occur in children. PLGA is being diagnosed more often as pathologists became more aware of its existence. It may mimic a pleomorphic adenoma and adenoid cystic carcinoma from a microscopic standpoint. Recurrences can occur after many years, mandating long-term follow-up. Perineural spread is not uncommon, but it does not appear to adversely affect prognosis, as is the case for adenoid cystic carcinoma. Clear cell salivary carcinoma must be distinguished from clear cell variants of other salivary tumors, odontogenic tumors, and renal cell metastases. These tumors generally behave in a low-grade fashion.

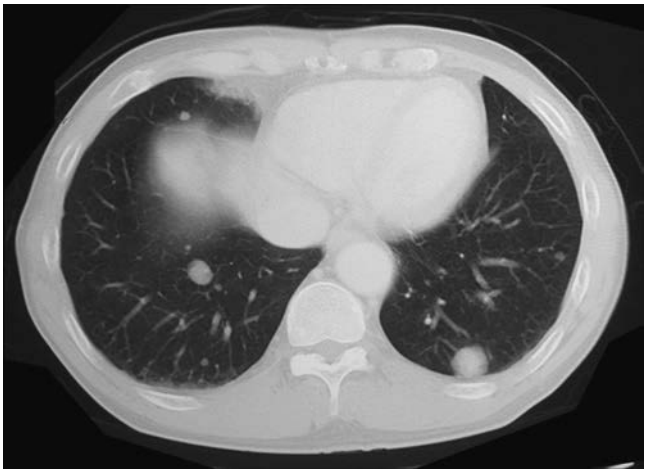
Although adenoid cystic carcinoma is slow growing, its relentless infiltration and invasion and its tendency to spread along perineural spaces make this a high-grade malignancy with a poor prognosis over a 10- to 20-year follow-up period. The tumor rarely metastasizes to lymph nodes, but hematogenous spread to lung, bone, and liver is common (Figure 20-20). These metastases are slow growing



• **Figure 20-18** **A,** Young patient with a large minor salivary gland pleomorphic adenoma in the hard palate. **B,** Computed tomography scan reveals large pressure resorption of the bony hard palate with communication into the maxillary sinus (coronal not shown). **C,** Appearance of the resected bed. Note the large bony defect with extension into the maxillary sinus and nasal cavity. **D,** Resected specimen. **E,** Harvested anterior lateral thigh free flap to reconstruct the defect. **F,** View of the reconstructed palate 2 months postoperatively. No debulking procedure has been done. Patient has good speech and no communication with the sinus or nasal cavity.



• **Figure 20-19** **A,** Patient with a large recurrent polymorphous low-grade adenocarcinoma of the left maxilla, extending to the cheek and invading the orbit. **B,** Computed tomography scan revealing the extent of recurrence and orbital invasion.



• **Figure 20-20** Patient with previously resected adenoid cystic carcinoma of the retromolar region now with metastatic adenoid cystic carcinoma to the lungs, the so-called cannon balls.

and compatible with many years of survival. In the palate and maxillary sinus, involvement of the greater palatine nerves can lead to early orbital, skull base, and brain involvement. Histologic typing is important in determining prognosis; canalicular tumors have the best prognosis in terms of survival, cribriform tumors have an intermediate prognosis, and solid tumors with necrosis have a very poor prognosis. The presence of perineural spread is an indicator of increased local recurrence and distant metastases. Radical resection with wide margins (identifying major nerves and following them with frozen section) is the recommended treatment. Adjuvant radical radiation therapy given with high fractionation and wide fields is usually recommended. Distant metastases are frequently slow growing and, when symptomless, do not usually require therapy. However, excision of solitary or symptomatic pulmonary or brain metastases has been advocated. There is no good evidence that chemotherapy is beneficial.

High-grade mucoepidermoid carcinoma behaves similarly to squamous cell carcinoma, which it may closely resemble microscopically (Table 20-5). This tumor frequently metastasizes early to lymph nodes and is regarded as relatively radioresistant. Radical surgery with 1- to 2-cm margins and neck dissection, as indicated, is usually followed by radiation therapy. However, these patients frequently succumb to distant metastases.

Salivary Diseases Associated with Systemic Disease

There are a number of systemic diseases, usually causing swelling or xerostomia, that may involve the salivary glands.

Sarcoidosis may have swelling of the parotid gland and occasional facial nerve palsy. Involvement of the lacrimal gland, uveal tract, and parotid gland (known as Heerfordt uveoparotitis) is also a manifestation of sarcoidosis.

Bilateral swelling of the major salivary glands is also an accompaniment of many endocrine diseases (e.g., thyroid disease, diabetes) and metabolic conditions (e.g., alcoholism). This condition is called sialosis.

There are a number of diseases characterized by bilateral swelling of the major salivary glands, dry eyes, and xerostomia. The best known is Sjögren syndrome, in which the patient also suffers from a collagen autoimmune disease, most commonly rheumatoid arthritis. Diagnosis is based on

TABLE 20-5 Grading System for Mucoepidermoid Carcinoma

Parameter (Auclair)	Point Value
Cystic component	+2
Neural invasion	+2
≥4 mitoses/10 hpf	+3
Necrosis	+3
Anaplasia	+4
Grade	**Point Score**
Low (1)	0-4
Intermediate (2)	5-6
High (3)	≥7

Parameter (Brandwein)	Point Value
Cystic component <25%	+2
Tumor front invades in small nests and islands	+2
Pronounced nuclear atypia	+2
Lymphatic and/or vascular invasion	+3
Neural invasion	+3
Necrosis	+3
Four or more mitoses/10 hpf	+3
Bony invasion	+3
Grade	**Point Score**
Low (1)	0
Intermediate	2-3
High (3)	≥4

hpf, High-power field.
From Auclair PL, Goode RK, Ellis GL: Mucoepidermoid carcinoma of intraoral salivary glands. Evaluation and application of grading criteria in 143 cases, *Cancer* 69:2021-2030, 1992; Brandwein MS, Ivanov K, Wallace DI et al: Mucoepidermoid carcinoma: a clinicopathologic study of 80 patients with special reference to histological grading, *Am J Surg Pathol* 25:835-845, 2001.

history and examination, but may be confirmed by special tests, including antibody profiles (anti-SS-A and anti-SS-B antibodies) and a salivary gland biopsy to confirm the presence of lymphocytic infiltration. Although the common site for a biopsy is the lip (involving the removal of three to four minor salivary glands), a parotid gland biopsy is recommended by some authorities.[86] Treatment is symptomatic, with artificial tears and saliva and the use of fluoride trays with regular dental follow-up. If the parotid glands become very enlarged, they may be removed for improved cosmesis. However, this is difficult surgery because of the fibrosis and microabscesses present. Rapid growth of any gland should alert the surgeon to the possibility of lymphomatous change.

Lymphomas may occur in the parotid gland without antecedent Sjögren syndrome or AIDS. In children with AIDS, bilateral lymphocytic infiltration of the major glands may be seen.

Xerostomia is a symptom associated with a variety of underlying disease states, including endocrine and metabolic disorders and psychiatric disease. The clinician should always obtain a list of the patient's medications because sed-

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21

Diagnosis and Management of Medication-related Osteonecrosis of the Jaw

SALVATORE L. RUGGIERO

Introduction

Antiresorptive medications such as bisphosphonates and more recently the receptor activator of nuclear factor-κB ligand (RANKL) inhibitors are a class of agents used to treat osteoporosis and the complications associated with malignant bone metastases. Despite these benefits, osteonecrosis of the jaws is recognized as a significant complication in a subset of patients receiving these drugs. Based on a growing number of case reports and institutional reviews, antiresorptive therapy may cause exposed and necrotic bone that is isolated to the jaw. This complication usually presents following simple dentoalveolar surgery. The pathogenesis for this complication appears to be related to the profound inhibition of osteoclast function and bone remodeling. The emergence of jaw necrosis in bisphosphonate-naive patients receiving monoclonal therapy with RANKL inhibitors[1-4] prompted the American Dental Association to introduce the more generic term ARONJ (antiresorptive associated osteonecrosis of the jaw).[5] MRONJ (medication-related osteonecrosis of the jaw) is the most recent nomenclature change, proposed in the 2014 position paper of the American Association of Oral and Maxillofacial Surgeons (AAOMS).[6] This modification was considered necessary in order to address the growing number of osteonecrosis cases affecting the jaws that were associated with antiangiogenic therapies.

In this chapter we review the clinical indications for antiresorptive therapy and certain antineoplastic agents along with the osteonecrosis risks associated with their long-term use. Diagnostic strategies, risk stratification and guidelines for staging and management of patients with established MRONJ are also reviewed.

Antiresorptive Agents: What Are They and How Do They Work?

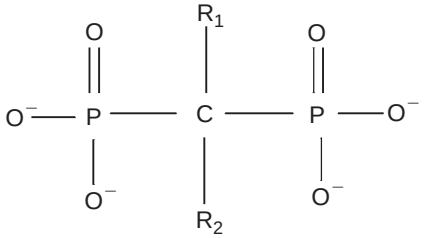
Bisphosphonates were developed in the 19th century, but were first investigated in the 1960s for use in disorders of bone metabolism. Their nonmedical use included water softening in irrigation systems used in orange groves.[7] The initial rationale for their use in clinical practice was centered on their potential for preventing the dissolution of hydroxyapatite, the principal bone mineral, and hence arresting bone loss.

All bisphosphonates are non-metabolized synthetic analogues of pyrophosphate. There are a variety of bisphosphonates that are approved for clinical use in the United States. They are segregated based on potency and route of administration (Table 21-1). Bisphosphonates bind avidly to exposed bone mineral around resorbing osteoclasts, resulting in very high levels of bisphosphonate in the resorption lacunae. Because bisphosphonates are not metabolized, mediated bone resorption at various levels.[8] At the tissue level, bisphosphonates will inhibit bone resorption and decrease bone turnover as assessed by biochemical markers. The degree to which these compounds will also alter bone formation is related to their effects on bone turnover, which is closely coupled to bone formation. On a cellular level, the bisphosphonates target the osteoclasts and may inhibit their function in several ways: (1) inhibition of osteoclast recruitment,[9] (2) reduction of osteoclast life span,[10] and (3) inhibition of osteoclastic activity at the bone surface.[11] At a molecular level it has been postulated that bisphosphonates modulate osteoclast function by interacting with a cell surface receptor or an intracellular enzyme.[12]

TABLE 21-1 Antiresorptive Medications

Generic Name	Brand Name (Delivery)	RAP*
Etidronate	Didrone (PO)	1
Tiludronate	Skelid (PO)	10
Alendronate sodium	Fosamax (PO)	1,000
Risedronate	Actonel (PO)	5,000
Ibandronate	Boniva (PO/IV)	10,000
Zoledronic acid	Zometa (IV)	100,000
Pamidronate	Aredia (IV)	100
Denosumab	Xgeva (IV), Prolia (PO)	Similar to zoledronic acid

*Relative antiresorptive potency.



• **Figure 21-1** Chemical structure of the basic bisphosphonate molecule.

Each bisphosphonate has a different R1 or R2 side chain attached to the central carbon atom (Figure 21-1). The R1 side chain determines affinity for bone, whereas the R2 side chain is responsible for potency and antiresorptive properties. In general, side chains that contain a nitrogen atom are more potent than the non-nitrogen bisphosphonates. Etidronate, tiludronate, and clondronate are older-generation (risedronate and ibandronate). Zoledronic acid, the most potent bisphosphonate, is a tertiary amine that is part of a ring structure. The nitrogen-containing bisphosphonates inhibit the activity of the enzyme farnesyl diphosphate synthase in the mevalonate pathway, which blocks the phenylation of small signaling proteins (GTPases) that are required for osteoclast function and survival.

Bisphosphonates also have demonstrated effects unrelated to osteoclast inhibition. Pamidronate has been associated with an acute-phase reaction characterized by fever and transient changes in various cytokine levels such as interleukin-6, tumor necrosis factor-alpha, C-reactive protein, and elastase.[13] More importantly, pamidronate was reported to significantly depress bone blood flow in rats.[14,15] The mechanism of this effect may be attributable to a complex interaction of pamidronate with growth hormone and insulin-like growth factor 1, both of which are thought to play a role in the regulation of blood circulation in bones. Bisphosphonates can also inhibit endothelial cell function in vitro and in vivo.[16] Those cells treated with bisphosphonates demonstrated decreased proliferation, an increased rate of apoptosis, and a decrease in capillary-tube formation. In that same study, there was a marked reduction in the number of blood vessels in pagetic bone marrow after bisphosphonate treatment when compared to pretreatment biopsies. Bisphosphonates have also demonstrated potent antiangiogenic properties due to their ability to significantly decrease circulating levels of vascular endothelial growth factor (VEGF) in breast cancer patients with bone metastases.[17] Wood and colleagues[18] demonstrated the antiangiogenic properties of bisphosphonates on several levels: (1) potent inhibition of vessel sprouting in a chick embryo model, and (2) potent inhibition of angiogenesis induced by subcutaneous implants impregnated with bFGF in a murine model. These antiangiogenic properties have generated interest in the potential of bisphosphonates as antitumor agents.[19,20]

Denosumab (Prolia, Xgeva) is a novel antiresorptive agent that exists as a fully humanized antibody against RANKL. This receptor activator is a cytokine that is important for the formation, function, and survival of osteoclasts.[21] Denosumab prevents the interaction of RANKL with its receptor (RANK) on osteoclast and osteoclast precursors, resulting in profound inhibition of osteoclast function and osteoclast-mediated bone resorption. Interestingly, these agents do not bind to bone, and their effects on bone remodeling are reversible within 6 months of treatment cessation.

Antiresorptive and Antiangiogenic Therapy in Clinical Practice

The complications associated with metastatic bone disease, osteoporosis, and Paget disease are related to perturbations in osteoclast function. Therefore, it is not surprising that antiresorptives, which are potent inhibitors of osteoclast function, have demonstrated clinical efficacy in these diseases.

Malignant Bone Disease

Annually, about 1 million women worldwide will develop breast cancer.[22] Of those progressing to advanced disease, close to 70% will develop bone metastases.[23,24]

The efficacy of intravenous bisphosphonates and RANKL inhibitors in reducing bone pain, hypercalcemia, and skeletal complications has been extensively documented in patients with advanced breast cancer, multiple myeloma, and prostate cancer.[1,25-36] This has resulted in widespread use of antiresorptives in medical oncology practices. Myeloma-related lytic disease is now understood to be

TABLE 21-2 Antiangiogenic Medications Associated with Osteonecrosis of the Jaw

Drug	Drug Class
Bevacizumab (Avastin)	Monoclonal antibody
Sunitinib (Sutent)	Tyrosine kinase inhibitor
Sorafenib (Nexavar)	Tyrosine kinase inhibitor
Sirolimus (Rapamune)	Mammalian target of rapamycin pathway

secondary to increased osteoclastic activity and impaired osteoblastic activity. Myeloma cells are known to secrete both stimulators of osteoclast activation such as RANKL and soluble molecules such as dickkopf 1 (DKK) that inhibit osteoblastic activity.[37] Bisphosphonates and RANKL inhibitors suppress osteoclast function and therefore block the formation of "punched-out" lytic bony lesions and consequent manifestations of lytic bony disease.

Thus antiresorptives are frequently administered to patients with osteolytic metastases, especially if there is risk for significant morbidity. Based on clinical practice guidelines established by the American Society of Clinical Oncology, the use of antiresorptives is considered the standard of care for treatment of: (1) moderate to severe hypercalcemia associated with malignancy and (2) metastatic osteolytic lesions associated with breast cancer and multiple myeloma in conjunction with antineoplastic chemotherapeutic agents.[38,39] In patients with osteolytic metastases, oral bisphosphonate therapy is not as efficacious as the intravenous form in preventing skeletal complications and therefore is not indicated for patients with cancer.

Tumor formation and propagation often requires the formation of new blood vessels. This process of angiogenesis requires binding of signaling molecules such as VEGF, which then promotes growth, migration, and differentiation of vascular endothelial cells. Angiogenesis inhibitors (tyrosine kinase inhibitors and monoclonal antibody targeting VEGF) function by interfering with the formation of new blood vessels by binding to various signaling molecules, disrupting the angiogenesis-signaling cascade. These classes of medications have demonstrated efficacy in the treatment of a variety of neuroendocrine and gastrointestinal tumors (Table 21-2). Recently, these novel chemotherapeutic regimens have been associated with the development of jaw necrosis. Several case series have reported jaw necrosis in patients receiving combination therapy (antiangiogenic medication and an antiresorptive) and when an antiangiogenic drug is used as a single agent.[40-45]

Osteoporosis

Osteoporosis, a disease that is characterized by increased skeletal fragility and low bone mineral density, is responsible for more than 1.5 million fractures in postmenopausal women each year at an annual cost of $18 billion.[46] It is estimated that 35% of postmenopausal Caucasian American women have some degree of osteoporosis in the hip, spine, or forearm and that 40% of these women will experience some type of osteoporotic fracture.[47] This is in contrast to men over the age of 50, of whom only 13% are estimated to have an osteoporotic fracture.[47] Although bone quality cannot be measured directly, bone mineral density is a relatively easy parameter to measure. Osteoporosis is characterized clinically by the T score, which represents the number of standard deviations the bone mineral density is above or below the normal mean bone density of a young Caucasian individual.

As a potent suppressor of osteoclast activity, bisphosphonates slow the remodeling process and increase bone mineral density, thereby reducing the risk of fracture in women with osteopenia and osteoporosis.[48,49] All bisphosphonates currently approved for osteoporosis treatment have been shown to significantly reduce the risk of osteoporotic fractures. Alendronate has been shown to prevent bone loss at the spine and hip in menopausal women and reduce fractures at these sites by approximately 50%.[50-52] In a large prospective trial, risedronate produced a 30% reduction in hip fractures.[53,54] Because of their proven clinical efficacy, bisphosphonates are considered first-line therapy in the treatment of osteoporosis and are the most widely prescribed antiresorptive agent.

As an inhibitor of RANKL expression, denosumab is also a potent inhibitor of osteoclast function and has also been demonstrated to reduce the risk of osteoporotic fractures.

A significant reduction in the risk of vertebral, nonvertebral, and hip fractures in osteoporotic patients was reported when denosumab administered subcutaneously on a biannual schedule.[55-57]

Medication-related Osteonecrosis of the Jaw

Pathophysiology

Since 2003 numerous reports have highlighted the adverse effect profile of this class of agents, including the development of osteonecrosis of the jaw in patients treated with bisphosphonates.[58-65] Since its discovery, numerous animal and in vitro studies have shed some light on the potential mechanisms for MRONJ and have generated several hypotheses regarding the etiopathogenesis of this medication-related complication.

The most popular and researched hypothesis focuses on the inhibition of osteoclast-mediated bone remodeling. The profound inhibition of osteoclast function can also inhibit normal bone turnover to such an extent that local microdamage from normal mechanical loading or injury (tooth extraction) cannot be repaired. This position is supported by several studies that have demonstrated bone necrosis isolated to the alveolar component of the jaw in animal models exposed to bisphosphonates.[66-68]

Denosumab is an antiresorptive agent that exists as a fully humanized antibody against RANKL. As such, it is a

profound inhibitor of osteoclast function and bone remodeling. Interestingly, these agents do not bind to bone, and their effects on bone remodeling are reversible within 6 months of treatment cessation. Recent case reports[2-4] and large-scale clinical trials[1] have shown that osteonecrosis of the jaw (ONJ) occurs in patients treated with denosumab. These findings strongly suggest that suppression of osteoclast-mediated bone remodeling, a common feature of both denosumab and the bisphosphonates, is likely a key factor in the pathogenesis of ONJ.

Local inflammation and infection within the bone and adjacent soft tissue is also considered to be an important aspect of this process.[69,70] Bacteria in the form of biofilms have been demonstrated to exist on many necrotic bone specimens.[71,72] Unlike the typical planktonic bacteria, these polymicrobial bacterial colonies form a dense polysaccharide matrix that effectively isolates them from circulating or topical antimicrobial medications. This may be responsible for the recalcitrant infections that are common in patients with stage 2 and 3 disease. Bisphosphonates have also been demonstrated to interact with macrophages and other immune-modulating cells, causing a blunted response to local infection.[73,74]

Alternatively, the antiangiogenic properties of certain bisphosphonates (not denosumab) may affect the local bone blood supply, contributing to the apparent ischemic changes noted in the affected patients' jawbones. This has been supported by reports of bisphosphonate-induced inhibition of angiogenesis in culture and animal tumor models[16,18] and long-term suppression of VEGF levels in cancer patients.[17,75] Furthermore, a growing number of reports describe jaw necrosis in cancer patients receiving antiangiogenic medications.[40,43,76] However, these findings are opposed by other animal studies in which bisphosphonates had no effect on angiogenesis associated with endochondral ossification[77] or at regions of bisphosphonate-induced matrix necrosis.[66]

Direct mucosal toxicity from high bisphosphonate concentrations in the bone has also been considered as the primary etiology for bone exposure and necrosis.[78-80] This is based on culture data in which high concentration of bisphosphonate were found to be toxic to oral mucosal cells. In order to recapitulate this effect in vivo, the oral mucosa would need to be exposed to high concentrations of bisphosphonate for a prolonged period of time. This situation can theoretically occur at surgical sites or regions of inflammation where there is a local reduction in pH and a release of bisphosphonate from the bone.[81] However, the clinical scenario where ONJ presents spontaneously in the non-dentate region of the jaw does not fit this hypothesis well.

Because only a minority of patients receiving antiresorptives develop bone necrosis, it is also conceivable that individual genetic variations in drug metabolism or skeletal homeostasis may confer susceptibility or resistance to developing MRONJ. Several pharmacogenetic studies have established a potential relationship between MRONJ and certain single nucleotide polymorphisms (SNPs) occurring at a gene location associated with bone metabolism and disease.[82-84] In these genomic studies, patients with SNPs that were associated with perturbations in bone density, collagen formation, and bone turnover were noted to have an elevated risk of developing MRONJ. In one study an SNP associated with activity of farnesyl diphosphate synthase, the enzyme that is specifically targeted by bisphosphonates, was linked to a higher risk of jaw necrosis.[83] These findings provide additional support for the existence of a germline sensitivity to bisphosphonates.

It appears likely that the etiology of MRONJ is the result of a multifactorial process, with intense inhibition of bone remodeling being the central initiating event. The apparent selective involvement of the maxilla and mandible may be a reflection of the unique environment of the oral cavity. Typically, healing of an open bony wound (e.g., extraction socket) in the presence of normal oral microflora occurs quickly and without complication. However, when the healing potential or the vascular supply of the jaw is compromised by either tumoricidal radiation doses or some other agent(s) or pathologic process, then minor injury or disease in these sites increases the risk for osteonecrosis and osteomyelitis.

Risk Factors

Jaw necrosis occurs as a drug-related complication following medical therapy for both malignant and non-malignant disease. The most common indication for antiresorptive therapy studies that have estimated the risk of ONJ associated with oral bisphosphonate use. These survey studies report a risk level that ranges from 0.00038% to 0.1%.[85-88]

In the setting of intravenous zoledronate therapy for the treatment of malignant disease, the risk of MRONJ is 50 to 100 times higher, with a range of 0.7% to 6.7%.[89,90] The risk of MRONJ in cancer patients receiving RANKL inhibitors is similar to that in patients receiving zoledronate therapy and ranges from 0.7% to 1.9%.[1,25,27,91,92]

Osteonecrosis of the jaw has also been reported in patients receiving antiangiogenic therapy for a spectrum of malignant diseases. Guarneri and colleagues reported a risk of 0.2% but noted that the risk may be higher (0.9%) in patients who are receiving zoledronate as well.[93] Several case reports have also been published, describing jaw necrosis in patients receiving antiangiogenic medications in conjunction with zoledronate and also in patients who are bisphosphonate naïve.[40,41,43,76]

Several retrospective and prospective studies have identified other potential risk factors associated with the development of MRONJ in patients at risk.[94-98] In the majority of MRONJ cases, dentoalveolar trauma is the most prevalent and consistent risk factor.[90,96,99,100] In case-control and longitudinal studies, cancer patients receiving zoledronate who had tooth extractions had a 16- to 33-fold increase in

ONJ risk.[90,101] Based on the best level of current evidence, the estimate of ONJ risk for extraction patients receiving IV bisphosphonates ranges from 1.6% to 14.8%.[102-104] A prospective study by Kunchur and colleagues reported a MRONJ risk estimate of 0.5% for extraction patients who were receiving oral bisphosphonates.[105] An increased risk of necrosis has also been reported in denture wearers.[106] In one study of more than 1600 cancer patients receiving IV bisphosphonate therapy, denture use was associated with a twofold increase in MRONJ risk.[90]

Patients with a history of inflammatory dental disease, such as periodontal disease or periapical pathology, were also at an increased risk for developing MRONJ.[104,107,108] Saad and co-workers reported that pre-existing inflammatory dental disease was associated with MRONJ in 50% of the cases in their series.[100] This underscores the importance of maintaining good oral health and avoiding extractions in this population.

The duration of antiresorptive therapy also appears to be related to jaw necrosis, with longer treatment regimens associated with a greater risk of developing disease.[94,107] Several prospective studies have reported an escalation of MRONJ risk as the duration of exposure increased in cancer patients receiving either zoledronate or denosumab.[27,100]

The PROBE study reported a similar trend in osteoporosis patients receiving oral bisphosphonates, where the prevalence of ONJ increased from 0% at baseline to 0.21% after 4 years of exposure.[85,87] Though MRONJ is found in both sexes, the literature reports more cases in females than males, which is likely a reflection of the large number of cases reported in breast cancer patients and patients with osteoporosis.

In 2005 the Food and Drug Administration (FDA) responded to the growing number of MRONJ cases by issuing broad drug class warning of this complication for all bisphosphonates. More recently, the FDA has issued an ONJ advisory for the antiangiogenic medications bevacizumab and sunitinib.[109,110] This has also prompted a change in clinical practice. With the benefit of bisphosphonate therapy beyond 5 years coming into question for patients with osteoporosis[111] and the growing concern about long-term suppression of bone turnover,[112] some clinicians have emphasized the importance of a drug holiday. In a consensus statement from the Mayo Clinic, the use of bisphosphonates in the treatment of multiple myeloma was modified to limit the exposure of intravenous bisphosphonates and minimize the potential for MRONJ.[113]

The usefulness of an antiresorptive drug holiday to minimize MRONJ risk or to expedite the healing of existing MRONJ lesions continues to be a point of controversy across several disciplines. Despite the lack of evidence, position papers from various professional associations have advocated for the use of a drug holiday for those patients at highest risk.[5,114,115] In 2011 the FDA failed to find any meaningful data that would guide decision making regarding a drug holiday.[85] Although the AAOMS position paper in 2014 acknowledged the current lack of data to support or refute a drug holiday, they continue to support this approach, citing a theoretical benefit for those patients at risk.[6] This theoretical benefit is based on bone physiology, the pharmacokinetics of bisphosphonates, and their effect on local osteoclasts.[116]

Clinical Presentation

The patient history and clinical examination are the most sensitive diagnostic tools for this condition. A diagnosis of MRONJ should be considered if a patient presents with all of the following criteria[6]:

1. Current or previous treatment with antiresorptive and/or antiangiogenic agents
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than 8 weeks; and
3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.

Areas of exposed and necrotic bone may remain asymptomatic for weeks, months, or years and may result in pain or exposed maxillary or mandibular bone. The size of the affected area can range from a non-healing extraction site to necrosis and exposure of the entire jaw.

These lesions are most frequently symptomatic when surrounding tissues become inflamed or there is clinical evidence of exposed bone. Signs and symptoms that may occur before the development of clinically detectable osteonecrosis include pain, tooth mobility, mucosal swelling, erythema, and ulceration. These may occur spontaneously or more commonly at the site of prior dentoalveolar surgery. Intraoral and extraoral fistulae may develop when necrotic jawbone becomes secondarily infected (Figure 21-2). Some



• **Figure 21-2** Stage 2 medication-related osteonecrosis of the jaw with an area of exposed alveolar bone and a draining intraoral fistula.



• **Figure 21-3** Panoramic radiograph of a patient with stage 3 medication-related osteonecrosis of the jaw. There is a non-healing extraction site with a sclerotic lamina dura and osteolysis extending to the inferior border of the left mandible.

patients may also present with complaints of altered sensation in the affected area as the neurovascular bundle becomes compressed from the inflamed surrounding bone. Chronic maxillary sinusitis secondary to osteonecrosis with or without an oral-antral fistula can be the presenting symptom in patients with maxillary involvement. It has been observed that lesions are found more commonly in the mandible than the maxilla (3:1 ratio); however, simultaneous areas of necrosis in the maxilla and mandible have also been reported.[100]

Radiographic changes are typically not evident until there is significant bone involvement or demineralization. Therefore, panoramic and periapical radiographs may not reveal significant changes in the early stages of osteonecrosis. Little or no ossification at a previous extraction site may represent an early radiographic sign. Early or late radiographic changes may mimic classic periapical pathology or osteomyelitis or, in cancer patients, may raise the suspicion of primary (myeloma) or metastatic bone disease. When there is extensive bone involvement, regions of mottled bone or sequestrum similar to that of diffuse osteomyelitis are noted. Widening of the periodontal ligament space may also be noted radiographically. In more advanced cases, osteosclerosis of the bone may be noted radiographically, especially osteosclerotic lamina dura (Figure 21-3).

The findings on computed tomography (CT) are also nonspecific, but this modality is significantly more sensitive to changes in bone mineralization and therefore is more likely to demonstrate areas of focal sclerosis, thickened lamina dura, early sequestrum formation, and presence of reactive periosteal bone (Figure 21-4).[117]

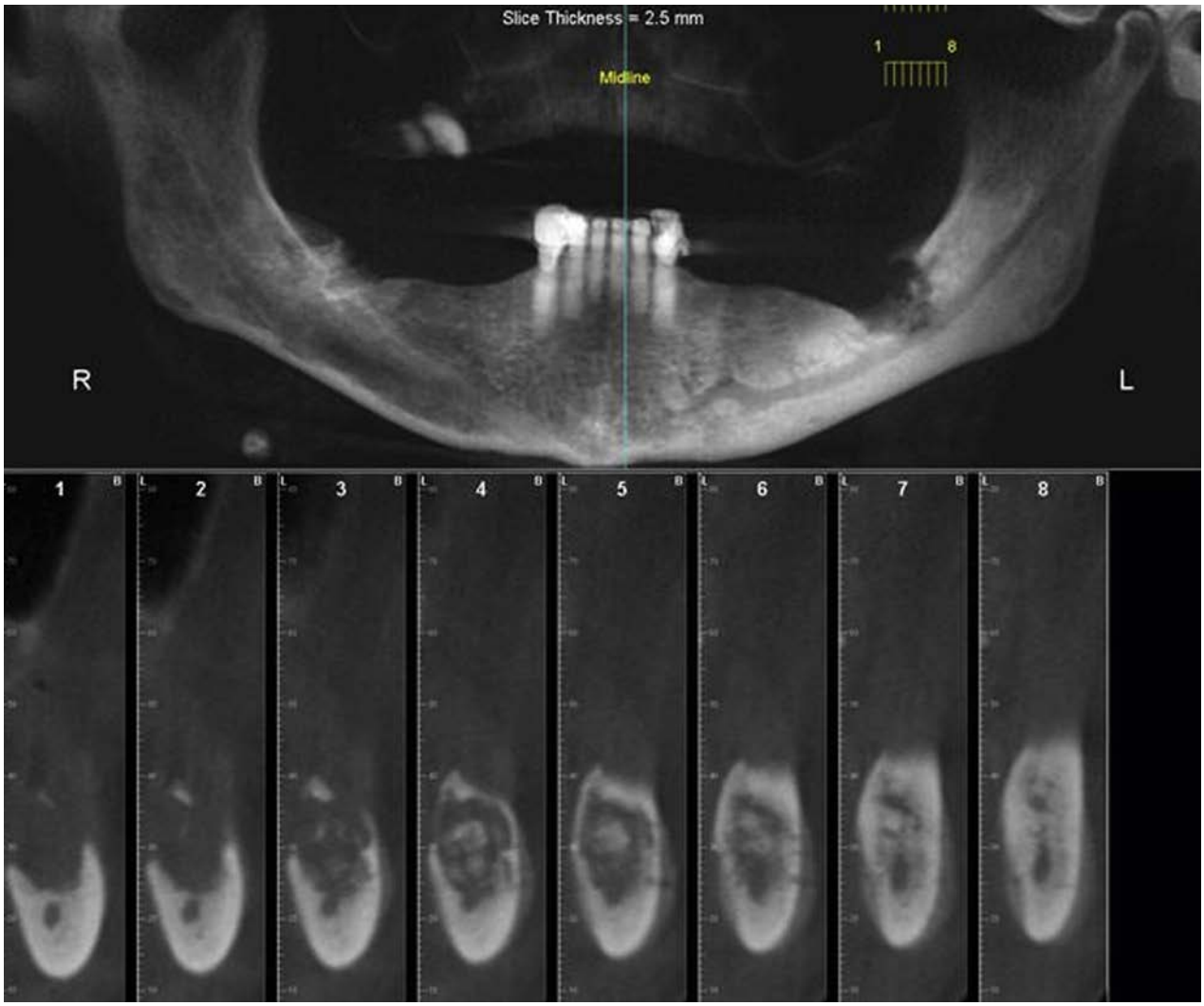
CT images have also proved to be more accurate delineating the extent of disease, which is very helpful for surgical treatment planning.[118,119] Technetium-99 bone scanning is a highly sensitive imaging modality for the identification of inflammation, which is commonly present in patients with established MRONJ. The utility of bone scintigraphy in patients at risk of MRONJ has received growing attention following reports of increased tracer uptake in regions of the jaws that subsequently developed necrosis.[120,121] Although nuclear imaging has limited value in patients with existing disease because of its poor specificity, its use as a predictive tool in patients with preclinical disease (stage 0) appears to have some level of theoretical benefit and therefore requires continued evaluation. Magnetic resonance imaging (MRI) is also a highly sensitive imaging modality for the presence of osseous edema and inflammation and is often used to identify the early acute phase of osteomyelitis. The imaging characteristics of MRI in patients with MRONJ have been described[122,123]; however, because of its low level of specificity. MRI has limited predictive value for detecting early disease. The use of positron emission tomography (PET) has also been reported in MRONJ patients with established disease. However, because of a low level of sensitivity, specificity, and accuracy, this imaging modality has limited diagnostic value.[124]

Staging

The presentation and symptomatology of MRONJ can vary in patients despite similar disease processes, drug dosing regimens and treatment duration. A clinical staging system has been developed in order to more accurately categorize patients with MRONJ, direct rational treatment guidelines and collect data to assess the prognosis in patients who have been exposed to antiresorptive (IV or oral) and antiangiogenic medications (Table 21-3).[6]

Patients who are considered *at risk* have no evidence of exposed or necrotic bone but have been exposed to either antiresorptive or antiangiogenic medications. The potency of the antiresorptive used, the duration of exposure, and dentoalveolar surgery are consistent factors in assessing ONJ risk. The risk associated with targeted antiangiogenic cancer therapies is also associated with jaw necrosis, but further studies are needed to assess risk stratification.

A stage 0 (non-exposed bone variant) category was created to identify "at-risk" patients with nonspecific clinical signs and symptoms such as pain, abscess formation, altered sensory functions or osteosclerosis on radiographic exam but no clinical evidence of necrosis or exposed bone. Several



• **Figure 21-4** Cone-beam computed tomography scan of the left mandible demonstrating osteosclerosis and sequestration of the left mandibular body at a non-healing extraction site. There is also reactive periosteal bone formation at the lateral cortical bone surface.

TABLE 21-3 MRONJ Staging

At Risk Category	No apparent exposed/necrotic bone in patients who have been treated with an antiresorptive or antiangiogenic medications
Stage 0	No clinical evidence of exposed bone. Nonspecific clinical findings, radiographic changes or symptoms
Stage 1	Exposed/necrotic bone or fistulas that probe to bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed/necrotic bone or fistulas that probe to bone with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage
Stage 3	Exposed/necrotic bone or fistulas that probe to bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, oral antral or oral nasal communication or osteolysis extending beyond the alveolar bone

case studies have reported that up to 50% of patients with stage 0 have progressed to stage 1, 2, or 3.[121,125]

Patients with *stage 1* disease have exposed bone or bone that can be probed but are asymptomatic. There is no evidence of significant adjacent or regional soft tissue inflammatory swelling or infection. *Stage 2* disease is characterized by exposed bone or bone that can be probed with associated pain, adjacent or regional soft tissue inflammatory swelling, or secondary infection. Patients with *stage 3* disease have exposed bone or bone that can be probed in association with pain, adjacent or regional soft tissue inflammatory swellings or secondary infections in addition to one or more of the following findings:

1. Exposed necrotic bone extending beyond the region of alveolar bone, that is, inferior border and ramus in the mandible, maxillary sinus, and zygoma in the maxilla
2. Pathologic fracture
3. Extraoral fistula
4. Oral antral/oral nasal communication
5. Osteolysis extending to the inferior border of the mandible or sinus floor

Treatment Guidelines

The goal of treatment for patients at risk of developing MRONJ or who have active disease is to preserve the quality of life by controlling pain, managing infection, and preventing the development of new areas of necrosis. Although eliminating all areas of necrosis is sometimes impossible, patients can remain asymptomatic with treatment intervention. The management strategy for these patients will vary according to their risk of developing MRONJ or their stage of disease. Consideration must also be given to patients who are about to initiate antiresorptive or antiangiogenic therapy and therefore assume a level of risk at a future point in time. The degree of risk will depend on the type of drug and the duration of exposure. Guidelines for prophylactic management or treatment have been structured to address three distinct clinical scenarios: (1) patients who are about to initiate antiresorptive or antiangiogenic therapy for cancer or osteoporosis, (2) asymptomatic patients receiving antiresorptive or antiangiogenic therapy for cancer or osteoporosis, and (3) patients with established MRONJ.

Patients Who Are About to Initiate Antiresorptive or Antiangiogenic Therapy

The treatment objective for cancer patients who are about to initiate antiresorptive or antiangiogenic therapy is to minimize the risk of developing MRONJ. Although a small percentage of patients receiving these medications develop osteonecrosis of the jaw spontaneously, the majority of affected patients experience this complication following some type of dentoalveolar surgery. Therefore, efforts to optimize dental health and avoid future extractions should be the main goal in patients who will receive these medications. In the clinical setting of cancer therapy, initiation of antiresorptive or antiangiogenic therapy should be delayed, if possible, until the dental health is optimized. This decision must be made in conjunction with the treating physician, dentist, and other specialists involved in the care of the patient. The time-tested dental care protocols instituted to prevent osteoradionecrosis in radiated cancer patients serve as an appropriate model for patients at high risk for MRONJ. Nonrestorable teeth and those with a poor prognosis should be extracted. Other elective dentoalveolar surgery should also be completed at this time. Based on our understanding of osteoradionecrosis, it appears advisable that antiresorptive or antiangiogenic therapy be delayed at least 2 to 3 weeks to ensure that adequate osseous and soft tissue healing has occurred. Dental prophylaxis and caries control are critical to maintaining functionally sound teeth and must be continued throughout therapy. Patients with full or partial dentures should be examined for areas of mucosal trauma, especially along the lingual flange region. The use of early dental screenings and preventative dental therapies has been demonstrated to lower the risk and frequency of MRONJ.[100,126-129]

The likelihood of MRONJ developing in the osteoporosis patient is significantly lower than in the cancer patient. Moreover, the duration of antiresorptive medication exposure required to develop ONJ is much greater in the noncancer setting. Therefore, patients who are about to begin antiresorptive therapy for osteoporosis are at no immediate risk. However, considering that most osteoporosis patients will require antiresorptive treatment that extends beyond 4 years, they should be informed at the initiation of therapy of the impending risk of MRONJ and the importance of maintaining optimal dental health.

Asymptomatic Patients Receiving Antiresorptive/Antiangiogenic Therapy for Osteoporosis or Cancer

Osteoporosis patients receiving oral bisphosphonates are at a much-reduced risk of developing MRONJ, given limited bioavailability and reduced potency of the oral medication. Nonetheless, numerous cases of MRONJ have been reported in patients exposed to oral bisphosphonates. Population survey studies estimate the risk of ONJ associated with oral bisphosphonate to range from 0.00038% to 0.1%.[85-88] Similar to patients exposed to intravenous bisphosphonates, the duration of oral bisphosphonates therapy appears to be an important factor, with most cases of MRONJ occurring after 4 years of exposure.[85] Therefore, no alteration or delay in the planned dentoalveolar surgery is typically necessary for patients who have received antiresorptive therapy for less than 4 years. Shortened exposure times and an elevated risk of MRONJ may exist for patients with comorbid risk factors such as corticosteroid or antiangiogenic therapy.[100,108]

For those osteoporosis patients who have taken bisphosphonates for more than 4 years (or less if other comorbid conditions exist), discontinuation of the medication for 2 months before oral surgery may reduce the risk. The bisphosphonate can be restarted once osseous healing has occurred. The rationale for this approach is based on a pharmacokinetic and bone physiology studies that examine the interaction of antiresorptive medications with the surrounding bone and the bone remodeling cells (osteoclast, osteoblasts, and osteocytes).[116,130] Although the risk of MRONJ associated with denosumab therapy in osteoporosis patients has been considered equivalent to that with bisphosphonates, prospective population studies similar to those conducted for bisphosphonates are needed to accurately assess the risk of anti-RANKL treatment in the setting of osteoporosis.

Although limited supportive data exist for such a strategy (level 5 evidence), several professional societies including the American Association of Oral and Maxillofacial Surgeons have advocated the use of a drug holiday for those patients at highest risk due to the theoretical benefit that may exist.[5,6,114]

Efforts to assess risk by measuring fluctuations in bone turnover markers are problematic and remain controversial.[105,131-135] The rationale for this approach is based the knowledge that markers for bone remodeling will increase

within months following withdrawal of oral bisphosphonate medications, thereby suggesting that osteoclastic function and bone remodeling are normalizing.[136,137] However, these markers are a reflection of total bone turnover throughout the entire skeleton and are not specific for bone remodeling within the unique environment of the maxilla or mandible. From a more practical perspective, using bone turnover markers to estimate the level of bone turnover suppression is only meaningful when compared to baseline, pretreatment levels, and these are rarely obtained in clinical practice.

Cancer patients receiving *intravenous* bisphosphonate therapy, subcutaneous denosumab therapy, or antiangiogenic drugs are at risk of developing MRONJ following dentoalveolar surgery. The estimates of cumulative incidence of MRONJ for cancer patients receiving IV bisphosphonate therapy was similar to zoledronate therapy and ranged from 0.7% to 1.9%.[1,25,27,91,92] The risk of MRONJ associated with antiangiogenic therapy (with or without concomitant antiresorptive therapy) ranged from 0.2% to 0.9%.[93]

Dentoalveolar trauma remains as a major contributing factor to the development of necrosis. In some studies, patients receiving intravenous bisphosphonates and undergoing dentoalveolar surgery were significantly more likely to develop MRONJ than patients who did not have dentoalveolar surgery.[90,107] Therefore, maintaining good oral hygiene and dental care is critical in preventing dental disease that may require dentoalveolar surgery. In general, procedures that involve direct osseous injury should be avoided. Nonsurgical endodontic therapy is the preferred treatment for teeth that are symptomatic. Patients with symptomatic nonrestorable teeth that would otherwise require extraction may be treated by removal of the crown and performing endodontic treatment of the remaining roots.[139-141] Similarly, placement of dental implants or any type of periodontal flap surgery that would expose or injure bone should be avoided in these patients.

The use of a drug holiday for cancer patients receiving IV bisphosphonates or antiangiogenic therapy remains controversial with limited data to support or refute such a practice. However, in an animal study, improved healing of induced MRONJ lesions was noted when denosumab was terminated. The same healing benefit was not identified in those animals receiving IV bisphosphonate therapy.[142]

It is critical that all patients who are receiving antiresorptive or antiangiogenic treatment be educated as to the importance of dental hygiene and regular dental evaluations. Patients should be specifically instructed to report any pain, swelling, or exposed bone that would either predict or characterize MRONJ. Multiple studies have demonstrated the efficacy of dental screenings and prophylactic dental treatment in lowering the risk of MRONJ. These include prospective studies that have reported significant reductions in the incidence of MRONJ when preventative dental measures are instituted before and during drug therapy.[100,126-129] It is equally important that general dentists and the dental specialist become knowledgeable about this complication so that dental treatment and procedures that are not associated with a risk of MRONJ can be delivered and oral health maintained.

Patients with Established MRONJ

The main goal of therapy for patients with established MRONJ is to maintain or preserve the quality of life while supporting the oncologic or osteoporotic treatment. This can be achieved by controlling pain and the secondary infection that is common for most of these patients. It is also important to prevent the extension of existing areas of necrosis and the development of new lesions. Patients with an established diagnosis of MRONJ are certainly at higher risk of developing osteonecrosis following any type of dentoalveolar surgery. Therefore the guidelines for dental treatment It is important that patients with established MRONJ avoid elective dentoalveolar surgical procedures (i.e., extractions and implant surgery), because these surgical sites are the most likely to result in new areas of exposed necrotic bone.

The treatment algorithms for MRONJ are based on a compilation of clinical data and treatment experiences from multiple cases series.[63,64,143,144] There are a limited number of prospective studies evaluating management strategies that include long-term outcomes.

Earlier strategies for treating these patients with exposed bone were similar to those for osteomyelitis or osteoradionecrosis and were associated with a variable degree of success. This might be due, in part, to the difficulty in obtaining a surgical margin that remains viable. More recent studies have reported successful treatment outcomes with operative therapies (resection, sequestrectomy)[145-151] and nonoperative therapies (systemic and local antimicrobial treatment).[103,146,152-154] In addition to cases of advanced disease (stage 3), surgical treatment should be considered for stage 2 disease when nonoperative therapies have failed to control infection or pain.

The efficacy of hyperbaric oxygen (HBO) therapy as a treatment adjunct has been studied in a prospective randomized controlled trial. The study was underpowered and failed to demonstrate that HBO improved gingival coverage of exposed bone to a statistically significant degree.[155] The use of other adjunct therapies such as platelet-rich plasma,[156] low-level irradiation therapy,[157] pentoxifylline/α-tocopherol.[158] and bone morphogenetic protein[159] has been described, but only in small case series. Therefore additional prospective controlled studies are warranted to establish the efficacy of these treatments.

The use of parathyroid hormone (PTH) appears to be the most promising nonoperative therapy for MRONJ. Recombinant human PTH or teriparatide is the only anabolic agent approved in the United States for use in humans for the treatment of osteoporosis. Daily PTH injections

stimulate enhanced bone formation through positive effects on osteoblast life span and direct stimulation of quiescent bone lining cells.[160] PTH also has potent anti-inflammatory effect within bone marrow and can enhance soft tissue healing and collagen formation.[161,162] In several case reports, the use of systemic low-dose PTH was successful in resolving an area of necrosis when other modalities of treatment had failed.[163,164] In each case, when combined with other standard treatment strategies, PTH therapy resulted in a relatively rapid resolution of the exposed bone. In a recent prospective, placebo-controlled study of 40 patients, low-dose systemic PTH in conjunction with vitamin D and oral calcium was associated with greater resolution of periodontal bone defects and accelerated intraoral osseous healing.[165] In a small animal study, PTH was shown to enhance bone healing in compromised bone wounds that were exposed to bisphosphonates.[166] Although systemic PTH is currently contraindicated in patients with osteolytic bone metastases, these promising findings may have real applicability for ONJ cases in the non-cancer setting. If these agents can be delivered locally to the regions of necrosis, the concern about enhanced medullary cellular proliferation in the cancer patient may be ameliorated.

For patients with established MRONJ, regardless of disease stage, exposed, necrotic bone that is a constant source of soft tissue irritation should be removed or recontoured without exposing adjacent bone so that soft tissue healing can be optimized. Loose segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of grossly mobile or symptomatic teeth within exposed, necrotic bone should be considered, because it is unlikely that the extraction will exacerbate the established necrotic process.

Stage-specific treatment strategies have been proposed for the management of necrotic bone (Table 21-4).[6] By definition, patients with stage 1 MRONJ are asymptomatic and have no clinical evidence of infection. These patients may benefit from the use of oral antimicrobial rinses such as chlorhexidine 0.12%. Surgical treatment is not required unless areas of exposed bone are a physical irritant to the surrounding soft tissue. In that instance surface recontouring of the exposed bone is helpful. Surveillance of these regions of jaw necrosis is important to detect the early signs and symptoms of disease progression. These patients should be examined every 3 to 4 months.

Patients with stage 2 MRONJ will have exposed necrotic bone that is painful and associated with a local infection. The disruption in the bone remodeling process has now resulted in regions of necrotic bone, possibly with biofilm formation, that are now secondarily infected. These patients benefit from the use of oral antimicrobial rinses in combination with antibiotic therapy. If reliable culture data are obtainable, they can be used to direct the appropriate antibiotic regimen. In general, been used with success in patients who are allergic to penicillin. In refractory cases, patients may require surgical therapy in combination with oral or intravenous antibiotic therapy. In special circumstances where patients with multiple myeloma are being considered for stem cell transplantation, the maintenance of an "infection-free" oral environment is important. However, despite aggressive therapy, some patients will have persistent infection and exposed bone. The risks and benefits of proceeding with the transplantation in this setting must be considered on a case-by-case basis.

Patients with stage 3 disease are the most challenging. These patients typically have pain and infection that affects their quality of life (Figure 21-5). The large burden of necrotic bone that results in fistulization, pathologic

TABLE 21-4 Stage-specific MRONJ Treatment Recommendations

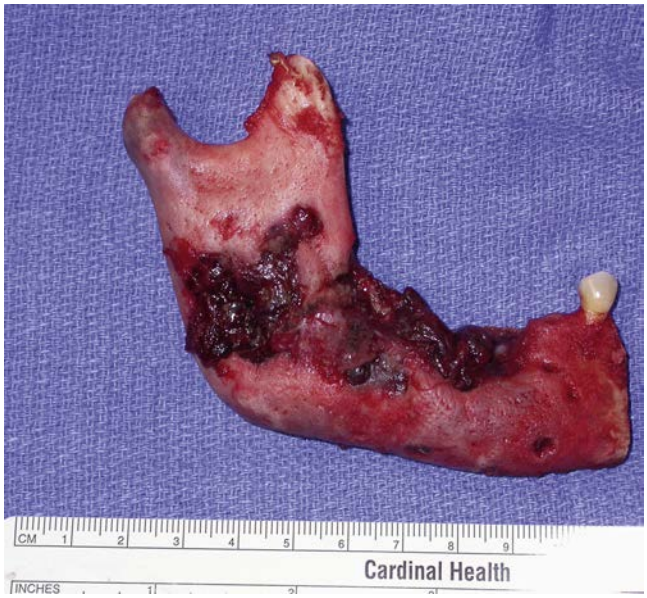
At Risk Category	No surgical or medical treatment indicated Patient education and routine dental care
Stage 0	Systemic management including pain medication and systemic antibiotics
Stage 1	Antibacterial mouth rinse Clinical follow-up on a quarterly basis Patient education and review of indications for continued antiresorptive/antiangiogenic therapy
Stage 2	Oral antibacterial mouth rinse Symptomatic treatment with oral antibiotics and pain medication debridements to remove mobile sequestrum or to relieve soft tissue irritation
Stage 3	Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement/resection for longer term palliation of infection and pain



• **Figure 21-5** Extensive extraoral fistula in a patient with stage 3 medication-related osteonecrosis of the jaw.

fracture, or extensive sinusitis is typically refractory to antibiotic therapy (Figure 21-6). At this stage, aggressive surgical management is indicated so that palliation or resolution of acute infection and pain can be achieved. Persistent regions of exposed bone may remain or develop at the periphery of the resection/debridement because of the generalized effects of antiresorptives and the compromised bone healing throughout the jaw. For patients with mandibular necrosis that is associated with a pathologic fracture or osteolysis extending to the inferior border, segmental resection is indicated. Immediate reconstruction with nonvascularized or vascularized bone has been reported,[167-169] but the potential for necrotic bone to develop or persist at the margins of the recipient site remains a persistent concern with this approach. Stabilization of the residual mandibular segments with a reconstruction plate is a viable alternative, but patients should be aware of the potential for hardware failure at the margin of the resection (Figure 21-7). Soft tissue coverage of the hardware and surrounding bone should be accomplished with local or distant flaps.

Patients with stage 3 maxillary disease, characterized by large areas of exposed bone with facial swelling and/or sinusitis, will often require a maxillary resection. In cases where chronic sinusitis exists, resection of the infected maxillary alveolar bone with creation of an oral antral communication will serve to reduce or eliminate the infected bone and provide immediate and long-term drainage of the sinus. Reconstruction of maxillary defects can be immediate or delayed with fabrication of a partial denture or maxillary obturator. Surgical management of maxillary disease seems to follow a more predictably successful course postoperatively than patients who have had marginal or segmental resections of the mandible. This may be due in part to the vascularity of maxillary bones.

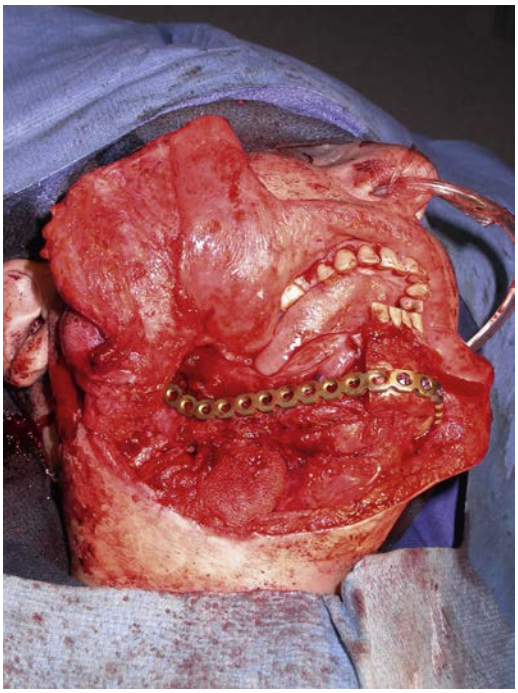


• **Figure 21-6** Necrotic right mandible from a patient with stage 3 medication-related osteonecrosis of the jaw.

Future Research

Medication-related osteonecrosis of the jaw is a well-recognized complication of antiresorptive and antiangiogenic therapy that can have serious dental and medical consequences for patients with cancer and osteoporosis. However, the efficacy of these medications in treating and preventing the significant skeletal complications associated with osteoporosis and bone metastases has had a major positive impact on quality of life for most patients. Basic science research, including animal and human studies that were funded through various government and private institutions, have provided significant advances in our understanding of this disease process since it was first described in 2004. The development of a valid animal model has provided additional insight into the pathophysiology of MRONJ and has established a framework for future translational research. Future studies can now focus on confirming the efficacy of existing guidelines related to prevention, operative and nonoperative therapies, and risk assessment and reduction strategies. The efficacy of novel targeted therapies for the treatment of various cancers has been established, but jaw necrosis has also emerged as a complication within this cohort of patients. Clinical and animal studies are now warranted to further clarify how these agents, which have no effect on bone remodeling, can result in jaw necrosis.

As our understanding of the etiopathogenesis of MRONJ continues to evolve, health care providers will be able to make more accurate judgments about risk, prognosis, treatment selection, and outcome.



• **Figure 21-7** Intraoperative view of a hemi-mandibulectomy procedure and immediate reconstruction with a plate in a patient with stage 3 medication-related osteonecrosis of the jaw.

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22

Langerhans Cell Histiocytosis

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Treferred to as histiocytosis X, eosinophilic granuloma, Letterer-Siwe disease, Hand-Schuller-Christian disease, Hashimoto-Pritzker syndrome, self-healing histiocytosis, pure cutaneous histiocytosis, Langerhans cell granulomatosis, type II histiocytosis, and the generic term nonlipid reticuloendotheliosis. The common feature of these diseases is the proliferation of clonal CD1a-positive immature dendritic cells (LCH cells) in the skin, bone, lymph nodes, and other organs. Langerhans cell histiocytosis is a rare disease that affects 5 children per million population and about 1 to 2 adults per million population.[1] It is predominantly a disease of children: More than 50% of affected individuals are younger than 15 years of age, with an average age of presentation of 25 years.[2] The peak incidence is between 1 and 4 years. The prevalence of LCH seems to be higher among whites than other races.[2]

The first case of LCH was described by Dr. Thomas Smith in 1865 in a 4-year-old patient with punched-out lesions of the calvarium.[1,3,4] The skull defects were originally thought to be congenital based on drawings, as x-ray was not developed until 1895. The child died 1 month later of respiratory complications related to whooping cough. Hand-Schuller-Christian disease was independently described by Hand in 1893, Schuller in 1915, and Christian in 1920 in patients with exophthalmos, polyuria, and skull defects.[1-3] The disease was initially attributed to tuberculosis infection. Letterer-Siwe disease was described by Letterer in 1924 and Siwe in 1933 as an acute disorder of the reticuloendothelial system in two young children.[1-3] This disease was characterized by marked hepatosplenomegaly, lymphadenopathy, bone tumors, anemia, and hyperplasia of nonlipidized histiocytes. Eosinophilic granuloma of bone was first described by Mignon in 1930 as a granulomatous bone lesion in an adolescent male.[1,3,4]

In 1940 Lichtenstein and Jaffe described a case of a solitary lesion of bone.[5] They decided that the lesion represented neither a myeloma nor an osteomyelitis, as had been suggested by others, but rather some type of granuloma. This notwithstanding, the lesion did not fit into any of the recognized granuloma categories. Moreover, they proposed that the granuloma existed in response to a virus. The name *eosinophilic granuloma of bone* was applied because of the preponderance of eosinophils, although the authors fully recognized that the basic cells were histiocytes. The authors pointed out those specific clinical features that might lead one to suspect the presence of eosinophilic granuloma of bone even before surgical intervention is attempted. Among these were the occurrence of the lesion in a child or a very young adult; a short history of painful localized swelling of only several weeks' duration; radiographic evidence of a rarefied and destructive bone lesion, especially in the calvarium, but also in the ribs or in a long bone, and with perforation of the cortex; and perhaps a palpable soft tissue mass overlying the affected bone. Jaffe and Lichtenstein were quick to point out that these features may lead the clinician to suspect malignant disease, specifically a Ewing sarcoma.[6]

Jaffe and Lichtenstein also reported the realization that multiple bone lesions may be encountered, and of the same kind as the solitary lesions.[6] They therefore recommended that even in cases in which there was supposedly only a solitary lesion in bone, additional lesions that may be present should be searched for radiographically. This radiographic investigation is now known as a skeletal survey. Aside from the known focus of LCH, a negative skeletal survey in combination with no suspicion for visceral involvement means that a patient has single-system unifocal LCH, as will be discussed.

The clinical varieties of LCH range from a curable solitary destructive lesion of bone to a lethal leukemia-like disorder that primarily affects infants.[7] The clinically evident pathology in LCH is broadly divided into two categories: direct involvement with the disease (i.e., bone or organ lesions) and secondary consequences resulting from permanent damage by the primary disease (i.e., exophthalmos,[8]

like collections of histiocytes. Earlier reports suggested the possibility of myeloma with prevalence of eosinophilic cells or osteomyelitis with an eosinophilic reaction.[5] The authors

TABLE 22-1 Contemporary Anatomic Classification of Langerhans Cell Histiocytosis (LCH)

Classification System	Organ/System Involvement
Single-system LCH (SS-LCH)	Bone: unifocal or multifocal Skin Lymph node Lungs Hypothalamic-pituitary/CNS Other (thymus, thyroid)
Multisystem LCH (MS-LCH)	2 or more organs with or without risk organs Risk organs = bone marrow, spleen, liver, lung



• **Figure 22-1** This panoramic radiograph demonstrates a unifocal site of Langerhans cell histiocytosis of the left mandible.

SS disease, RO-negative MS disease, and RO-positive MS disease are almost equivalent to eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease, respectively.[9] The cause of LCH is unknown, with many researchers debating whether LCH represents a reactive immune condition or a malignancy. The identification of activating *BRAF* gene mutations strongly supports the hypothesis that LCH is a neoplastic process.[10,11]

Langerhans cell histiocytosis affects the head and neck region quite commonly, particularly the skull and jaws.[1] It has been estimated that the head and neck region is involved in approximately 90% of cases.[12] In addition, osteolytic bone lesions are a common manifestation of single-system LCH in adults.[2] With jaw involvement, 90% of patients are younger than 40 years of age, with a mean of 19 years.[1] Unifocal involvement of the jaws represents about 50% of maxillofacial LCH, with multifocal, single-system disease and multifocal multisystem disease equally accounting for the other 50%. The mandible is involved approximately three times more commonly than the maxilla. The posterior region of the jaws is more commonly involved than the anterior region. Early disease in the oral and maxillofacial region is manifested by lytic lesions of the jaws, often seen as localized, punched-out radiolucencies with no calcification and no sign of sclerosis or reaction at the borders[13] (Figure 22-1). The most common symptom is pain, although a mass may also be a presenting symptom.[14] With advanced disease, there may be severe alveolar bone resorption, producing the appearance of "teeth floating in air" (Figure 22-2). Interestingly, isolated mucosal lesions occurring in the absence of osseous lesions have been reported.[15] As discussed in detail in this chapter, the extent of the disease process often dictates the specific form of surgical therapy for a single-system unifocal LCH of the jaws in terms of whether an enucleation and curettage or a resection of the affected jaw is indicated. Prompt diagnosis of disease is essential to providing curative surgical therapy with little or no deformity. Thus the surgeon should consider LCH on a differential diagnosis of lucent lesions of the jaws, especially in patients younger than 40 years of age.

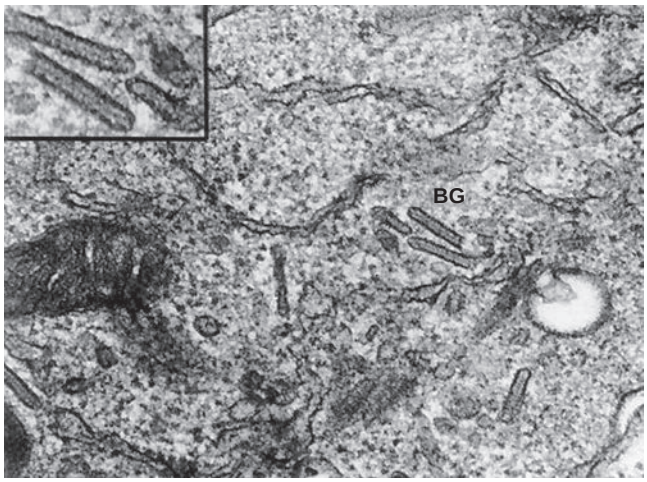
The Langerhans Cell

mononuclear cell of bone marrow origin that belongs to the dendritic cell family. It can be generated from peripheral blood monocytes by the action of granulocyte-macrophage colony-stimulating factor and tumor necrosis factor-a (TFN-α). The normal Langerhans cell is recognized to be an important antigen-presenting cell in the skin that represents the most peripheral extension of the immune system. Langerhans cells are normally found in mucosa, lymph

endocytosed antigens are presented to naïve helper T cells. Langerhans cells have not proven to be clonal.[1] In 1868, Paul Langerhans, a 21-year-old medical student at the University of Berlin under the mentorship of Professor Virchow, described the cell that bears his name.[16] His initial impression was that the cell was a nerve receptor cell because of its stellate, dendritic appearance. Only in later years did Langerhans realize that his original supposition was incorrect. In 1961 Birbeck and colleagues[17] described the organelle that has become the unique label of the cell. Interestingly, there are stages of the cell's development when the Birbeck granule is not identified. Typically, two characteristics are observed in Langerhans cells. The first is the presence of Birbeck granules. These intracellular structures are rod-shaped with a



• **Figure 22-2** An advanced case of Langerhans cell histiocytosis of the bilateral mandible manifested by "teeth floating in air." This patient proved to have multifocal, single-system disease. The second deposit of eosinophilic granuloma was found in the fibula.



• **Figure 22-3** An electron micrograph demonstrating a characteristic Birbeck granule *(BG)* found in Langerhans cell histiocytosis. Original magnification 50,000×. Inset = original magnification 100,000×.

develop as invaginations of the cell membrane. These findings resulted in a hypothesis that the granules represented the cellular response to an antigen being presented on this cell, and therefore reflect the normal function of Langerhans cells. One theory with respect to the pathogenesis of LCH, therefore, is that immunologic stimulation of this normal antigen-presenting cell may continue in an uncontrolled manner, and that this results in proliferation and accumulation of these cells.[8] The second characteristic of Langerhans cells, which is diagnostic of the pathology, is that they stain strongly positive for the presence of CD1a on their surfaces. This property is highly characteristic of Langerhans cells, but not of other cells of histiocytic origin.

• BOX 22-1 Classification of Histiocytosis X

Histiocytosis X, localized to bone (eosinophilic granuloma, solitary or multiple
Histiocytosis X, disseminated, acute, or subacute (Letterer-Siwe syndrome)
- With destructive skeletal lesions (eosinophilic granuloma)
- With transition to chronic phase (Schuller-Christian disease)

Histiocytosis X, disseminated, chronic (Schuller-Christian syndrome)
- With destructive skeletal lesions (eosinophilic granuloma)
- With early extraskeletal lesions (indicate sites) resembling eosinophilic granuloma
- With acute or subacute exacerbations (Letterer-Siwe disease)
- With involvement predominantly of bone, lungs, pituitary, and/or brain, skin, mucous membranes (oral, anal, genital), liver or lymph nodes, etc. (in varying combinations, as the case may be)

After Lichtenstein L: Histiocytosis X. Integration of eosinophilic granuloma of bone, "Letterer-Siwe disease" and "Schuller-Christian disease" as related manifestations of a single nosologic entity, *Arch Pathol* 55:84-102, 1953.

Classification of Langerhans Cell Histiocytosis

In 1953 Lichtenstein[18] lamented that his 1944 paper did not offer acceptable nomenclature for his discovery published in 1940. He believed that some designation built around histiocytosis was appropriate, because this term had the reference to an inflammatory proliferative reaction and it was the one feature common to all of the various pathologic expressions of the disease. Lichtenstein considered and discarded the designation *idiopathic histiocytosis* because it lacked specificity, in that it might apply as well to lesions of sarcoidosis, for example. As such, he presented "histiocytosis X" for the disease under consideration[18] and suggested the classification seen in Box 22-1 in

1953. The designation *histiocytosis X* was proposed for reasons of brevity as well as to imply the need to search for the specific etiologic agent. In 1953 Lichtenstein reorganized his thoughts on histiocytosis X and proposed a simpler classification in his landmark paper, as seen in Box 22-2. This classification is widely accepted in the 21st century,

Langerhans cell histiocytosis

and patient management in cases of Langerhans cell histiocytosis.[19,20] Their initial publication reinforced the correct nomenclature for this disease process as Langerhans cell histiocytosis rather than histiocytosis X as had previously been designated. The most current method of categorization of LCH is based on risk stratification of affected individuals into recommended treatment protocols formulated by the Histiocyte Society[21] (Table 22-2). Unifocal single-system disease most commonly affects young children and is present when several lesions are identified in a single organ system. Bone is most commonly involved, and this represents multifocal eosinophilic granuloma. The prognosis is intermediate. Multifocal multisystem disease

ears of age represent the

• BOX 22-2 Modern Classification of Langerhans Cell Histiocytosis

Monostotic or polyostotic eosinophilic granuloma of bone: Solitary or multiple bone lesions without visceral involvement.

Chronic disseminated histiocytosis: A disease involving bone, skin, and viscera. This is referred to as Hand-Schuller-Christian disease and may involve a triad consisting of punched-out calvarial lesions, exophthalmos, and diabetes insipidus.

Acute disseminated histiocytosis: A disease with prominent cutaneous, visceral, and bone marrow involvement occurring mainly in infants. This is referred to as Letterer-Siwe disease.

After Lichtenstein L: Histiocytosis X. Integration of eosinophilic granuloma of bone, "Letterer-Siwe disease" and "Schuller-Christian disease" as related manifestations of a single nosologic entity, *Arch Pathol* 55:84-102, 1953.

Clonality of Langerhans Cell Histiocytosis

For decades, it had been thought that LCH was a reactive proliferation rather than a neoplastic process, at least in part due to the dearth or absence of mitotic figures.[22] Moreover, the issue of clonality of the lesion was questioned. A distinguishing feature of a neoplasm is its origin from a single clone of cells, whereas a reactive process is generally considered polyclonal. As such, work has been revealed that has identified the clonality of LCH. Willman and colleagues[7] studied 10 female patients with various forms of LCH whose ages ranged from 3 months to 25 years. Molecular analysis revealed evidence of clonal cells in 9 of the 10 patients in whom results could be interpreted with confidence. It is notable that all three forms of LCH exhibited a clonal pattern. The authors concluded their study by stating that LCH is probably a clonal neoplastic disorder with highly variable biologic behavior. This notwithstanding, other authors contend that LCH represents a reactive process, similar to sarcoidosis.[16] Closer examination of the authors' comments, however, reveals that they indicate that a benign neoplastic process cannot be completely ruled out in the light of current knowledge. Further, they state that there is no evidence that LCH is a malignant neoplastic process based on their experience of 238 cases over a 50-year period.[16] Although there are rare malignancies featuring cells with Langerhans cell phenotype, malignant LCH is not recognized.[23] Malignant disorders of histiocytes are quite rare, with fewer than seven cases per year reported in the literature.[21] The malignant histiocytic disorders include the monocyte-related leukemias and

TABLE 22-2 Current Classification of Langerhans Cell Histiocytosis Formulated by the Histiocyte Society

Classification	Anatomic Distribution	Features
Unifocal disease (eosinophilic granuloma)	Single-system disease with single site of involvement	• Most commonly bone • Older children and adults • Good prognosis
Multifocal single-system disease (Hand-Schuller-Christian disease)	Multiple sites of involvement in single organ system	• Most commonly bone • Young children • Intermediate prognosis
Multifocal multisystem disease (Letterer-Siwe disease)	Multiple involved sites in more than one organ system	• Most commonly bone, skin, liver, spleen, and lymph nodes • Children younger than 2 years of age and infants • Poor prognosis

After Hicks J, Flaitz CM: Langerhans cell histiocytosis: current insights in a molecular age with emphasis on clinical oral and maxillofacial pathology practice, *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 100:542-566, 2005; Favara BE, Feller AC: Contemporary classification of histiocytic disorders, *Med Pediatr Oncol* 29:157-166, 1997.

other malignancies; the dendritic cell–related histiocytic sarcomas; and the macrophage-related histiocytic sarcomas.[21] In the final analysis, LCH is an obscure disease that ranges from a highly curable lesion resembling an inflammatory process to a highly lethal multisystem process. Whether LCH represents a reactive or neoplastic process still remains unclear, although treatment is regimented and highly effective in many cases.

Histopathology of Langerhans Cell Histiocytosis

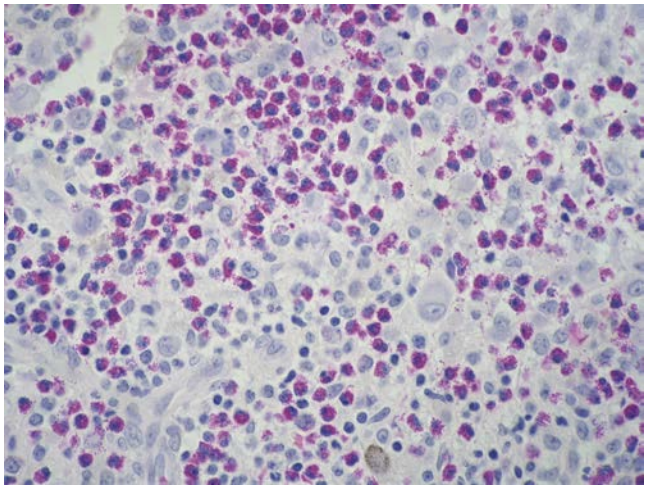
For many years the definitive diagnosis of LCH was impaired by the lack of an agreed-upon set of diagnostic criteria.[8] The diagnostic criteria for LCH, which are histopathologic, are standardized and include the presence of CD1a cell surface staining or the finding of Birbeck granules in lesional cells for definitive diagnosis. A presumptive diagnosis made with less rigid criteria is no longer appropriate.

The basic lesion of LCH is formed by collections of pathologic Langerhans cells (PLCs), indeterminate cells, interdigitating cells, and macrophages accompanied by T lymphocytes with variable numbers of multinucleated giant histiocytes and eosinophils[24] (Figure 22-4). The hallmark of the lesion is the PLC, which is cytologically benign and resembles the normal Langerhans cell described previously, but is not morphologically dendritic.[24] Despite the activated state of Langerhans cell histiocytes, their ability to carry out antigen presentation is absent or rarely observed.[1] These cells do not have the ability to migrate from the lesional tissue, and along with inflammatory cells, they recruit other cells to the lesion. Additional diagnostic characteristics of the pathologic bone, skin, and lymph nodes, among others. Osseous lesions are present in most cases of LCH, either as a solitary focus or as part of multisystem disease. There is a predilection for hematopoietically active medullary sites, the skull being most frequently involved. Other common locations are the femur, pelvis, tibia, scapula, jaw, humerus, vertebrae, and ribs. The small bones of the hands and feet are uncommonly involved. Histologically, osteoclast-like multinucleated giant histiocytes with bone destruction, necrosis, hemorrhage, and eosinophilic abscesses may be present. Skin involvement is present in more than 80% of patients with disseminated disease and in 30% of patients with less extensive multisystem disease.[24] Isolated cutaneous involvement may occur.[24] Skin of the head and neck region, trunk, groin, and extremities are common sites of involvement, with a diversity of clinical appearances. Seborrhea-like papular scaling eruptions, petechial and purpuric lesions, and papular xanthoma-like lesions may be noted. Histologically, diffuse bandlike or multifocal nodular aggregates of pathologic Langerhans cells in the papillary dermis are accompanied by violations of the epidermal-dermal interface and occasionally epidermal ulcerations.

Lymphadenopathy may be the sole manifestation of LCH. It may occur in occur in multisystem disease, or it may be a focal process associated with adjacent bone or skin disease. Cervical lymph nodes are most often involved, followed by inguinal, axillary, mediastinal, and retroperitoneal sites. Histologically, lymph node involvement is characterized by the presence of PLCs and related dendritic cells, macrophages, multinucleated giant histiocytes, T lymphocytes, and eosinophils.

Diagnosis, Treatment, and Prognosis of Langerhans Cell Histiocytosis of the Oral and Maxillofacial Region

A patient with LCH of the oral and maxillofacial region typically presents with pain and swelling (Figure 22-5).



• **Figure 22-4** Characteristic histopathology of Langerhans cell histiocytosis. A preponderance of eosinophils and histiocytes is noted. Hematoxylin and eosin, original magnification 100×.

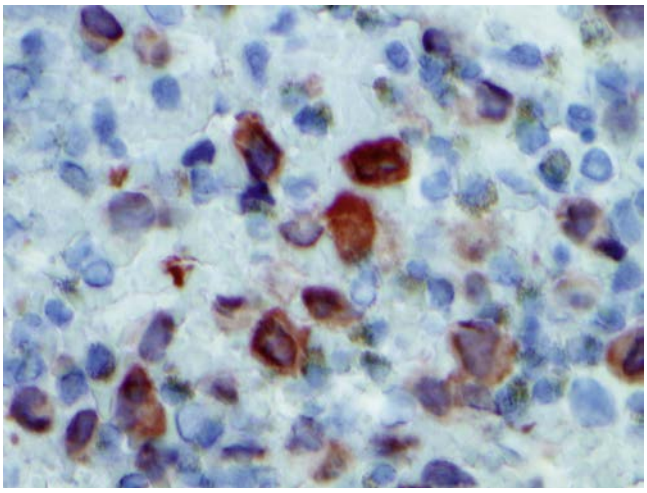


• **Figure 22-5** A 13-year-old boy with a painless swelling of 16 days duration at the time of presentation.



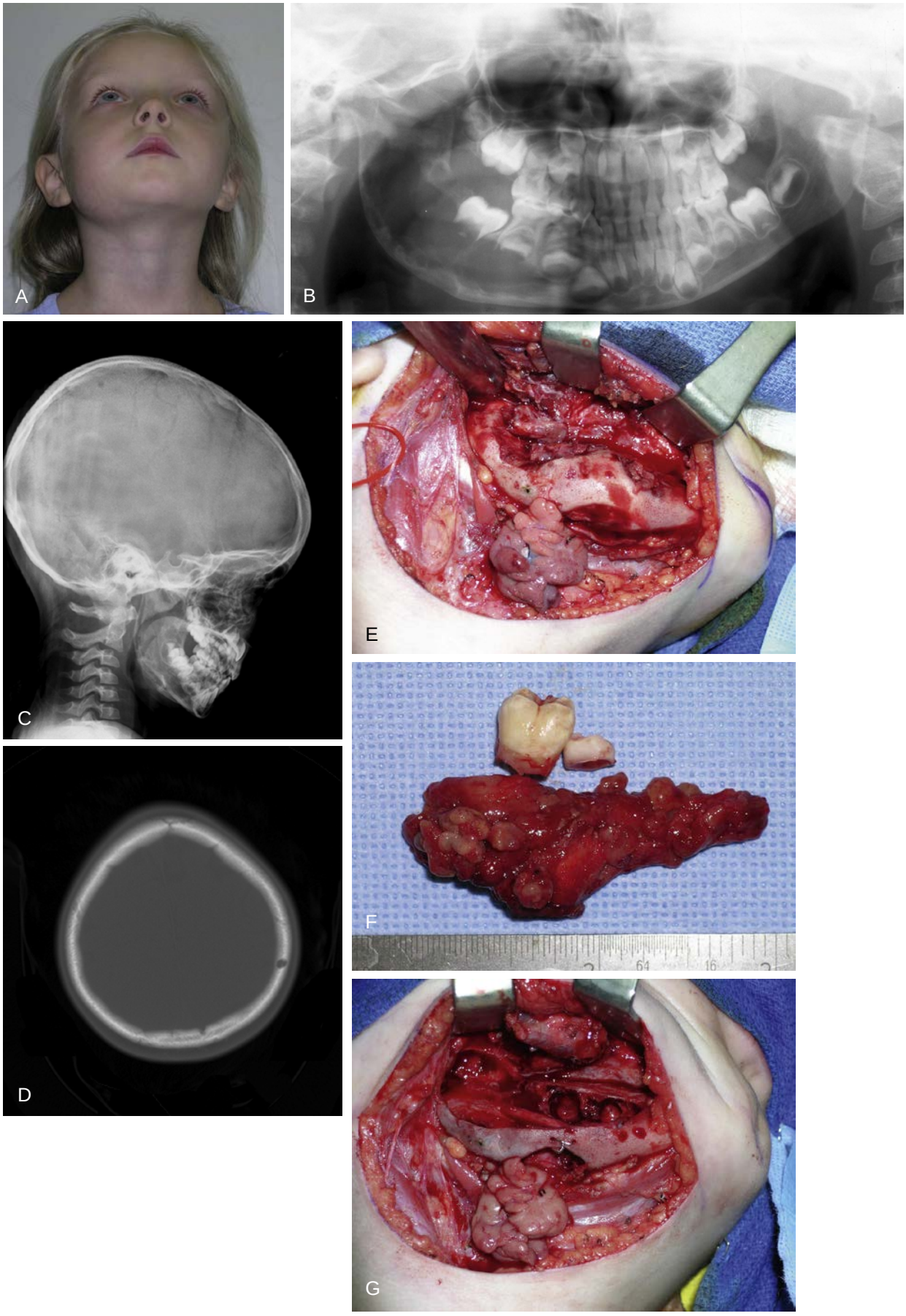
• **Figure 22-6** The panoramic radiograph of the patient in Figure 22-5 shows an ill-defined and destructive radiolucency of the right mandible ramus.

In the case of advanced disease, "teeth floating in air" may be noted radiographically. A panoramic radiograph will most commonly depict a destructive, ill-defined osteolytic process of the mandible (Figure 22-6). A differential diagnosis of osteomyelitis and benign or malignant tumor might be established. Because 75% of patients are younger than 20 years of age,[1,13] however, eosinophilic granuloma should be placed formidably on the differential diagnosis. This notwithstanding, an incisional biopsy is an essential step in the workup because of the varied number and classification of possible diagnoses. Histopathologic examination of representative tissue in the osteolytic lesion is paramount for diagnosis, and the specimen must be examined by a pathologist familiar with the microscopic features of LCH. Examination with hematoxylin and eosin stains, supplemented with confirmatory S-100 and CD1a immunohistochemistry, forms



• **Figure 22-7** CD1a immunohistochemistry of a case of Langerhans cell histiocytosis showing strong positivity. Such a result is confirmatory for this diagnosis.

sis. Once a diagnosis of LCH has been established, it is important to classify and stage the disease process. To this end, a skeletal survey must be undertaken to search for other skeletal lesions (Figure 22-8). This will permit distinguishing unifocal versus multifocal disease. In years past, a radionuclide bone survey was commonly obtained to identify skeletal involvement. Parker and colleagues[26] compared the results of radionuclide studies and a plain skeletal series in 18 patients with untreated Langerhans cell histiocytosis. They concluded that radiographic skeletal survey is more sensitive than radionuclide studies in detecting the skeletal lesions of this disease process. It might also be useful to reexamine the patient's history and physical examination to search for signs suggestive of disseminated involvement. Reevaluation of the patient for a subtle exophthalmos or historical symptoms of polyuria might lead to a diagnosis of Hand-Schuller-Christian disease that would be treated very differently from a solitary eosinophilic granuloma of the jaws. Additional laboratory studies should include complete blood count (CBC), platelet count, liver function tests (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase, bilirubin, total protein and albumin), coagulation studies (prothrombin time [PT], partial thromboplastin time [PTT], and fibrinogen), chest radiographs if not included in the skeletal survey,

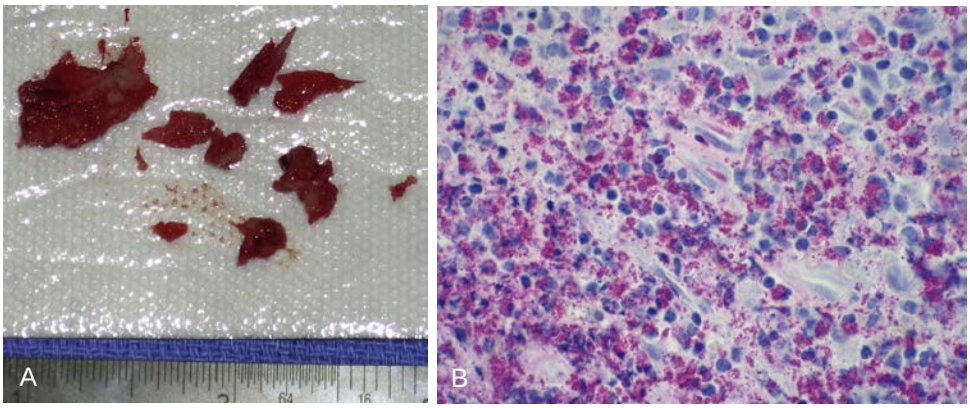


• **Figure 22-8** **A,** A 4-year-old girl with a 6-week history of right facial swelling. **B,** Panoramic radiograph demonstrates a destructive radiolucency of the right mandibular body and ramus. Incisional biopsy revealed Langerhans cell histiocytosis. **C,** A skeletal survey was obtained that demonstrated a second lesion in the left parietal bone. **D,** A head computed tomographic scan was also obtained that demonstrated enucleation and curettage of her mandibular lesion **(E-G),** followed by postoperative chemotherapy.

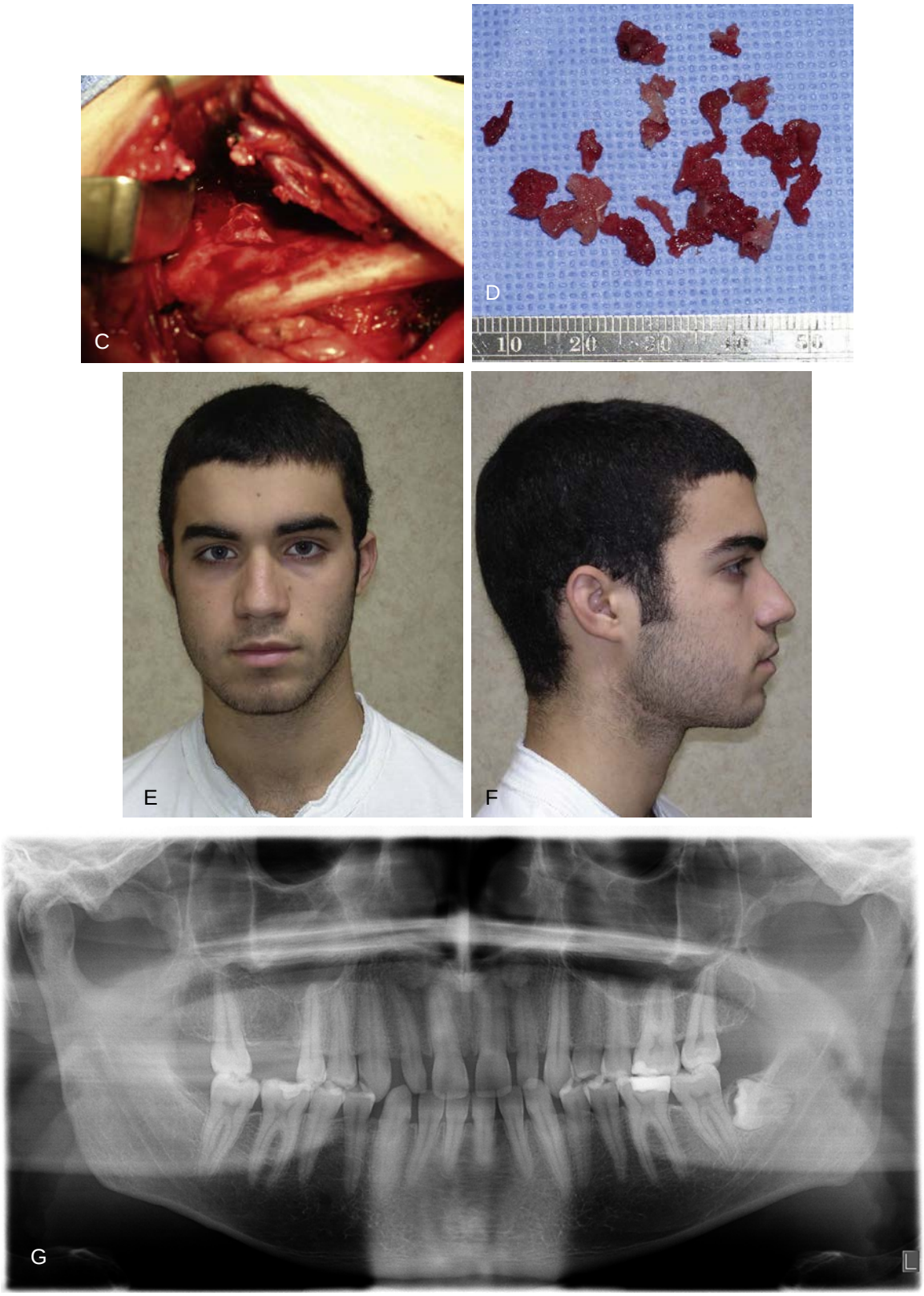
and urine osmolality measurement after overnight water deprivation.[20]

The diagnostic value of ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG PET) and magnetic resonance imaging (MRI) in LCH has been investigated for primary staging and disease follow-up.[27] One study compared 21 ^{18}FDG PET scans with 21 MRI scans in 15 patients with biopsy-proven histiocytosis. Six patients had unifocal disease, 4 had single-system multifocal disease, and 5 had multisystem disease. Primary criteria for the lesion-based analysis were contrast enhancement for MRI and standardized uptake value (SUV) greater than the mean SUV of the right lobe of the liver for PET. The sensitivity and specificity of PET were 67% and 76% and of MRI were 81% and 47%, respectively. This retrospective analysis suggested a pivotal role of ^{18}FDG PET in lesion follow-up after chemotherapy. MRI showed a higher sensitivity for primary staging of LCH, evaluation of brain involvement, and biopsy planning. The authors concluded that combined MRI/PET analysis improved sensitivity by decreasing the false-negative rate during primary staging, indicating a future role of simultaneous whole-body PET/MRI for primary investigation of LCH.

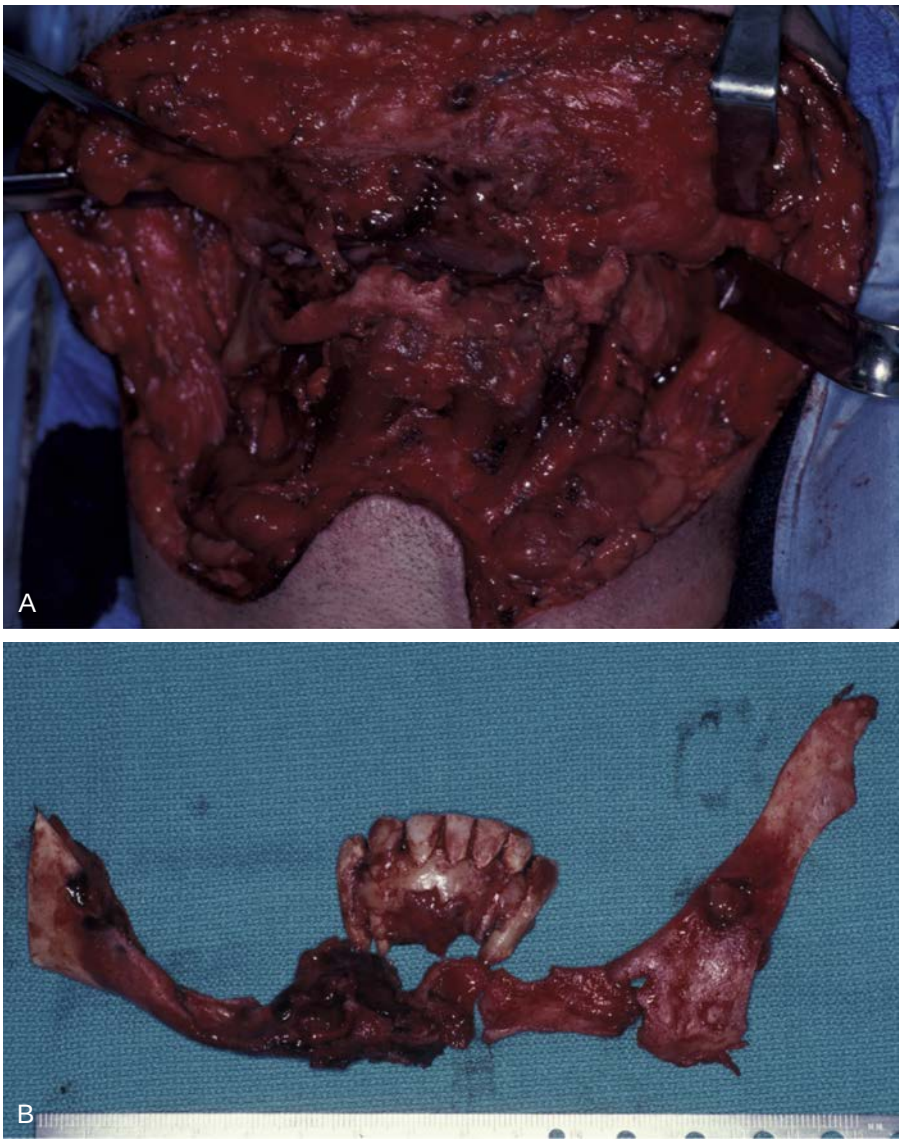
From an oral and maxillofacial surgery standpoint, the initial workup of a patient with LCH is performed with the possibility of *ruling in* a unifocal focus of eosinophilic granuloma. Surgery for a single focus of eosinophilic granuloma of the head and neck region is a preferred method of treatment and is highly curative. Curettage is most commonly employed for accessible and relatively small lesions where sufficient bone remains to permit bony regeneration (Figure 22-9). When disease is extensive, a segmental resection may be required and preferable (Figure 22-10). The use of radiation therapy may play a role in the management of lesions that recur after surgery, and in the management of lesions in surgically inaccessible areas. It has been recommended that the dose of radiation be under 1000 cGy, and preferably in the range of 550 to 600 cGy.[28] With unifocal bone disease, local excision with or without radiation therapy has led to more than 95% disease-free survival. Relapse has been found to occur in about 10% of cases.[1] Howarth and colleagues presented 314 patients with LCH, including 342 osseous lesions in 188 patients.[29] Of these osseous deposits, 121 (35.4%) were in the skull and jaws. Of the 211 relapses observed in these 314 patients, the median time from the end of initial treatment to relapse was 12 months.[29] Lieberman and co-workers reported that patients with eosinophilic granuloma do not die of their disease.[16] Multifocal bone disease may have similar surgical treatment with or without the addition of chemotherapy. Relapses are more common in multifocal disease than in unifocal disease and are noted in approximately 76% of cases.[1] Approximately 3% of patients die of their disease. Treatment of multifocal multisystem disease employs the combination of surgery, chemotherapy, and radiation therapy. A large percentage of patients (95%) develop relapses.[1] One in six patients with multifocal multisystem disease will die of their disease. Azreen and colleagues[12] have pointed out that the prognosis of this disease is closely related to the age at disease onset; involvement of high-risk organs including the bone marrow, lungs, liver, and spleen; and response to initial therapy that should be assessed at 6 to 12 weeks following chemotherapy. Children younger than 2 years have a higher mortality rate than older children and adults. The presence of organ dysfunction and multi-organ involvement are poor prognostic signs. Clearly, patients showing response to initial chemotherapy have a better prognosis.



• **Figure 22-9** Surgical treatment of the patient in Figures 22-5 and 22-6. **A,** An incisional biopsy was obtained that led to a diagnosis of LCH. **B,** A full workup, including a skeletal survey, failed to disclose other lesions, thereby indicating the patient had unifocal disease. (H&E, original magnification 100 ×.) An enucleation and curettage of this lesion was performed



• **Figure 22-9, cont'd (C-D).** At 2½ years after surgery, he showed no clinical signs of recurrent disease **(E-F),** and no radiographic signs of disease at 10 years after surgery **(G).**



• **Figure 22-10** The surgery **(A)** for the patient whose panoramic radiograph is noted in Figure 22-2. Because of the advanced nature of his disease, a segmental resection was required **(B)**.

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23

Vascular Anomalies of the Oral and Maxillofacial Region

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The rapidly evolving field of vascular anomalies combines the expertise of several surgical, radiologic, and medical specialists. In the past, the field was obscured by a cloud of confusing descriptive and histologic words. Improper terminology and classifications led to incorrect diagnosis, inappropriate treatment, and ill-conceived research endeavors. Vascular anomalies were often called "hemangioma" and specified by adjectives such as "capillary," "strawberry," "cavernous," "central," "venous," and so forth. Unfortunately, the generic label "hemangioma" was applied to many types of vascular lesions, both congenital and acquired, with different etiologies and clinical presentations.

In 1982 Mulliken and Glowacki analyzed the cellular features of the various vascular lesions seen in infancy and childhood and correlated their findings with physical examination and natural history.[1] They concluded that, on the basis of cellular kinetics, there are two major types of vascular anomalies: infantile hemangioma (IH) and vascular malformations. In 1996 the International Society for the Study of Vascular Anomalies adopted an expanded schema by categorizing vascular anomalies into *tumors* and *malformations*.[2] In modern medical usage, the Greek nominative suffix "-oma" refers to a lesion that arises by upregulated cellular growth. Hence, the word *hemangioma* denotes a benign vascular tumor, almost exclusively occurring in infancy. There are other vascular tumors with borderline or intermediate malignant features specified as hemangioendotheliomas. The least common are malignant vascular tumors, angiosarcomas, and lymphangiosarcomas.

Vascular malformations arise as the result of abnormal embryonic development. They are subdivided anatomically and rheologically into *slow-flow* lesions (i.e., capillary malformation [CM], lymphatic malformation [LM], and venous malformation [VM]) and *fast-flow* lesions (i.e., arterial malformations, such as aneurysm, ectasia, stenosis, fistula, and arteriovenous malformation [AVM]) (Box 23-1).

More than 90% of vascular anomalies can be differentiated by history and physical examination.[3] About one third of IHs are nascent at birth; two thirds appear postnatally. Rapid growth in early infancy is the defining feature. In contrast, many vascular malformations are noted at birth, and they expand commensurately with the child. Radiologic examination, ultrasonography (US), and magnetic resonance imaging (MRI) are commonly used to confirm the clinical diagnosis, document the extent and flow characteristics, and search for other vascular lesions. A biopsy is mandatory if there is equivocation about the clinical or radiologic diagnosis.

Histologically, hemangiomas demonstrate endothelial hyperplasia and glucose transporter-1 protein (GLUT1) immunopositivity, whereas vascular malformations have slow endothelial turnover and are GLUT1 negative.[4]

There are no specific hematologic abnormalities associated with IHs. Slow-flow vascular malformations, specifically venous and lymphaticovenous types, exhibit stasis, causing localized and disseminated intravascular coagulopathy.

IHs rarely cause skeletal hypertrophy or deformation of nearby bone by a mass effect, whereas slow-flow vascular malformations can cause bony deformation, and fast-flow lesions typically cause osteolysis.[5]

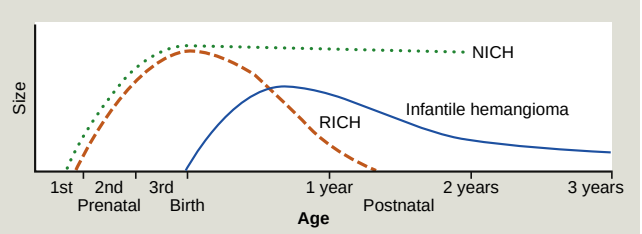
Since the single case report in 1940, the double eponym Kasabach-Merritt has been used to include profound thrombocytopenia, petechiae, and bleeding in association with a "giant hemangioma."[6] Unfortunately, the eponym continues to be commonly applied to the disseminated intravascular coagulopathy seen with slow-flow anomalies. Kasabach-Merritt coagulopathy is not a syndrome; rather, it is a phenomenon that occurs only with more invasive vascular tumors, kaposiform hemangioendothelioma (KHE), and tufted angioma (TA).[7,8]

Infantile Hemangioma

The term *hemangioma* should be restricted to the endothelial tumor of infancy that displays a unique biologic behavior of rapid growth and slow regression.

• BOX 23-1 Binary Classification of Vascular Anomalies, According to the International Society for the Study of Vascular Anomalies

Tumors
Hemangioma
Hemangioendotheliomas
Angiosarcoma
Miscellaneous
Malformations
Slow flow
  Capillary
  Lymphatic
  Venous
Fast flow
  Arterial
Combined



• Figure 23-1 Life cycle of common infantile hemangioma, as well as rapidly involuting infantile hemangioma *(RICH)* and noninvoluting infantile hemangioma *(NICH)*. (From Mulliken JB, Enjolras O: Congenital hemangiomas and infantile hemangioma: missing links, *J Am Acad Dermatol* 50:875-882, 2004.)



• Figure 23-2 Ulcerated hemangioma of the lower lip and tongue in a 3-month-old. *Note* the macular appearance of the tongue hemangioma.

This most common tumor of infancy occurs in 4% to 10% of Caucasian infants[9]; it is less frequent in dark-skinned infants. By age 1 year, approximately 10% to 12% of Caucasian children have a hemangioma. Females are more affected with a gender ratio of 2.4:1. Hemangiomas occur most frequently in the head and neck region (60%).[3] There is an increased incidence of 23% in premature infants weighing less than 1200 g.[10] Eighty percent of cutaneous hemangiomas are single, and 20% are multiple. Multiple cutaneous lesions often are associated with hemangiomas in other organ systems, especially liver, brain, gastrointestinal tract, and rarely in the lung.[9]

The typical infantile hemangioma (IH) is usually not evident at birth, although in 30% of patients, there may be a precursor lesion, such as a small macular red spot, pale area, telangiectasia, or ecchymotic lesion.[3] IHs appear during the first to fourth weeks of life and are followed by rapid postnatal growth, peaking by 5 to 6 months (proliferating phase). After the first year, the IH stabilizes and for a time grows at the same rate as the child, and then slowly regresses (involuting phase). Proliferation and involution are not distinct stages in the life cycle; rather, proliferation continues as involution slowly begins to predominate. As the hemangioma regresses, it becomes softer and its erythematous color changes to a gray hue. Complete resolution (involuted phase) occurs in more than 50% of children by age 5 and in more than 70% by the age of 7, with continued improvement until ages 10 to 12 (Figure 23-1). After involution is complete, there may be redundant atrophic skin, yellow discoloration or scarred patches if there was previous ulceration, residual fibrofatty tissue, and telangiectasia (Figure 23-2).[11]

The three phases of the IH's life cycle can be distinguished clinically, microscopically, and immunohistochemically.[12] In the proliferating phase, the tumor is composed of Angiogenic proteins (e.g., basic fibroblast growth factor [bFGF] and vascular endothelial growth factor [VEGF]) and enzymes involved in remodeling of extracellular matrix (e.g., type IV collagenase and high-molecular-weight matrix metalloproteinases) are prominent in proliferating hemangiomas and diminish to normal levels during regression.[13,14] In the involuting phase, there is decreasing endothelial proliferation, increasing apoptosis, preponderance of stromal cells (e.g., mast cells, fibroblasts, and macrophages) and the first evidence of fibrofatty replacement of the tumor.[15] After regression is complete, all that remains are a few tiny capillary-like feeding vessels (encased in multilaminated basement membrane) and draining veins surrounded by islands of fibrofatty tissue admixed with dense collagen and reticular fibers.

If the tumor grows in the superficial dermis, the skin becomes raised, crimson in color, and firm and rubbery



• **Figure 23-3** **A,** Rapidly involuting infantile hemangioma on chin of newborn. Raised with red-violaceous color. **B,** Ten months later, lesion has nearly resolved.

to palpation. However, if the hemangioma develops in the lower dermis and subcutis, the lesion may appear slightly raised with a bluish hue or the overlying skin can be smooth and of normal color. These deeper lesions, once labeled "cavernous hemangiomas," often are not detected until 3 to 4 months of age. Both superficial and deep lesions are firm to palpation and exhibit the characteristic to-and-fro murmur on continuous-wave Doppler examination.[16] During the proliferative phase, they can become ulcerated and infected.[17] Multifocal hemangiomas can involve visceral organs (e.g., liver, gastrointestinal tract, brain, and lung) and, if large, can divert significant intravascular volume, resulting in high-output cardiac failure.[18]

Associated Malformative Anomalies

IHs in the head and neck can arise in association with structural anomalies, which are not necessarily vascular in nature. This was not well appreciated until these various malformations were compiled as the acronym PHACE: **P**osterior fossa anomalies, **H**emangioma of the face, **A**rterial abnormalities, **C**ardiac defects and coarctation, and **E**ye anomalies.[19,20] PHACE association occurs in a spectrum; the female preponderance is 9:1, higher than in isolated IH. The facial hemangioma typically manifests at birth as a diffuse (regional) reticular stain in the frontal and maxillary areas that tends to become plaquelike and pebbly. If the cheek and mandibular areas are involved ("beard distribution"), there also may be an obstructing laryngeal (subglottic) hemangioma. PHACE-associated anomalies also can occur with focal and multifocal hemangiomas. PHACE association should be promptly diagnosed by MRI or magnetic resonance angiography (MRA). Vascular anomalies include persistent embryonic intracranial and extracranial arteries, hypoplasia or absence of the ipsilateral carotid or vertebral vessels, aneurysmal dilatation of the carotid artery, and coarctation and right-sided aortic arch. Cerebrovascular occlusive changes, resembling moyamoya disease, can develop in these infants.[21] Seizure and stroke, secondary to cerebral infarction, can occur in infancy, and progressive stenosis and tortuosity can cause neurologic sequelae in childhood and adolescence.[22,23] The original acronymic designation PHACE did not include the possibility of sternal nonunion or supraumbilical raphe; these were included later by adding S to make PHACES.[20,24]

Congenital Hemangioma

There are rare vascular tumors that occur fully grown at birth and do not exhibit the expected postnatal course and life cycle of the common IH. These are defined as *congenital* hemangiomas, and there are two subtypes: rapidly involuting congenital hemangioma (RICH) and the noninvoluting congenital hemangioma (NICH) (see Figure 23-1). Both RICHs and NICHs have an equal sex ratio. RICH is raised with a characteristic red-violaceous color, central telangiectasias, and frequently with a peripheral pale halo (Figure 23-3). There may be superficial ulceration, central



• **Figure 23-4** Noninvoluting infantile hemangioma on the mandibular border of a 5-year-old. Well-circumscribed macule, coarse telangiectasias, and prominent to-and-fro murmur on handheld Doppler examination.

nodularity, or scar. Rapid arteriovenous shunting can simulate an AVM. Transient thrombocytopenia can also occur; however, the hematologic profile is more that of consumptive coagulopathy (i.e., it is not a Kasabach-Merritt phenomenon). Platelet levels rise rapidly as the tumor regresses. RICH commonly occurs on the trunk and extremities, but also in the head and neck and the liver. RICH involutes rapidly during the first few weeks or months of life.[25]

NICHs are typically ovoid, macular, or slightly raised; light gray in color with prominent coarse telangiectasias; and warm on palpation (Figure 23-4).[26] There is a predisposition for the mandibular border.[26] An NICH is typically a well-circumscribed lesion, averaging 5 to 6 cm in diameter.[27] An NICH is usually not diagnosed until later in childhood because it was mistaken for common IH or presumed to be a small AVM. NICH can occur as a large lesion in the cervical and occipital areas. Sometimes lesions in this location expand during adolescence and exhibit polypoid excrescences.

RICHs and NICHs have overlapping radiologic and histologic features with IHs; however, curiously, neither type of congenital tumor immunostains for glucose transporter-1 protein (GLUT1).[27] This raises the question of whether these congenital hemangiomas are variations in the hemangiomatous spectrum or entirely different tumors that arise in fetal life. There are more similarities than dissimilarities between IHs, RICHs, and NICHs. Furthermore, RICHs and NICHs can coexist with IHs.[11]

Management

Observation and waiting for involution is appropriate for small hemangiomas that cause no harm or disfigurement. Spontaneous ulceration has been reported to occur in up to 20% of cutaneous hemangiomas[28]; this most frequently involves lesions on the lips, perineum, anogenital area, and extremities (see Figure 23-2). An ulcerated hemangioma can become infected or destroy a lip, nose, or eyelid. For small superficial ulcerations, treatment includes cleansing with application of hydrated petrolatum dressing or a topical antibiotic.[29] Scarring is worse in ulcerated areas compared with nonulcerated areas following regression. There is some evidence to suggest that pulsed dye laser therapy can be effective for ulcerated hemangiomas.[30] Nevertheless, pulsed dye laser therapy for proliferating and early involuting hemangiomas is not indicated because the laser cannot penetrate deep enough into the tumor to be effective.[31] Laser application during proliferation of the hemangioma can cause ulceration, hypopigmentation, and scarring.[31,32] Laser therapy does not alter the life cycle of the hemangioma. A pulsed dye laser is effective for photocoagulation of the residual telangiectasias that persist after involution.

Pharmacologic therapy is indicated if a hemangioma causes destruction, distortion, or obstruction—for example, a proliferating hemangioma producing subglottic narrowing and distortion of the growing cornea, resulting in astigmatic amblyopia or blockage of the visual axis, causing deprivation amblyopia and failure to develop binocular vision. Subglottic hemangioma can be life threatening. The symptoms are hoarseness and biphasic stridor, generally manifesting between 4 and 12 weeks of age. Approximately 50% of these infants have a cutaneous hemangioma in a beardlike distribution.[33] A tracheostomy may be necessary if the lesions are large or unresponsive to pharmacologic therapy. Other alternatives include a carbon-dioxide laser (for unilateral lesions) and open resection.[34]

Intralesional steroids are useful for small lesions on the face (less than 2 cm in diameter).[35] Systemic steroids and propranolol (a beta-blocker[36]) should be used only in infants with a hemangioma that (1) is rapidly growing and seriously distorting facial features; (2) is causing recurrent bleeding, ulceration, or infection; and (3) is impinging on critical anatomic structures.[37] Endangering and life-threatening complications, such as high-output cardiac failure with a large tumor or multiple intrahepatic tumors, occur in 10% of hemangiomas.[38] The responsiveness to corticosteroids, the first-line treatment, is as high as 85%, with stabilization of growth or accelerated regression.[39] Indications for second-line therapy (vincristine) are failure of response to corticosteroids/propranolol, contraindications to prolonged systemic corticosteroids, and complications of corticosteroids or propranolol.

Resection is a consideration in all three phases of the hemangioma life cycle. Indications for excision in infancy include obstruction of a vital structure, recurrent bleeding, and ulceration. Resection during early involution can be carried out if excision is inevitable because of postulceration scarring, expanded skin, or high possibility of fibrofatty residuum and if the scar is easily concealed or if staged excision will be necessary. Indications for resection during late childhood include damaged skin, excess skin, abnormal contour (fibrofatty residuum), distortion, and loss of tissue.[40] Resection of a facial hemangioma, in any of the phases of its life cycle, requires careful planning. The

conventional method is excision in a lenticular format with linear closure in the axis of the relaxed cutaneous tension lines, either as a single or staged procedure. This technique is applicable in some locations, such as the lips, eyelids, neck, and sometimes the scalp. Most hemangiomas are spherical, and lenticular excision (to minimize "dog ears") causes central tension that flattens a convex area, such as the cheek or forehead, or may cause distortion of nearby structures. Hemangiomas act as a tissue expander; therefore circular excision and purse-string closure should always be the first consideration. This technique converts a circular lesion into a small circular or ellipsoid scar. Thereafter, a second excision can be either circular or lenticular. The result is the smallest possible scar with minimal distortion of surrounding structures.[41]

RICH often leaves behind loose skin and prominent draining veins. Resection may be indicated in an end-stage RICH. NICH can be resected, and diagnosis is established; usually the indication is cosmetic.

Vascular Malformations

Vascular malformations are localized abnormally formed lymphatic or blood vessels. Present at birth, some vascular malformations are obvious, whereas others manifest later in life. They grow commensurately with the patient. Malformations are divided by the preponderant vessel type and the rheologic characteristics (i.e., flow [slow- or fast-flow]). The in the head and neck region are lymphaticovenous (LVM) and arteriovenous (AVM).

US is helpful in distinguishing lymphatic, venous, and arteriovenous malformations.[16] MRI is the gold standard to determine the type and extent of the lesion; gadolinium is given as a contrast agent for enhancement.

Slow-Flow Vascular Malformations

Capillary Malformation

A capillary malformation (CM) occurs at birth as a macular pink stain that blanches with pressure. It is also known by the 19th-century term "port-wine stain." CM should not be confused with *nevus flammeus neonatorum* ("stork bite" or "angel kiss"), a common fading birthmark located on the forehead, eyelids, and nuchal region. CM has an equal sex ratio, and the incidence is 0.3%.[42] They can occur anywhere on the body and can be localized or extensive. Facial CMs often occur in a dermatomal distribution: 45% are restricted to one of the three trigeminal dermatomes, whereas 55% overlap sensory dermatomes, cross the midline, or occur bilaterally (Figure 23-5).[43]

Histologically, a CM is characterized by ectasia of capillary-to-venular sized vessels in the upper dermis. Facial CMs tend to gradually darken to an intense red hue during young adulthood and to a deep purple during middle age. The skin thickens and becomes raised and studded with nodular fibrovascular lesions, giving the appearance of cobblestones. Often there is associated soft tissue, gingival, and skeletal overgrowth in the area of the stain. This typically occurs in the maxilla and particularly the alveolar ridge, although the malformation does not involve the bone (see Figure 23-5). Patients with a CM of the alveolar ridge frequently develop gingival overgrowth, and pyogenic granulomas are common. To prevent these lesions, patients should practice good oral hygiene and receive regular dental cleaning. Operative procedures in the oral cavity, such as gingivectomy, extractions, and osteotomies, can be done without concern for excessive bleeding in the presence of a CM.

Although most CMs occur sporadically, if they are located in the upper face, Sturge-Weber syndrome should be considered. Sturge-Weber syndrome is defined as a CM in the V1 ± V2 trigeminal areas associated with leptomeningeal capillary and venous anomalies and vascular lesions of the ocular choroid. The leptomeningeal vascular lesions can cause refractory seizures, contralateral hemiplegia, and variably delayed motor and cognitive development. Anomalous choroidal vascularity can result in retinal detachment, glaucoma, and blindness.[44] Patients with Sturge-Weber syndrome can have an extensive facial CM and stains on the trunk and extremities. Some patients exhibit major maxillary and/or mandibular overgrowth with evidence of vascular changes in bone. CMs can rarely be a red flag of an underlying structural anomaly. Midline occipital CMs can overlie ectopic meninges or an encephalocoele.[45] CMs over the cervical or lumbar spine may be a clue to occult spinal dysraphism.



• **Figure 23-5** Sixteen-year-old boy with extensive bilateral facial capillary malformation in V_1, V_2, V_3 (Sturge-Weber syndrome); note soft tissue, gingival, and skeletal overgrowth in the area of the stain. Bony enlargement involves the maxilla and mandible and particularly the alveolar ridge.



• **Figure 23-6** Infant with lymphatic malformation (LM) in floor of mouth, elevating tongue. LMs in this position must be differentiated from a ranula.

Management

A pulsed dye laser is standard treatment; photocoagulation might prevent fibrovascular overgrowth ("cobblestoning"). Significant lightening of the CM occurs in approximately 80% of patients. Multiple sessions are generally required and often need to be repeated several years later.[46,47]

If there is cutaneous overgrowth despite laser treatment, staged excision and skin grafting should be considered.[48] The most common operation for a facial CM is contour resection for labial hypertrophy. Orthognathic correction may be indicated for occlusal canting caused by asymmetrical maxillary overgrowth or mandibular prognathism.

Lymphatic Malformation

acterized as microcystic ("lymphangioma") or macrocystic ("cystic hygroma") or combined forms. LMs in the head and neck region occur in the neck, cheek, and cervicofacial region, extending into the mediastinum, and, less commonly, in the orbit (Figure 23-6).[49]

An LM in the forehead and periorbital tissues causes swelling of the supraorbital area and upper eyelid and usually proptosis as a result of intraorbital involvement.[50] Facial LMs appear as unilateral or bilateral hypertrophy, macrocheilia, and macrotia. LMs in the tongue and oral floor cause macroglossia with dark-stained vesicles on the dorsal surface. Cervicofacial LMs are associated with overgrowth of the mandibular body and resulting open bite and anterior crossbite (Figure 23-7).[49]

Prenatal US will detect relatively large lesions as early as the second trimester.[51] Most LMs are noted at birth or within the first year of life. Tracheostomy in a neonate may be needed to secure the airway in the presence of an extensive cervical LM that involves the supraglottic region (pharynx). Two major complications are infection and intralesional bleeding. LMs enlarge commensurate with the child's growth, but can suddenly expand as a result of cellulitis, often occurring along with an upper respiratory infection. The inflamed tissue is typically tense, warm, and erythematous and can lead to airway obstruction if there is involvement of the floor of the mouth and tongue. LMs can also expand as a result of an intralesional hemorrhage from small vessels within the malformation and present as oozing from mucosal and cutaneous vesicles.[52]

Management

Recurrent cellulitis may be caused by periodic seeding with common oral microorganisms. Infections should be treated promptly with broad-spectrum antibiotics continued for weeks rather than days.[49] Intravenous antibiotic administration is necessary if oral treatment fails or if there are signs of respiratory compromise. Antibiotic prophylaxis is controversial, but can be effective in diminishing the infective episodes. Meticulous oral hygiene along with regular dental cleaning every 4 months is recommended to minimize gingival inflammation. Many patients have multiple dental caries leading to premature tooth loss, which is usually related to the inability of the patient or dentist to access teeth for cleaning and restoration.[49] Teeth can be extracted without concern for bleeding.

Sclerotherapy is effective primary treatment of macrocystic disease or secondarily for recurrent cysts following partial extirpation.[53] Doxycycline, sodium tetradecyl sulfate, OK-432, absolute ethanol, and bleomycin have all been used as sclerosing agents.[54-57] The success of sclerotherapy in treating patients with LMs has made this modality preferable to resection, whenever possible.[58]

Resection of a large macrocystic LM is appealing, but it is often incomplete, and persistent swelling is predictable.[53] Staged excision, limiting each procedure to a defined anatomic area, is recommended for a diffuse microcystic LM.

Repeated resection in the same area becomes increasingly difficult. Nerve damage is more likely with each procedure because dense scar tissue distorts the usual anatomic location of nerves, especially the facial, hypoglossal, lingual, phrenic, and spinal accessory nerves.[49] The possibility of intraoperative nerve damage cannot be overemphasized. Facial nerve weakness only adds to the deformity in these patients, who are often already disfigured. Bilateral hypoglossal nerve loss is a devastating complication of repeated excision. An annoying problem after resection is the appearance of vesicles in

custom-made elastic compression garment should be worn after a major facial resection in an effort to minimize swelling.

Total resection may be possible for the child with an isolated LM of the dorsal tongue. Reduction for macroglossia



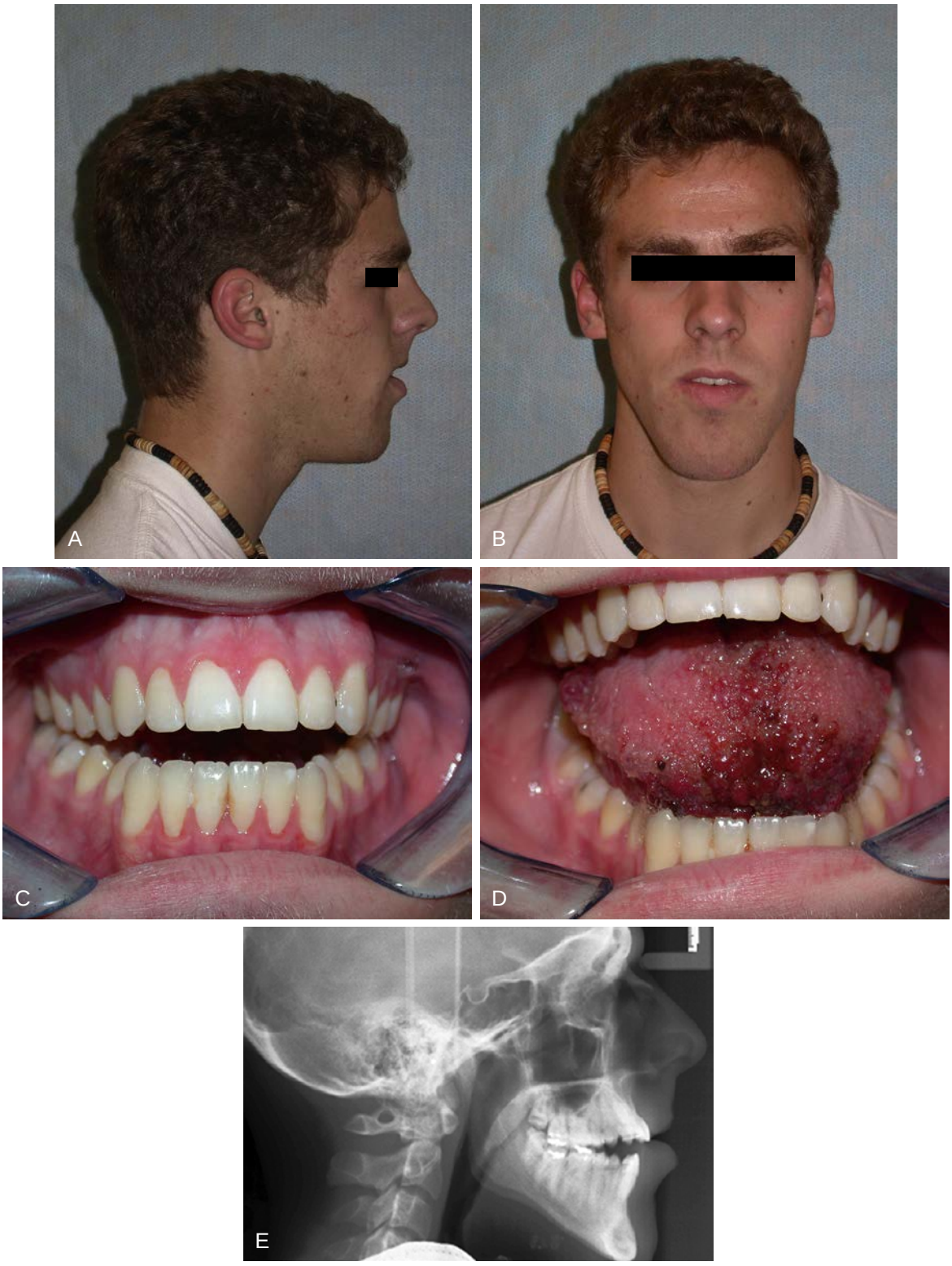
• **Figure 23-7** **A,** Child with lymphatic malformation (LM) of tongue and floor of mouth. Lingual movement diminished by fibrosis from previous episodes of infection, bleeding, and sclerotherapy. **B,** Cervicofacial LM is typically associated with overgrowth of mandibular body with resulting open bite and anterior crossbite. **C,** LM in tongue with blood-filled vesicles on dorsal surface; these are aggravated by trauma or infection.

is indicated for persistent protrusion or to allow for correction of a malocclusion.[49,53] The timing of resection is based on functional and emotional issues. Lingual reduction alone will not obviate a tracheostomy or decannulation. This requires removal of the lesion from the floor of the mouth via a cervical incision. Transoral resection of the floor of the mouth and tongue base should be avoided because of the high likelihood of postoperative functional problems. Debulking an enlarged and protruding tongue to return it to the oral cavity can have a negative impact on speech and feeding secondary to insufficient functional lingual mass.[53] Many patients have speech problems that are related to the intraoral bulk of the lesion, reduced lingual mobility, tooth loss, palatal immobility, and poor oral competence.[49,53]

Bleeding vesicles on the lingual dorsum are often aggravated by trauma or infection.[53] The bleeding is typically a daily oozing that can be a minor annoyance, but can also cause chronic blood loss and anemia.

Vesicles of the mucous membranes and dorsal tongue can be treated by laser (carbon dioxide, yttrium-aluminum-garnet [Nd:YAG], or potassium titanyl phosphate), or radiofrequency ablation.[46] Radiofrequency ablation is similar to laser photocoagulation. Most patients require a combination of these modalities to adequately treat LM of the lingual base and floor of the mouth.[49,53] Embolization can control bleeding from these vesicles.[53]

Cervicofacial LMs can be disfiguring, not only because of soft tissue hypertrophy, but as a result of bony enlargement and malocclusion. Most patients with a cervicofacial LM have progressive mandibular overgrowth and prognathism, class III malocclusion, a steep mandibular plane angle, effacement of the gonial angle, and anterior open bite (Figure 23-8).[49] Orthognathic procedures can be undertaken



• **Figure 23-8** **A,** Frontal and **(B)** lateral photographs of 18-year-old man with lymphatic malformation of floor of mouth and tongue. Note long lower face height. **C,** Anterior open bite and **D,** blood-filled vesicles on dorsal tongue. **E,** Lateral cephalogram demonstrates steep mandibular plane and anterior open bite.



• **Figure 23-9** **A,** Frontal and **(B)** lateral photographs of patient in Figure 23-8 1 year after Le Fort I osteotomy shows improved lower face height. **C,** Anterior open bite has been closed. **D,** Lateral cephalogram demonstrates normalized occlusal planes.

at the appropriate age only after lingual size and position is acceptable. Orthognathic operations should ideally be postponed until lower jaw growth is complete; however, severe deformity with functional impairment can be so devastating that early osteotomy may be indicated (Figure 23-9). Le Fort I osteotomy and mandibular anterior segmental osteotomy allow for correction of the sagittal discrepancy and closure of the open bite without compromising the posterior airway space. Similarly, an ostectomy at the angle of the mandible with counterclockwise rotation of the mandibular body allows for correction of the steep mandibular plane and anterior open bite.[49]

Preoperative treatment is unnecessary for extractions, resection, or osteotomy, but the airway must be considered and managed accordingly. In addressing the mandibular deformity, it is important to remember the competing goals of improving jaw position without impinging on the airway.[53]

Judicious use of antibiotics is necessary in the perioperative period. Antibiotics should be administered for 2 to 3 weeks postoperatively, rather than just for days.



• **Figure 23-10** Small venous malformation of buccal mucosa can easily be treated in office with injection of sclerosing agent. Consider ultrasound or magnetic resonance imaging (with gadolinium) before treatment to determine size and extent of lesion.

Venous Malformation

Venous malformations (VMs) are the most common type of vascular malformation. These lesions have erroneously been referred to as "cavernous hemangiomas." They are not tumors, because they do not demonstrate endothelial proliferation unless there is intravascular clotting and fibrodeficient smooth muscle.[9] Venous lesions are blue-purple in color, soft, compressible, and nonpulsatile (Figure 23-10). VMs generally occur in skin, subcutis, and submucosa, but can involve muscle, viscera, and the central nervous system. Most VMs are solitary. Multifocal forms occur and should raise suspicion that there is a hereditary basis. Causative genes are known for cerebral cavernous malformation *(KRIT1),*[59] cutaneomucosal VM *(TIE2),*[60] and glomuvenous malformation (GVM) *(glomulin)*. GVM is the most common familial type of VM and can have macular lesions in infancy with expansion to plaquelike or nodular facial lesions. *TIE2* mutations are multiple focal lesions, often located in mucous membranes and the tongue.[61] Blue rubber bleb nevus syndrome is familial, although the gene has not been identified. These venous lesions can involve the face and oral cavity, but typically are located on the trunk, palms and soles, and gastrointestinal tract.

Venous anomalies usually grow in proportion to the child, but enlargement can occur with trauma or may coincide with puberty and pregnancy.[62] VMs characteristically expand with a Valsalva maneuver, when the patient bends over with the head in a dependent position, or with jugular vein compression.[51] Phlebothrombosis is common within venous anomalies because of stasis, and recurrent localized pain, distention, and tenderness are frequent presenting complaints. Phleboliths can be palpated or seen on plain radiographs and on all MRI sequences.[52]

VMs can cause progressive distortion of facial features (Figure 23-11). Patients with an extensive VM or LVM generally involve the overlying soft tissue and commonly cause skeletal alteration and hypertrophy without intraosseous involvement.[63] There are, however, rare instances of VMs within the facial bones. The most common intraosseous craniofacial location is the mandible, followed by the maxilla.[63] They are rarely found in the frontal, zygomatic, and nasal bones. Unfortunately, these lesions have been called "central" or "intraosseous" hemangiomas in the literature. Oral VMs can cause malocclusion as a result of the mass effect on the dentoalveolus.[51] VMs in the buccal mucosa can also involve the gingiva, tongue, palate, and oropharynx, but rarely interfere with speech and feeding.[51] VMs in the pharynx may compress and deviate the upper airway, leading to obstructive sleep apnea that is usually insidious in onset.[51]

The anatomic location and extent of the VM is best visualized by MRI with contrast. Stasis in large or extensive venous anomalies is frequently associated with a low-grade localized or generalized intravascular coagulopathy.[51] International normalized ratio and prothrombin time are often within normal limits, whereas fibrin split products and D-dimers are elevated, with concomitant decreased fibrinogen and platelet levels. It is important to correct coagulopathy preoperatively; even dental extraction in the presence of gingival venous lesions can result in a life-threatening hemorrhage. Indications for therapy include appearance, pain, and functional problems.[51] The primary therapeutic modalities are sclerotherapy, surgical resection, or a combined approach.[51]

Management

A patient with a large VM can be managed nonoperatively by giving daily aspirin (81 mg) to help prevent thrombosis and control the associated pain. Sclerotherapy is the mainskin can easily be treated in the office with a local injection of 1% sodium tetradecyl sulfate (see Figure 23-10). How-

Direct injection of a sclerosing agent, such as sodium tetradecyl sulfate (3%) or absolute ethanol, into the anomaly is sometimes performed with the arterial inflow and venous outflow occluded during the procedure.[65,66] Multiple sclerotherapeutic sessions are often necessary to shrink a lesion because of the perverse tendency for recanalization. The success rate for sclerotherapy has been reported to be 76%; possible complications include blistering, full-thickness cutaneous and/or mucosal necrosis, and nerve injury.[67]



• **Figure 23-11** **A-B,** Fifteen-year-old girl with extensive cervicofacial venous anomaly that involves glottis, floor of mouth, tongue, anterior neck, chin, and lower lip. **C,** She has an anterior open bite secondary to vertical mandibular growth and tongue position with deformation of anterior maxilla.

Intralesional photocoagulation with the Nd:YAG (1064 nm) laser has been used successfully to treat deep VMs of the oral cavity.[68]

Resection without preoperative sclerotherapy is indicated only for small, solitary lesions or VMs in anatomic sites that are dangerous to sclerose (e.g., around major nerves).

socket can be sutured tightly and/or the wound packed, the head wrapped, coagulopathy reversed, the patient kept intubated, and hypotension maintained. Resection is indicated to reduce bulk and to improve contour and function. Total excision of the venous anomaly is the therapeutic goal, but is not usually achievable because of the extent of the lesion and its location in relation to vital anatomic structures. In this case only subtotal or contour resection is possible.

by expansion of

ken safely, but should be done with preoperative treatment of localized coagulopathy, protection of the airway with a tracheostomy for extensive involvement of the oral cavity and glottis, and the use of preoperative sclerotherapy (Figure 23-13).

Fast-Flow Vascular Malformations

Arteriovenous Malformation

An AVM is composed of abnormal communications between arteries and veins without the normal intervening capillary bed. An AVM may result from an error of vascular development between the fourth and sixth weeks of gestation. Causative mutations for familial AVMs include *RASA1* for capillary malformation–arteriovenous malformation[69] (CM-AVM) and *PTEN* for *PTEN*-associated vascular anomaly.[70]



• **Figure 23-12** **A-B,** Multiple sclerotherapy sessions diminished size of venous malformation. **C,** Dentition has been leveled and aligned in preparation for orthognathic surgery. **D,** Lateral cephalogram shows dentoalveolar maxillary protrusion, vertical mandibular excess, and multiple phleboliths.

Expansion of an AVM is the result of increased blood flow through the lesion and subsequent tortuosity of adjacent feeding arteries and dilation of veins (collateralization and recruitment).[71] Recent evidence supports the theory that vasculogenesis may be involved in the enlargement of arteriovenous malformations. Hypoxia in the nidus may cause recruitment of endothelial progenitor cells, because ischemia is a potent stimulator of vasculogenesis.

AVMs are present at birth, but they may not be clinically evident or are misdiagnosed as a CM or hemangioma.[51] They rarely expand in infancy or early childhood; more typically, they grow proportionately starting in late childhood. Usually, years go by before they pose a threat to the patient as the signs and symptoms of their fast-flow nature become obvious. Nevertheless, rapid expansion can occur following local trauma, attempted excision or ligation, or hormonal changes associated with puberty or pregnancy.[72]

AVMs of the head and neck are less common than slow-flow anomalies (capillary, lymphatic, and venous malformations). Primary skeletal involvement occurs in the tooth-bearing bones, which are invariably expanded by the malformation.[72] AVMs in the maxilla and mandible constitute 4% and 5%, respectively, of all craniofacial AVMs (Figure 23-14).[72] AVMs of the jaws may be asymptomatic or present as a pulsatile swelling, localized throbbing pain, toothache or earache, or unexpected hemorrhage following dental extraction or exfoliation. A loose tooth in a bleeding socket should be treated with extreme caution.

Bleeding can be fatal. The most effective measure is immediate packing and pressure. Preoperative embolization before extraction of teeth is useful to help control bleeding. The typical radiographic findings are an ill-defined radiolucency or a well-defined multilocular lesion.



• **Figure 23-13** **A-B,** One year following Le Fort I osteotomy to close anterior open bite and further sclerotherapy. Temporary tracheostomy to protect airway after sclerotherapy and surgical correction has been removed. **C,** Final occlusion after orthodontic appliances removed is stable. **D,** Lateral cephalogram shows improved jaw relations.

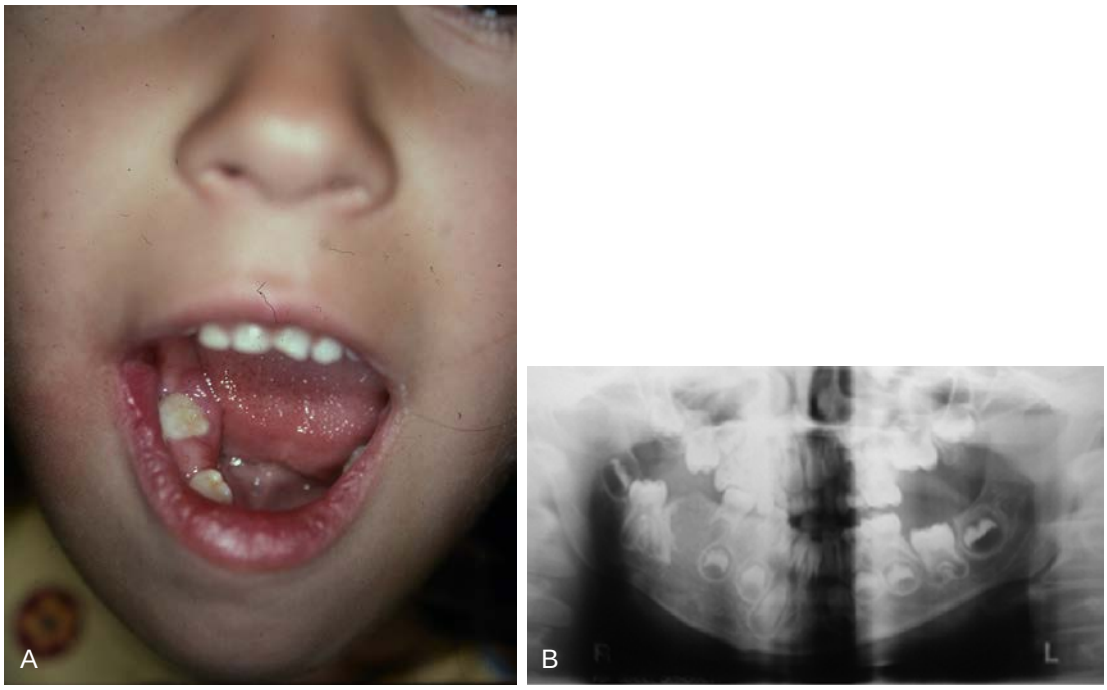
The Schobinger clinical staging system for AVMs, introduced at the 1990 meeting of the International Workshop for the Study of Vascular Anomalies, is useful for documenting the presentation and evolution.[71] Stage I (quiescence) is characterized by a cutaneous blush, warmth, and arteriovenous shunting by Doppler examination. Stage II (expansion) is similar but with enlargement, pulsations, bruit, thrill, and tense and/or tortuous veins. Stage III exhibits dystrophic skin changes, ulceration, tissue necrosis, bleeding, and persistent pain. Cardiac failure (decompensation) constitutes progression to stage IV.

AVMs can remain stable for years in stage I. A bruit is of little significance unless it increases in intensity. The onset of pain, pruritus, or enlargement heralds likely progression to the next stage of ulceration and hemorrhage. Once pain, ulceration, or bleeding become established, progression is inevitable unless the lesion is treated.[73]

Clinical diagnosis is confirmed by US and color Doppler examination. MRI and/or MRA define the extent of soft tissue involvement.[74] Angiography shows variable degrees of arterial dilatation and tortuosity, arteriovenous shunting, and dilated draining veins. Angiography is rarely performed unless intervention is planned under the same anesthetic.

Management

The mainstays of AVM management are embolization, sclerotherapy, surgical resection, and reconstruction.[75] Intervention is indicated for complications, such as repeated hemorrhage, persistent pain, ischemic ulceration, or cardiac failure. The therapeutic strategy for these



• **Figure 23-14** **A,** Six-year-old with arteriovenous malformation (AVM) of mandible diagnosed after frightening hemorrhage following exfoliation of primary molar. **B,** Panoramic radiograph shows AVM of right mandible and bony overgrowth.

lesions is selective embolization and sclerotherapy with or without resection. Embolization involves placement of coils or glue by either accessing the malformation from a proximal arterial or retrograde venous approach or by direct transosseous puncture.[76,77] Sclerotherapy involves direct puncture of the nidus to permit local arterial and venous occlusion.

Endovascular treatment can be palliative or preoperative, but almost never curative.[78,79] For extensive or inaccessible lesions, endovascular therapy can be used as the primary treatment. However, this is regarded as only for temporary control; in time, recanalization and reexpansion usually occur. Embolization can be used to relieve symptoms, reduce frequency of bleeding episodes, and diminish the size of the AVM.[51]

Preoperative endovascular therapy is used to diminish blood loss during the operation and facilitate extirpation.[51] Usually the resection is planned 48 to 72 hours after endovascular occlusion. Although it is preferable to totally resect an AVM, this is often not feasible because of the extent of the lesion, or inaccessibility may preclude total removal. Determining whether the resection is complete can be problematic because of troubles in delineating the limits of the malformation. Venous runoff, difficulty controlling blood loss, absence of tissue planes, and the need to preserve blood supply to neighboring structures make complete extirpation challenging. The most useful guidelines are intraoperative Doppler examination and the bleeding pattern of tissue at the resection margin; frozen sections are not particularly helpful.[73] For AVMs of the jaw, endovascular treatment represents the therapy of choice in these sometimes life-threatening lesions. Surgery, often leading to facial mutilation and necessitating massive reconstruction, should be avoided, at least as the initial therapy.[80]

Combined treatment is used for localized early stage (I and II) and for painful or rapidly enlarging lesions (stage III and IV). Intervention for an extensive stage I to II AVM is controversial because one cannot predict when and if they will progress, resection will likely be incomplete, and the deformity produced may be worse than that created by the AVM.[73] Resection of a stage I AVM should be considered only if it can be easily accomplished without causing major deformity, particularly in a young patient. There is no indication for proximal ligation or embolization of feeding vessels, which causes only recruitment of flow from nearby arteries to supply the nidus and denies access for embolization.

Kohout and colleagues reported an overall control rate of 60% for AVMs in the head and neck region, defined as radiographic absence of the lesion.[72] Control for small malformations was 69% with excision only and 62% for extensive malformations with combined embolization and resection. The control rate was 75% for stage I, 67% for stage II, and 48% for stage III malformations. Outcome was not affected significantly by age at treatment, sex, Schobinger stage, or treatment method. Mean follow-up was 4.6 years. Treatment failures are due to persistence of the lesion because of the surgeon's inability to appreciate the extent of the lesion during resection, impossibility of complete resection because of involvement of vital structures, and a second nidus that was not seen on initial radiographic examination.[51,73]

Summary

Treatment of patients with vascular anomalies requires an interdisciplinary team and translational research efforts. This combined approach will provide insight into the molecular basis of these disorders and a deeper understanding of vascular morphogenesis. In the future, this emerging knowledge will contribute to novel ways to treat vascular anomalies and to regulate pathologic angiogenesis.[81]

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24

Vesiculobullous Diseases

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Introduction

acquired diseases, as well as idiopathic and autoimmune diseases. Clinically, they generally produce some discomfort to the patient, with variability in duration and severity. However, some foundation therapeutic paradigms apply to all these diseases regardless of cause. In addition, some of these diseases are managed rather than cured. Thus control of low-level disease processes is often a key to long-term patient care. In our clinical oral and maxillofacial pathology referral practice, it is not uncommon for many of our referrals to have been treated with the appropriate medications, but the referring clinician did not consider overall maintenance of an intact oral mucosal surface along with the salivary pellicle. In addition, simply educating the patient about the expected disease course and prognosis is often essential.

These foundation principles, which are discussed in this chapter, are not therapeutic in and of themselves. It is best to think of them as providing the best scenario for therapeutic regimens to be most effective. The desired effect is less potent medications, less complicated regimens, and more time between exacerbations.

- Decrease all possible irritants
- Avoid mucosal irritants such as pyrophosphates, cinnamon, menthols, and phenols
- Avoid destruction of "salivary pellicle"
  - Especially avoid sodium lauryl sulfate (SLS)
  - Also minimize ethanol
- Maintain and build salivary pellicle
  - Counteract xerostomic agents as much as possible
  - Hydration
  - Prescribe cholinergics or buffered citrate
- Manage bugs
  - Bacteria
  - Fungi

Oral health care products are notorious for having potential irritants incorporated right into the product. Pyrophosphates are one of the more common irritants in mouth rinses and toothpastes. They are actually seen in the majority of toothpastes. Pyrophosphates act several ways including to help potentiate the sodium lauryl sulfate and to decrease the possibility of mineralization. In those with irritated oral mucosae, they cannot be considered helpful. In addition, pyrophosphates are not very pleasant tasting, so they are generally masked with the use of cinnamic aldehyde or other strong flavoring agents. Cinnamic aldehyde in particular creates sensitivity reactions in some patients, but especially in those with mucositis, it is at least considered not helpful. In the mouth rinse category, menthol and camphors are not uncommon ingredients. Again, these essential oils all have some antibacterial effect but can also act as an irritant.

Maintenance of the salivary pellicle is one of the most essential aspects of protecting the mucosa. The salivary pellicle is the first barrier preventing antigenic presentation to the immune system. In addition, the salivary pellicle acts as a deflector for minor trauma secondary to mastication, habits, and oral health care. Sodium lauryl sulfate removes the salivary pellicle very efficiently. Sodium lauryl sulfate is in a number of oral health care products and, most notably, in every toothpaste that foams. Each time the salivary pellicle is removed, the patient's saliva must re-form it. Again, in a normal patient this is not a major complication, but in the patient with some sort of mucositis, it is best to have the mucosa protected as much and as long as possible. Ethanol also removes the salivary pellicle to a certain extent. Therefore minimization of ethanol-containing mouth washes is also desirable.

Of special note regarding toothpaste that is free of sodium lauryl sulfate is the fact that major distributors are constantly changing formulations. Some formulations are switched to an alternate surfactant named cocamidopropyl betaine. This is still a surfactant, and although studies need to be performed as to whether this is as damaging to the salivary pellicle as sodium lauryl sulfate, there is little doubt

that it does have some effect. Many previous brands such as Biotene, Tom's of Maine, Sensodyne, and Rembrandt have all been purchased by larger companies. Ingredient lists of brands all require close perusal because of the transient nature of some of the formulations. But, as of this writing in 2015, finding a well-known name brand without a surfactant in the formulation is extraordinarily difficult. The former go-to brands just named are no longer predictably surfactant free. In addition, finding one with no other irritant such as polyphosphates/pyrophosphates is extraordinarily difficult.

In a number of patients, xerostomia is what minimizes the effectiveness and production of the salivary pellicle. This is often due to multiple medicines that the patient is taking. Xerostomic medications include antidepressants, antianxiety agents, antihypertensives, and antihistamines, just to name a few. All are drying agents. If the patient is not taking an anticholinergic type of medication (i.e., bladder control medication), salivary flow can be stimulated with medications such as pilocarpine or cevimeline. However, it is very common to have some sort of anticholinergic in the patient history. For these patients, the only solution may be buffered malic tablets which are sold under the brand name of SalivaSure (Scandinavian Formulas, Sellersville PA). Even simpler and more basic is instructing the patient on proper hydration.

Good oral hygiene is also very important. It is appropriate to think of oral hygiene as managing the "bugs." For this, alcohol-free chlorhexidine or 2% zinc chloride mouth rinses may be less irritating for some patients. But finding the alcohol-free chlorhexidine can be problematic, and there is some loss of antimicrobial efficacy. When a patient is using any chlorhexidine product, it should be emphasized that fluoride within toothpastes can deactivate the chlorhexidine. Patients should wait 20 to 30 minutes after brushing before rinsing with the chlorhexidine.

Simply encouraging good plaque control through proper toothbrushing and actually instructing them to *avoid* commercial mouthwashes is often effective in at least minimizing possible confounding oral hygiene elements working against the therapeutic regimen. Often the patient's mucosal surfaces adjacent to the teeth and are very tender which makes it difficult to properly brush. Patients are often able to better manage a sonic type of toothbrush (as opposed to a manual toothbrush) to minimize trauma and maximize oral health. Although there is certainly movement associated with the sonic toothbrushes, these are somewhat better than the shearing action that can occur with many of the rotary-type electric toothbrushes. Manual toothbrushes are often just too difficult to control and always traumatize the adjacent mucosa. If manual toothbrushes are used, soft bristles are mandatory, and even softer bristles for sensitive patients are also available. They are often marketed with descriptors such as "supersoft for sensitive care."

A special note: When treatment is discussed in the various disease categories to follow, the reader will note the absence of some regimens with which they may be familiar. Specifically concoctions known variously as magic mouth rinse, special mouth rinse, or miracle mouth rinse will not be recommended. A quick note as to why this is omitted follows.

Many clinicians have used such rinses, perhaps even successfully. However, in my experience on numerous referrals, there is usually no place for such concoctions. The typical formulations for these prescriptions are as follows:

- Magic rinse, special rinse, and miracle rinse (all generally the same thing, may be known by other names regionally)
  - Nystatin 12,500 units/mL
  - Diphenhydramine 1.25 mg/mL
  - Hydrocortisone 0.25 mg/mL

Do these concentrations make any sense?

- Normal nystatin 100,000/mL
  - 12,500 units/mL represents an eightfold decrease
- 7.5 mg total dose of diphenhydramine is low
  - Probably acts as a topical anesthetic, not as an antihistamine
- Hydrocortisone 25 mg/mL
  - 10-fold decrease from Dexamethasone 0.5 mg/5 mL
  - 20-fold decrease from 0.1% triamcinolone acetonide

Please note the concentrations just outlined. They simply do not make any sense. If you think the patient needs steroids, use a potent enough steroid to do the work. If the patient needs an antifungal, why go with a concentration of an antifungal that is 8 times less than the mildest antifungal that we would ever prescribe? If you want a topical anesthetic effect, why would we choose diphenhydramine? If we want to use diphenhydramine, why wouldn't we just use it by itself in a more potent concentration or use viscous lidocaine if the patient is old enough? So in short, if you believe antifungals are needed, prescribe a proper antifungal. If you think they need an anti-inflammatory, prescribe a potent enough steroid to do the job. If they need some topical anesthetic, think about the potency of

at would be appropriate for the age

es or systemic steroids are used, candidal overgrowth is a common complication. In practice, it is generally useful to give forewarning to the patient about the possibility of candidal overgrowth and to alert them to what to expect. But don't empirically start antifungals on every patient. It is generally best to communicate this possibility to the patient or give a patient handout to cover this possibility. Anecdotally, candidal overgrowth probably occurs in only 25% or less of patients, and therefore antifungals are not necessary in most patients. Increasing age and immune status would predict increasing possibilities for thrush. With that said, some clinicians may prefer to go ahead and use adjunctive antifungal therapy when employing steroids.

Herpes Simplex Virus Infections



• **Figure 24-1** Primary herpes, adult case with punched-out papilla and buccal mucosa lesions.



• **Figure 24-2** Primary herpes, adult case with intact vesicle and marginal gingivitis.

through herpes type 8. Diseases caused by or associated with the herpes family include but are not limited to chicken pox, shingles, genital herpes, "cold sores," chronic fatigue syndrome, Kaposi sarcoma, lymphoproliferative diseases/lymphomas, and mononucleosis.[1-9] Herpes simplex 2 infections can also occur in the oral region. For simplicity, the oral and maxillofacial region herpetic infections (both primary and secondary) in this chapter for clinical purposes will be considered to be herpes simplex 1 because therapy and prognosis are the same for herpes simplex 2. Serum antibody conversion of patients exposed to herpes simplex 1 has decreased somewhat over the decades, at least in the Western world. Currently, in the United States, people in upper socioeconomic strata have a serum antibody conversion rate of only 50% to 60%. On the other hand, in undeveloped third world countries, the rate by adulthood may be as high as 95%.[10-15] When considering serum conversion rates, the main thing to remember is that a large number of Americans coming into your practice may indeed present with primary herpetic gingivostomatitis at *any* age.

Herpes simplex virus has been implicated in causing various immune-mediated reactions, most notably erythema multiforme.[16] Also, although secondary herpetic recurrences often create lesions, the lesions are not necessarily

and 24-2).

Clinical Features

As any oral and maxillofacial surgeon knows, the two expressions of herpes simplex 1 are in the form of primary and secondary infections.

Primary Herpetic Gingivostomatitis

In primary infections, the patients are generally children; however, as mentioned before, because of the relatively low serum antibody conversion rate in the United States, a primary infection may be diagnosed at any age. In addition, people who are immunosuppressed can have multiple recurrent episodes of primary herpetic-like lesions. In primary herpetic gingivostomatitis, the lesions can occur on any of the oral mucosal surfaces, regardless of whether they are "keratinized" or "nonkeratinized." Classically, the interdental papillae will be "punched out." Also, it is unusual for the lesions to be localized on only one type of mucosal surface or to be unilateral. Therefore, a clinical diagnosis of primary herpes should be entertained only in the presence of bilateral disease affecting both keratinized and nonkeratinized mucosa. The onset of the lesions should be rather rapid and sudden, generally over the course of 24 to 48 hours. There is often cervical lymphadenopathy as well as an elevated temperature. If lesions involve the skin, this may portend a more severe disease course than if only the oral mucosal surfaces are involved.[1,13,17-22]

Of particular note in skin lesions (whether lesions are primary or secondary): *involvement of the tip of the nose or in areas of V_1 distribution is an ophthalmologic emergency!* This presentation is known as Hutchinson sign. If present, it could portend herpetic involvement of the eye, which can result in blindness. Indeed, herpetic infections are one of the leading causes of acquired blindness in childhood.[23,24]

Both skin and oral mucosal lesions generally start out as small vesicular lesions that rapidly coalesce into irregularly shaped ulcers. The individual ulcers are often surrounded by an erythematous halo. The halo region can vary in width and erythematous nature depending on size and location. The primary outbreak can involve circumoral skin, the vermilion border, the oral mucosa, the oropharynx, and pharyngeal tonsillitis, although other surfaces are possible. The

and 24-4).



• **Figure 24-3** Recurrent herpes labialis with various stages of lesions.



• **Figure 24-4** Recurrent herpes of palate.

Secondary Herpes

On the oral mucosa, secondary herpes will uniquely involve the keratinized oral mucosal surfaces. This is in stark contrast to the distribution of aphthous type ulcers. The keratinized surfaces of the oral mucosa are the hard palate, dorsum of tongue, gingivae and lip vermilion (centered outside the wet line). In classic cases of recurrent herpes, a prodrome will present itself prior to vesicle formation. The prodrome usually starts out as a feeling of fullness, with or without tingling. Generally, within the next 24 to 48 hours, vesicles will appear. As with primary herpes, these small 1- to 3-mm vesicles will often coalesce. In recurrent herpes the lesions are often unilateral, though occasional multifocal bilateral expressions may occur. These bilateral occurrences are generally associated with some immunosuppression. Individual lesions generally last 7 to 10 days.

Reasons for recurrences are many. Triggering agents include trauma, drying, light exposure, and altered immune status. The number of Americans with a history of secondary herpes varies by report but is probably in the range of a quarter to one third of the population.[25]

Histopathology

The virus primarily reacts within the nucleus to create changes within the nuclei of the epithelial cells. This is generally observed as a chromatin pattern that is altered to create peripheralized chromatin granules with central clearing. The nuclei are often multiple, and each nucleus may also be enlarged, with the definition of the nucleolus impossible to discern. These nuclear changes have often been termed ballooning degeneration, and multinucleation is a common focal feature. The degeneration of the cells also results in loss of cohesiveness of the squamous cells. This results in free-floating acantholytic cells, commonly called Tzanck cells.

Diagnosis

The diagnosis of both primary and secondary herpes is generally clinical. The need for a biopsy is rare. Occasionally there may be some confusion between primary herpetic gingivostomatitis and erythema multiforme. Though culture can be performed in such cases, results generally take up to 48 hours. An additional complicating factor is that viral shedding can occur in people with erythema multiforme who originally had a subclinical case of primary herpetic gingivostomatitis. In acute cases the clinical acumen of the clinician will allow for proper diagnosis. The more difficult cases are those in immunosuppressed patients when lesions persist for long periods of time or do not conform to the 7- to 10-day period of immunocompetent patients. In these patients biopsy, cytology, or culture might be helpful. In some cases where there is some clinical doubt and an intact vesicle is present, puncturing of the vesicle with immediate retrieval of cells for cytologic evaluation can be helpful. However, this is usually more for curiosity than for obtaining a definitive diagnosis prior to therapy.[13,17,19]

Treatment and Prognosis

We begin with a short treatment regimen that will cover the great majority of adult patients. These treatments are rather straightforward, although many options exist. Management of the pediatric patient is more complicated and often requires consultation.

Premise #1

Topical antivirals are *not* usually a first-line therapy for secondary herpetic lesions in our clinical practice. There are some studies that show a reduction in the length of the lesions of half a day to 1 day or more, with some resultant decrease in discomfort. The literature is generally clear that topical agents help less predictably than the systemic ther-

to 1-day reduction was actually because 5% to 10% of the

patients never developed a vesicle after application of the topical agent at the prodrome. Therefore, the reduction in some reports was partially due to a small subset of patients. This appears to happen with many of these topical agents. It is possible that some patients misinterpreted what they perceived as a prodrome and would never have developed lesions. It seems prudent to use the topical agents only if the patient already knows that they are a member of that small subset of patients who generally benefit from topical agents. These topical agents are relatively expensive, and sometimes cost of the course of topical therapy is almost the same as that of the systemic therapy. If used, the general efficacy of topical agents may be as follows: penciclovir > acyclovir cream > acyclovir ointment > doconasol.[26-31]

Premise #2

Although, like the topical preparations, L-lysine may be beneficial in a subset of patients, this is not a first-line therapy. In some patients it may act best as a prophylactic agent, although scientific proof of this remains sketchy. Regardless, it must be the systemic version of L-lysine and not the topical version. The systemic version at least has the possibility of substituting into the protein synthesis of the viral replication.[32-34]

Premise #3

In primary herpetic gingivostomatitis, the major clinical problem to address will be maintenance of hydration. "Tilt tests," vascular rebound, decrease in diaper changes, skin turgor, and other methods for hydration evaluation are highly recommended in patients with primary herpetic gingivostomatitis. These methods will be further elucidated in the section on pediatric management.

Premise #4

Of the systemic medications, the a cyclovir family of drugs offer the best evidence of efficacy. Famciclovir, penciclovir, valacyclovir, and acyclovir all can alter the systemic course of the disease, whether it is primary or secondary. However, they are best given within 24 to 48 hours of prodromal onset.

Premise #5

After the 48- to 72-hour window, therapy is generally limited to managing the pain/discomfort and hydration problems the patient is experiencing.

Premise #6

Systemic medications as outlined next appear most efficacious, although valacyclovir, famciclovir, and acyclovir are very similar by class.

Systemic Agents for Herpes Simplex in the Non-immunosuppressed Patient

Cyclovir Antiviral Family

For all members of this antiviral family, use with caution in patients with renal or hepatic disease. Also consider patient's hydration status. Headache and/or nausea are dose-related side effects and may occur in about one of six patients.

Primary HSV

RX: Acyclovir 400 mg
Disp: 50 tablets
Sig: 400 mg 5 times daily for *10 days*

Recurrent HSV

RX: Acyclovir 400 mg
Disp: 25 tablets
Sig: 400 mg 5 times daily for *5 days*

Acyclovir for Herpes Labialis

Duration of pain and time to complete healing is unaffected with doses of 400 mg three times daily
Increasing dose to 400 mg five times daily decreases duration of pain by 36% and time to loss of crust by 27%
Only effective if initiated very early in recurrence
Valacyclovir is the authors' preferred drug for recurrent herpes—a prodrug of acyclovir that is 3 to 5 times more bioavailable than acyclovir
It is FDA pregnancy category B and has not been approved in prepubertal patients

Suggested prescriptions for adult immunocompetent patients follow.

Primary HSV

RX: Valacyclovir 1 g caplets
Disp: 20 caplets
Sig: 1 gram twice per day for *10 days*

Recurrent HSV Labialis

RX: Valacyclovir 1 g caplets
Disp: 6 caplets
Sig: 2 g immediately at prodrome, then 2 g more 12 hours later. Save last two caplets to use for next outbreak. (The goal is to always have an initial dose available even if the pharmacy is closed.)
RX: Famciclovir 500 mg caplets
Disp: 6 caplets
Sig: 3 caplets immediately at prodrome. Save 3 caplets to use for next outbreak. (The goal is to always have an initial dose available even if the pharmacy is closed.)

Prophylaxis for Recurrent HSV Infections (Immunocompetent Patients)

Long-term prophylaxis is indicated if patients have at least 6 or more herpetic outbreaks per year
Reassess need every 6 to 12 months
There is some concern for developing viral resistance; therefore long-term management should often be by an infectious disease specialist.

RX: Acyclovir 400 mg (Zovirax, generic)
Disp: 60 tablets

Sig: Take 1 tablet every 12 hours. Must be given in divided doses. Prophylactic doses between 400 and 1000 mg/day reduce the frequency of herpes labialis by 50% to 78%.

RX: Valacyclovir 500 mg (Valtrex)
Disp: 30 caplets
Sig: Take 1 caplet daily

This is an alternative regimen for patients with more than 9 episodes per year

It does not appear to have large advantage over acyclovir 400 mg twice daily and is more expensive

OTC: L-Lysine 500 mg Tablets

Review of clinical trials shows lysine *may* have a preventive value in doses of at least 1,000 mg/day. It is contraindicated with renal or hepatic impairment. Dietary supplements are not regulated for purity or efficacy. Topical lysine does not seem to have any predictable benefit.

Pediatric Herpes

peutic intervention is necessary. This is a key teaching point. If observed at the right time, it may be easily diagnosed as primary herpes, but intervention is not always necessary. Generally intervention is necessary if the patient becomes dehydrated or if the lesion extends out of the immediate perioral region. There are various definitions for "outside the perioral region." A good rule of thumb is that if the herpetic lesions extend past the nasolabial fold, onto the nose, or below the chin onto the inferior surface of the chin, referral to a physician is indicated. Along with dehydration, these are general signs that a patient's infection may be more sev [18,20-22,26,27,35-37]

fo

infectious disease physician.

In severe cases, the earlier that the infection is encountered and seen to pass the immediate perioral region, the more concern there should be. Referral or cooperative ther-

petic encephalitis or herpetic meningitis. Self-inoculation to involve additional sensory ganglia, especially during the initial infection, is of great concern. Keratoconjunctival extension is particularly problematic. Keratoconjunctival herpes can acutely result in blindness or possibly result in major problems later in life due to recurrences along that nerve region. Extension to involve the fingers is referred to as herpetic whitlow. Infections of the fingertip and their recurrent lesions can be very debilitating, especially in adulthood. Person-to-person spread of the viral particles is also of increased concern in these cases.[37-39]

Evaluation of infants especially and children under 6 must center on the patient's hydration status and to a lesser extent their nutritional intake. Evaluation of the hydrated state of the young child and infant is complicated because of the extreme adaptability of a young person's vascular system.

In general, assessment for dehydration is best made using skin turgor, breathing rate, and capillary refill time. Capillary refill time is best determined by pressing on the ball of the fingertip. Normal color should be established by 2 seconds; 1.5 to 2.0 seconds is borderline acceptable. Turgor is measured by pinching a small skin fold on the lateral abdominal wall at the level of the umbilicus. The fold should be promptly released and the time it takes to return to normal form measured. Clear norms are not established, and results are depicted as immediate, slightly delayed, and delayed. The clinician should test multiple "normal" children to get a feel for this reaction. Last, the respirations should be assessed from a distance, preferably as the child is in the waiting area.[40] Respiratory cutoffs that indicate elevated rates are greater than 60/min in children younger than 2 months, greater than 50/min for infants 2 to 12 months, and greater than 40 for children older than 12 months.[41]

These three tests used together are probably the best objective method for evaluating dehydration. However, experienced clinicians can observe clues for dehydration such as chalky or dry skin and by observing the general affect of the patient.

In the preschool child, the risk of meningitis and encephalitis is reduced in comparison to the infant but remain a concern.[42] This risk continues to decrease with age. In con-

primary infections, should not be underestimated. Likewise, daycare center settings are hotbeds for possible infectious outbreaks. The younger the child, the greater the chance for oral fomite transfer to occur.[37] The patient should be kept away from daycare centers as long as any open ulcers are present and generally 48 hours after these lesions have completely crusted. This is not a perfect system, because viral shedding can continue within the saliva for days or weeks afterwards and intermittently for the rest of the patient's life.

Treatment of systemic infections centers around maintenance of hydration and nutritional intake with symptomatic relief, pain management, and reduction of the patient's fever if present. Traditionally pain management with topical anesthetics has centered around coating agents. In the past, viscous lidocaine was a popular ingredient in the various mixes. It cannot be overemphasized that this has changed. Currently the use of viscous lidocaine in children less than 7 or 8 years old is contraindicated, and in some communities,

use could be considered malpractice. This is due to the toxic sensitivity associated with the viscous lidocaine and may be related as much to the patient's weight as to his or her age. In short, the patient can experience a methemoglobin anemia or cardiac arrhythmia, and without immediate intervention, multiple patients have died.[43]

Although this is a rare reaction, and use of viscous lidocaine in the dental practice is relatively common even in children under age 8, this is a changing paradigm in pediatric care, and lidocaine should be avoided at all costs. For this reason the recommended topical anesthetic coating is diphenhydramine hydrochloride 12.5 mg per 5 mL syrup mixed 1:1 with Mylanta or Kaopectate. When dispensed, the diphenhydramine generally comes in a 4-ounce (118-mL) bottle, so the total mixture may be 8 ounces (336 mL) and the patient is to rinse with 1 teaspoon every 4 hours for 2 minutes. Although the patient can swish and spit, it is also acceptable to swish and swallow. Children under age 4 often cannot swish and spit. If the child cannot rinse, the use of a cotton tipped applicator to swab the inside of the mouth is sometimes helpful. It is best to reserve the topical hesitance to use viscous lidocaine 2% solutions. Over-the-counter preparations such as Chloraseptic or Orajel may provide sufficient relief. Benzocaine has also been associated with methemoglobinemia, and some caution with its use is also advised.

In these older children over age 12, new topical coating agents such as Gelclair may be beneficial. The key aspect on when use of Gelclair is appropriate is whether the patient can faithfully expectorate or not. This is used by rinsing and spitting every 3 to 4 hours. This is a better coating agent than the previously described 50/50 mix of diphenhydramine and Mylanta, and many patients have expressed a

In most cases systemic antivirals should only be used if the infection is encountered in the first 48 to 72 hours. Antivirals should always be used whenever the primary gingival stomatitis extends past the previously mentioned perioral region. In the 48- to 72-hour window, the clinician will need to use best judgment on how the child is being affected by the infection and whether intervention is necessary.

In all pediatric dosage regimens, the normal dose of acyclovir package insert lists two studies of subjects 18 years dosages of approximately 30 mg/kg have been safely used. Valacyclovir is a prodrug of acyclovir and is eliminated the same way as acyclovir. The one complication of valacyclovir of major importance is that it is contraindicated in patients who are immunocompromised. This limitation has generally been for patients who are on the bone marrow transplant ward or have HIV infection. Although not necessarily replicated, one study did show a higher incidence of thrombocytopenic purpura in these specific patients.[44,45]

In general, valacyclovir is approved for use for herpes labialis only in children 12 or over. Off-label for herpes labialis and primary herpes stomatitis in children younger than 12 is best considered in consultation. There are no suspensions of valacyclovir, although the caplets could be reduced to powder and then compounded into a 25 mg/mL or 50 mg/mL suspension. Some compounding pharmacies have used Orasweet as a flavoring agent to counter the very bitter taste of valacyclovir, but if this is a concern about the patient's ability to swallow a tablet, then probably the patient should receive the acyclovir rather than the valacyclovir. Acyclovir comes in varying strengths. The suspension is a 200 mg/5 mL suspension. The appropriate volume should be dispensed. The directions should read to take the appropriate numbers of milliliters, which should be calculated at 20 mg/kg. This will be taken in four divided doses with a maximum dosage of 50 mg/kg per day.[27,36,46]

Herpes gingival stomatitis remains a complicated disease to control. It is extremely common, with 60% of the population having been exposed to the virus by age 21. There are many factors in the recurrence rate as well as the exposure causes, but the most important aspect of treatment is a proper diagnosis and assessment of the patient to decide whether systemic therapy or symptomatic therapy is the best approach for that particular patient.

Herpangina

Herpangina is a disease that generally occurs in epidemic fashion throughout the world. Some of the most well-documented epidemics occurred throughout areas of eastern Asia, most notably Taiwan and Japan.[47-52] Although as well as acute lymphonodular pharyngitis. These diseases probably vary only in clinical phenotypic presentation and have great overlap in the actual virus that acts as a causative agent in each.[53]

The enteroviruses are complicated by historical inconsistencies in nomenclature as well as evolvement of the classification system itself. The enteroviruses are a subset of the picornavirus family. As such they are, of course, RNA viruses. The Coxsackie virus species were first described by a laboratory in Coxsackie, New York. The echovirus species were first named because investigators believed that the

members of this family were not pathogenic in humans. As such, the "echo" in echovirus originally stood for enteric cytopathogenic human orphan virus. However, time has shown us that they are indeed pathogenic. Other branches of the enterovirus are rhinovirus, poliovirus, aphthovirus, simply as numbered enteroviruses beginning with enterovirus 68 and now including members or proposals through enterovirus 73. Of these recently described enteroviruses, enterovirus 71 is particular important clinically, as will be discussed later.[54]

ruses are numbered 1 to 34 although two numbers are not represented, for a total of 32 (Figure 24-5).

Clinical Findings

measles, rubella, and roseola, to name a few. When lesions involve the oral mucosa, the term is *enanthema*. In the past it was feasible to memorize for test-taking purposes which enteroviruses could possibly cause herpangina. Now with 21 different members of the family having been associated with herpangina, it is best to just think in generalities. The pangina. Enterovirus 71 can cause severe symptoms and has resulted in a number of reported deaths. Complications

In these more severe cases, the fever tends to be more elevated for a longer period of time and general presentation of the symptoms is also more severe. Thus the clinician is warned that in cases of hand, foot, and mouth disease; herpangina; or lymphonodular pharyngitis, if the systemic symptoms appear to be severe, further delineation of the viral subtype common presentation the diagnosis is made through simple clinical observation. With that said, serologic and culture tests may be performed.

The oral ulcers of herpangina are one of the first presenting signs of the disease. The oral ulcers generally present as only a handful of vesicles. The vesicles are often fragile and surrounded by a small region of erythematous change. The individual vesicles are generally small and on the order of 2 to 4 mm. The ulcers are almost always confined to the soft palate, faucial pillars, and tonsillar bed of the palatine tonsils. In the clinical setting of hand, foot, and mouth disease, the vesicles are not limited to the posterior portion of the oral cavity and may occur on other anterior surfaces. In addition, there are often more numerous vesicles, on the order of 15 to 25. In addition to the oral mucosa, in hand, foot, and mouth disease, either the hands or feet should also be involved.[53]

Following the oral vesicles, flulike symptoms will quickly ensue over and persist over several days. Though these systemic symptoms resolve, if they are severe or long lasting, again consideration of enterovirus 71 complications could be very important. Flulike symptom examples include cough, malaise, lymphadenopathy, nausea, rhinorrhea, muscle ache, and diarrhea.

Histopathology

As reported by Neville and colleagues, the histopathologic features, if biopsied, are nonspecific, with disruption of the epithelium. Inflammatory cells as well as intracellular and intercellular edema are also noted. The vesicle itself tends to be intraepithelial.[53]

Treatment

As mentioned previously, the disease is generally self-limiting, with no need for therapeutic intervention. Supportive care for the various symptoms is often necessary. These generally center around use of antipyretics, antiemetics, antidiarrheals, and analgesics. As with herpes, assessment of the patient's hydration status is important, and proper instructions for hydration should be established. Referral to an infectious disease consultant, pulmonary specialist, pediatrician, or primary care provider may be necessary in many cases. Isolation of the patient to prevent epidemic spread of the disease is necessary. Transmission can be by respiratory droplet or saliva in the acute phase, though the oral-fecal route of transmission is probably the most common method in epidemics. Therefore good hygiene practices and isolation of the patient are advised. Epidemics are most common in crowded



• **Figure 24-5** Herpangina lesion on the palate of an adult patient.

conditions, with the summer months and early fall being the most common times of year.[47,54,60-64]

Lichen Planus

Lichen planus is a relatively common inflammatory mucocutaneous disease with a distinct morphology affecting approximately 1% of the general population. It commonly affects middle-aged adults with a slight predominance in women.[65] Oral lesions can be seen alone or in combination with cutaneous disease. In contrast to skin involvement, oral lichen planus tends to be more persistent and refractory to treatment. Whether oral lichen planus constitutes a premalignant lesion remains controversial. A relatively low incidence of malignant change in oral lichen planus has been reported in some serial studies and is usually confined to patients with less common erosive or atrophic forms of oral lichen planus[64,66,67] (Figure 24-6).

Etiology

The pathophysiology of lichen planus is not fully understood. It is thought to be an autoimmune-mediated disease triggered by antigenic alterations on the cell surface of the basal layer of the epithelium. Langerhans cells act as antigen-presenting cells to T lymphocytes, stimulating their proliferation, with subsequent epithelial changes in a mechanism similar to that for allergic contact dermatitis.[68] Although many cases of lichen planus are idiopathic, some cases are linked to the use of medications, dental restorative materials, and, in some populations, infection with the hepatitis C virus.[69-72] The association of certain medications and oral lichenoid lesions has been well described.[73-76]

Clinical Features

Cutaneous lesions seen in lichen planus include violaceous polygonal papules and plaques. Upon closer examination, a delicate reticulated pattern of white scale known as Wickam striae is observed. Some have described the classic cutaneous lesions of lichen planus as pruritic, polygonal, planar (flat-topped), purple papules and plaques. The flexor surfaces of extremities are commonly involved and dystrophic changes in the nail beds can sometimes be seen. Lesions may erupt on surfaces exposed to trauma in a response known as the Koebner phenomenon.[65] This tissue response to trauma can also be seen in oral lichen planus.[77]

Reticular and erosive lichen planus are the two main forms of oral lichen planus, and it is not uncommon for patients to present with a combination of both forms. Reticulated oral lichen planus is the most common form and generally presents as asymptomatic delicate interlacing white striae found in a bilateral distribution. The buccal mucosa is the most common site of involvement, followed by the tongue, gingiva, and lips. An uncommon variant of reticulated oral lichen planus, known as plaque-type lichen planus, is sometimes found on the dorsal surface of the tongue and on the buccal mucosa and can clinically resemble leukoplakia.[64,78-80]

Erosive oral lichen planus presents as irregular centrally ulcerated atrophic and erythematous lesions, often with fine white lacelike striae at the periphery. Erosive lichen planus tends to be a multifocal process, with the degree and morphology of the erythematous and ulcerated lesions changing over time. Bullous and atrophic oral lichen planus are believed to represent variants of erosive lichen planus. Typically, symptomatic patients with erosive lichen planus complain of a painful burning sensation that can be debilitating and exacerbated by diet. Erosive lichen planus is sometimes limited to the gingiva and can present clinically as a painful desquamative gingivitis.[81-83] In some patients, a characteristic erosive gingival and genital involvement has been described in a syndrome complex referred to as the vulvovaginal-gingival syndrome.[84]

Histopathology and Laboratory Studies

Although the clinical presentation of reticulated oral lichen planus can sometimes be characteristic for the disease, biopsy is recommended to confirm the clinical diagnosis and, in erosive lichen planus,[64,85] can be essential in excluding other inflammatory and neoplastic diseases.[81] The histopathologic features of idiopathic lichen planus are characteristic, but not connective tissue interface with vacuolar degeneration of the basilar epithelial layer. Varying degrees of hyperkeratosis of the surface epithelium is seen and the spinous layer can be hyperplastic, ulcerated or atrophic depending on the clinical form of oral lichen planus. Scattered degenerating keratinocytes or colloid bodies can sometimes be found within the deeper epithelial layers. Direct immunofluorescence studies can be helpful in differentiating erosive lichen planus from other vesiculobullous diseases.[86] Skin patch testing is sometimes performed in suspected cases of lichenoid contact lesions.[87] Hepatitis C testing is recommended for newly diagnosed cases of oral lichen planus in some populations.[71,72,88]



• **Figure 24-6** Erosive lichen planus of the buccal mucosa.

Treatment

Patients with asymptomatic reticular lichen planus usually require no additional treatment other than periodic clinical follow-up once the diagnosis is established. Topical and systemic corticosteroids used alone or in combination are the most widely accepted therapy for erosive and symptomatic cases of oral lichen planus. Short-term use of systemic corticosteroids can be effective in the initial control of the disease or in cases refractory to topical therapy, but their inherent toxicity limits their use in the treatment of chronic disease. Other innovative therapies used in recalcitrant cases include the use of tacrolimus, retinoids, and immunosuppressant and cytotoxic drug therapy. Concomitant antifungal therapy is useful in reducing the incidence of candidiasis during corticosteroid and other immunosuppressant therapy.[77,85,89-91]

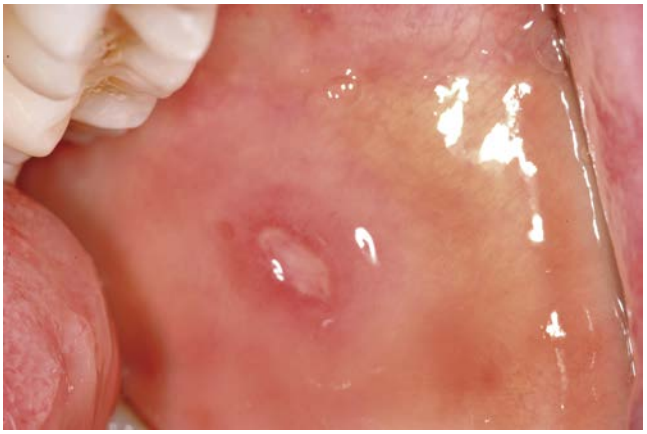
Aphthous Stomatitis

Recurrent oral aphthous ulcerations are often a frustrating, lifelong curse for patients and practitioners alike, as no single treatment modality is totally curative and no clearly defined etiology has been identified. Commonly referred to as canker sores, these painful oral ulcers present in three clinical variations: minor, major, and herpetiform lesions. In most studies, 20% of the population is affected, with a higher prevalence seen in whites younger than 40 years of age and with females outnumbering males.[92] In addition to genetic and familial factors, environmental and stress-related influences have been implicated as a cause for recurrent aphthous stomatitis.

Many factors are believed to initiate aphthous stomatitis, including medications such as Cox-2 inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), and antidepressants.[93] Anxiety or stress, hormonal changes, allergies, nutritional deficiencies, and antigen exposure that produces a hypersensitivity reaction as a result of minor trauma or bacterial infiltration are all factors in the development of aphthous lesions.[93-95] A tendency toward a familial inheritance pattern has also been observed[96] (Figure 24-7).

Clinical Features

The vast majority of patients, 80%, present with minor aphthous ulcers that do not reach a size greater than 1 cm and affect the nonkeratinized areas of the oral mucosa, specifically the buccal and labial mucosa, ventral tongue, anterior floor of the mouth, and vestibular fold. The lesional process starts with an initial painful sensation to a localized mucosal area that becomes erythematous and progresses to a quickly disappearing blister. This blistered area will then transform to an ulceration with an intense burning sensation that is surrounded by an erythematous halo and covered by a thin yellow-white layer of fibrin. These painful ulcers present as solitary lesions, although multiple sites can be involved at one time. These lesions heal spontaneously in 10 to 14 days.[93]



• **Figure 24-7** Aphthous minor ulcer of the mucosa.

The variant major aphthous ulcer, also termed periadenitis mucosa necrotica recurrens or Sutton disease, is seen in less than 10% of cases and are larger ulcers reaching 1 cm or greater in diameter. These ulcers show an irregular area of circumscription as well as a raised erythematous border surrounding a crater-like depression. These ulcers can form singularly, in multiples, and have been found to coalesce, forming larger lesions. Weeks or months may be necessary for these lesions to heal, and scarring may also be a resultant component.[94,95,97]

The third variant, herpetiform aphthae, are so named for their resemblance to recurrent herpes simplex, although no correlation has been noted between the processes. Recurrent herpes simplex typically affects the keratinized mucosa, whereas recurrent aphthous stomatitis avoids the keratinized mucosa. Successive crops of dozens of painful, pinpoint ulcers 1 to 3 mm in size appearing on the nonkeratinized mucosa characterize this variant.[93] These lesions heal in 7 to 10 days and normally without scarring.

Clinicians should remember that oral aphthae could also represent an initial sign of a more ominous systemic malady, in which case deeper investigation or a referral opinion should be sought. The ulcers of recurrent aphthous stomatitis should be distinguished from herpetic gingivostomatitis, herpes simplex, erythema multiforme, pemphigus, pemphigoid, Reiter syndrome, and Crohn disease.[98]

Histopathology

Histopathologic features are non-contributory. Biopsy is rarely indicated except possibly in lesions that persist for longer than 3 weeks. If biopsied, the features will be that of a nonspecific ulcer.

Treatment

Treatment, which is usually palliative, centers around the pain experienced with the ulcers and their subsequent

effect on daily life of the patient. A reduction in the number and duration of outbreaks and the promotion of healing are necessary treatment goals. Use of a twice-daily rinse of 0.12% chlorhexidine rinse (Peridex, Periogard)[97,99] as well as topical corticosteroids such as 1% triamcinolone paste (Adcortyl or Kenalog in Orobase)[94] have been shown to enhance healing. Topical gels of 0.05% fluocinonide, 0.05% clobetasol, or 0.05% amlexanox[98] have also proven beneficial in the treatment of mild cases of recurrent ulcers. Data demonstrating greater efficacy of systemic steroids rather than topical corticosteroids are lacking and there is a risk of adverse side effects such as hypertension and hyperglycemia. Therefore systemic use of steroids should be usually considered in consultation with verification of clinical diagnosis.[97]

Low-energy laser treatment has also been shown to be effective against recurrent aphthous ulcerations for immediate relief of pain and a possible reduction in the healing period. A CO_2 laser at a wavelength of 10.6 nm, continuous wave at 1.0-1.5 and placed on the ulcer in a circular motion over Elmex gel for 5 seconds, proved effective for immediate pain relief.[100,101] Additionally, a Nd:YAG laser with a 320-µm fiber optic cable set to 2 W and 20 pulses per second was shown to achieve long-lasting pain relief in recurrent lesions.[101]

Behçet Syndrome

Behçet disease has been known since ancient times. A description by Hippocrates reportedly describes the disease process well. In the 1930s, a Turkish dermatologist by the name of Behçet delineated the disease for the modern clinician. It should not be unexpected that a Turkish dermatologist and an ancient Greek physician saw enough of these patients to think that the disease warranted delineation. The disease itself is generally considered most likely in patients from countries along the ancient Silk Road that ran from China to the Mediterranean and then finally by ship to Greece and Italy. This is the famous trade route that Marco Polo is credited with opening. Though not 100%, people with HLA-B51 tend to be more prone to the disease. The anecdotal assumption is that the genetics associated with this HLA genotype successfully traveled the route along with tea, silk, and other goods.[102-107]

Once thought to be a spondyloarthropathy, today it is considered a vasculitis.[108] Other co-factors include immunodysregulation, antigenic reactions, and alteration in healing and repair, as well as possible viral or bacterial co-factors.[109,110] The disease is most important to oral surgeons in that these patients often present as aphthous ulcer patients who are very difficult to manage with standard therapies. In addition, the oral manifestations of the disease are usually the first sign of the disease. In considering Behçet's disease in a differential diagnosis list, it must be remembered that the other diagnostic signs of the disease may not be present during its first stages.

Clinical Features

Though the disease can present in childhood,[111,112] most patients first present as young adults or in middle age. As reported by Marshall, in Turkey the incidence may be as high as 420 per 100,000 people, with Japan having approximately 20 per 100,000 and the United States having 1 to 2 cases per 100,000.[113] The disease is extremely uncommon among African Americans and has not been reported in Native Americans. The actual time needed to establish the diagnosis of Behçet disease is often quite lengthy and difficult. This is due to the irregular presentation patterns as well as the often progressive and intermittent nature of the disease process. Patients tend to have exacerbations with varying lengths of remission.[102,103]

The aphthous-like ulcers present in Behçet disease can take up any of the three standard forms of aphthae. These include herpetiform aphthae, minor aphthae, and major aphthae. In general, the aphthae tend to come in crops rather than as single lesions. In addition, the lesions are often in areas not usually associated with aphthous ulcers. (As reviewed in the aphthous section, the most common locations for aphthae are the ventral surfaces of the tongue, floor of mouth, buccal mucosae, and labial mucosae.) In Behçet disease the ulcers are often in the oral pharynx, with the soft palate and tonsillar pillars being common sites of involvement. The ulcers themselves, though they may be small and herpetiform as previously mentioned, are often rather jagged along the periphery rather than being the uniform circular form of standard aphthous ulcers. The central area of ulceration is crater from as in normal aphthae though the surrounding erythematous halo is often more extensive than standard aphthae.[114-116] In this author's experience (JWH), the most common presentation for Behçet patient is that the ulcers also tend to last somewhat longer than the standard 10 to 14 days of regular aphthae. Thus, they tend to act more like aphthous major with multiple lesions and lengthened duration.

Systemically, Behçet disease can affect multiple parts of the body, although in contrast to most vasculitides, the kidneys usually seem to escape.[117] The clinician should remember that, like the oral lesions, the disease in other body regions tends to go through remissions and exacerbations with a variable periodicity.

As alluded to earlier, the actual process of establishing a definitive diagnosis of Behçet disease gets quite complicated because of variability and stage of presentation. In the international classification outlined next, recurrent aphthous ulcers are not just a major criterion but actually a mandatory criterion. For this reason other classification systems have evolved that allow for the possibility of not having oral involvement. It seems unlikely that an oral surgeon would

be called on to diagnose Behçet in a patient with no oral symptomatology or signs. For this reason only the international classification system is given. The interested reader could delve further into other classification systems.[17-20]

International Criteria for Classification of Behçet Disease

Obligatory criterion:

- Recurrent oral ulcerations
  - Including: minor aphthous, major aphthous or herpetiform ulceration. (Ulcers should be observed by a physician/dentist or judged to be reliable by patient history)
  - Ulcers should recur at least three times in one 12-month period

Plus two of the following:

- Recurrent genital ulceration
  - Recurrent genital aphthous ulceration or scarring—especially in males. (Ulcers should be observed by a physician or judged to be reliable by patient history)
- Eye lesions
  - Including: anterior uveitis, posterior uveitis, cells in vitreous on slit lamp examination ***or*** retinal vasculitis as observed by ophthalmologist
- Skin lesions
  - Including: erythema-nodosum-like lesions (observed or judged to be reliable by patient history), pseudofolliculitis, papulopustular lesions ***or*** acneiform nodules consistent with Behçet observed by a physician and in post-adolescent patients not receiving corticosteroids
- Positive pathergy test
  - Defined as an erythematous papule, >2 mm, at the prick site 48 h after the application of a sterile needle, 20-22 gauge, which obliquely penetrated avascular skin to a depth of 5 mm, and is read by a physician at 48 hours[17]

The other systems involved besides the eyes, skin, and genitalia include the joints, central nervous system, pulmonary system, and gastrointestinal systems.[118-120] When trying to confirm the diagnosis in an evolving clinical setting, consultation with multiple physicians is likely. Dermatologists, rheumatologists, and ophthalmologists are likely consultant sources. Some clinicians may not be familiar with what has been called the pathergy test. In this test a 20- to 22-gauge sterile needle is inserted into the forearm to a depth of 5 mm. The area is observed 48 hours after the needle penetration, and if there is a papule larger than 2 mm at the site of the needle stick, the test is said to be positive. The problems with this test include that in some populations there is less likelihood of positivity. For instance, positivity in Americans would be rather unlikely, whereas in a person of Turkish origin, a positive pathergy would be much more likely.[121] There also appears to be some difference based on how well the area overlying the needle stick was cleaned before the test. If the area is cleansed first, the rate of positivity goes down! If examined histopathologically, the area shows neutrophilic infiltrates with some perivascular aggregates. For the oral health care provider, the bottom line is that, if Behçet disease is considered in the differential diagnosis because of some suspicion of systemic involvement, appropriate referral should be accomplished.

Some of the more unusual complications associated with Behçet include central nervous system involvement. Such involvement can be severe, with psychoses, meningitis, and convulsions having been reported. However, the neurologic problems are generally a very late-stage presentation.[110,122-124] On the other hand, ocular involvement with the possibility of subsequent blindness does reveal the need for a thorough ophthalmologic consult in cases where Behçet disease is likely.[110,125]

A note must be made here concerning the need for referrals. Aphthous stomatitis is a very common disease. It certainly is not necessary to refer all cases aphthous with recurrences in people having more than three recurrences in 1 year to a specialist for further evaluation. The need for referral should be based on eliciting positive responses to skin, genital, ocular, or joint signs or symptoms.

Histopathology

Usually the oral ulcerations are similar enough to aphthous ulcers that a biopsy is not considered necessary and therefore not performed. In the few cases where a biopsy has been taken, the ulceration is nonspecific. Some deep myovasculitis may be seen, but this is also seen in other types of oral ulcerative diseases and is nonspecific. The only time biopsy is usually performed is in the case of longstanding lesions (longer than 2 to 3 weeks) and where possible granulomatosis disease is needed.[126]

Treatment

As mentioned previously, the main treatment paradigm associated with Behçet is to get adequate referral to a variety of health care providers and try to establish a definitive diagnosis. The actual treatment of the oral ulcerations centers around the same therapeutic regimes as used for aphthous stomatitis.

Reactive Arthritis (Reiter Syndrome)

Reiter syndrome, also referred to as reactive arthritis, is a rheumatic disease belonging to a category of seronegative spondyloarthropathies. Use of the designation *Reiter syndrome* is becoming more and more discouraged because of Dr. Reiter's involvement with the Nazi party during World War II.[127] A peripheral arthritis with characteristic extra-articular manifestations is the hallmark of this disease. In its classic description, a triad of arthritis, conjunctivitis, and non-gonococcal urethritis is seen, although this constellation of features is not found in all cases of Reiter syndrome. Reactive arthritis is an acute arthritis resulting from an

extra-articular infection that is usually venereal or enteric in origin. Peak onset is seen between 15 and 35 years of age with a significant male predilection seen in postvenereal disease.[128-131]

Etiology

Reactive arthritis is an autoimmune phenomenon triggered following urogenital or enteric infections generally seen in genetically susceptible individuals expressing the human leukocyte antigen (HLA)-B27.[132,133] Enteric bacterial infections associated with reactive arthritis include *Salmonella, Shigella, Campylobacter,* and *Yersinia* species, whereas *Chlamydia trachomatis* accounts for most of the reported postvenereal cases.[134] Additionally, an association of reactive arthritis and human immunodeficiency virus infection has been described.[135]

Clinical Features

Clinical symptoms of reactive arthritis usually begin 1 to 4 weeks after infection.[128,130,131,136,137] Peripheral articular involvement lasting longer than 1 month is a key symptom. Articular swelling, pain, and involvement of soft tissue similar to rheumatoid arthritis is seen, but unlike rheumatoid arthritis, it is asymmetrical in distribution and commonly oligoarticular. Lower back pain secondary to sacroiliitis is a common clinical feature. Inflammation of tendinous insertions of bone, particularly the Achilles and patellar insertions, can be a distinctive feature of reactive arthritis. Dactylitis in the form of "sausage digits" can also be observed.[128,129,138]

A spectrum of mucocutaneous lesions is associated with reactive arthritis. Balanitis circinata—shallow erythematous ulcerations at the meatus and on the glans penis—are sometimes seen. Painful hyperkeratotic plaques with an erythematous base known as keratoderma blennorrhagica can be seen on plantar and palmar surfaces. Although oral lesions are reported in less than 20% of cases, oral findings include serpiginous plaques on the tongue resembling geographic tongue, as well as diffuse erythematous papules and ulcerations of the oral mucosa.[128,129,139]

A urethritis with a nonpurulent discharge is a common finding. Prostatitis, cervicitis, and vulvovaginitis are other urogenital manifestations that may be encountered. Conjunctivitis is a common ocular finding and usually manifests before the onset of arthritis.[128-130]

Histopathology and Laboratory Studies

No single laboratory or imaging finding is diagnostic of reactive arthritis, as the diagnosis is based on clinical data. Although a positive HLA-B27 result is not specific of the disease, haplotyping can be used to diagnose reactive arthritis and can be particularly helpful in atypical cases lacking extra-articular findings. Documentation of bacterial infection through microbiologic examination of smears and cultures of the urethral or cervical discharge must be considered. Tests for *Chlamydia* species should be performed in suspected cases of reactive arthritis, and HIV testing should be considered. Tests for rheumatoid factor and antinuclear antibodies are negative.[128-130] Early in the course of the disease, radiographic findings are generally unremarkable. In chronic severe disease, periosteal reaction at tendon insertion sites can often be observed, as well as sacroiliitis and syndesmophyte formation.[140] Hematoxylin and eosin findings are non-contributory and reveal only a nonspecific ulcer.

Treatment

Curative treatment for reactive arthritis does not presently exist. Most patients have a self-limited clinical course and require only symptomatic and supportive care. NSAIDs are the mainstay in treating the musculoskeletal symptoms seen in reactive arthritis. Occasionally, intra-articular injections of corticosteroids or systemic steroids are prescribed in patients with poor response to NSAIDs. Cytotoxic therapy using methotrexate or azathioprine has been proposed in treating severe cases of reactive arthritis. Urethritis is usually treated with tetracyclines or broad-spectrum antibiotics because of the frequency of coexisting infections; however, the treatment of urethritis has not been shown to modify the clinical course of reactive arthritis.[128-130] The disease may be associated with chronic recurrent ocular inflammation that requires systemic therapy to control the inflammation and to prevent progressive visual loss.[141] The clinical course of reactive arthritis may be prolonged, with acute exacerbations and remissions occurring for weeks to months. An estimated recurrence rate of approximately 15% has been reported.[131,142]

Pemphigoid

lial blistering lesions involving mucosal surfaces and/or the skin. Mucous membrane pemphigoid is the preferred term when the condition is primarily mucosal. This condition has been commonly referred to in medical and dental literature as benign mucous membrane pemphigoid, cicatricial pemphigoid, oral pemphigoid, and ocular pemphigoid, which are not completely accurate terms. When the condition primarily involves the skin, bullous pemphigoid is the preferred term.

Mucous membrane pemphigoid affects 2 to 5 patients per 100,000 with more than 85% showing oral involvement. The most commonly affected areas are the oral cavity (90%) and eyes (65%), with the nose, nasopharynx, larynx, and skin (20%-30%) involved less often.[143] It affects women approximately 2:1 over men and presents at a mean age of onset over 50 years of age.[144,145] Although cases have been reported, the disease is extremely infrequent in children.[146]

Bullous pemphigoid, the most common autoimmune blistering disease, is considered a separate entity from mucous membrane pemphigoid.[147] Men are affected at the same rate as women, and both are generally elderly adults when the disease presents. The disease has been characterized as self-limiting but can last from a few months up to 10 years with considerable morbidity.[147] Lesions are located predominantly on flexural surfaces of the extremities, lower abdomen, groin, axillae, and less commonly, the head and neck areas.[148-150]

It has been suggested that an environmental factor, specifically a virus or drug, combined with genetic susceptibility leads to the development of autoantibodies to an antigen within the mucosal or skin basement membrane zone.[145] The use of ibuprofen, amoxicillin, captopril, clonidine, furosemide, and indomethacin, among others, has been reported to induce lesions of pemphigoid.[151] There is a defect in immune regulation, and autoantibodies, usually IgG but also IgA, are formed against components of the basement membrane zone. Numerous inflammatory mediators entice acute and chronic inflammatory cells to the basement membrane zone, where enzymes aid in the separation of the epithelium from the underlying tissues[152] (Figures 24-8 and 24-9).

Clinical Features

Mucous membrane pemphigoid is characterized by the development of a recurring vesicle or bulla which evolves to become an erosion or ulcer affecting the mucous membranes of the body. Healing may result in scarring of the affected area. The mucous membranes lining the mouth, specifically the gingiva, buccal mucosa, and palate, are most commonly affected,[145] with the initial sign being generalized erythema and edema, which can then progress to sloughing of the mucosal epithelium in large sheets or strands. Often the gingiva will appear quite erythematous and tender, leading to sloughing, referred to as desquamative gingivitis. Patients are symptomatic and have a chief complaint of oral pain due to mucosal ulceration and desquamation. Lesions of the tongue, soft palate, uvula, and lips prove difficult to treat because of repeated trauma.[145]

Extraoral involvement of mucous membrane pemphigoid includes inflammation or erosions forming on the conjunctiva. Ocular symptoms may include burning or grittiness in the eye, increased pressure within the eye (glaucoma), abnormal inward turning of the eyelid (entropion), and abnormal inward turning of the eyelashes (trichiasis), potentially causing irritation of the corneal surface. Symblepharon formation is a major concern for corneal damage and resultant scarring, which can lead to blindness. A symblepharon is formed by scarring and adhesion of the bulbar to the palpebral conjunctiva.[151]

Bullous pemphigoid consists of taut blisters that arise on normal or erythematous skin, often with pronounced pruritus. Pruritic urticarial plaques that progressively become more edematous, often for a long period of time before bulla formation, have been noted in two thirds of patients.[147] The bullae then rupture to leave an eroded base that does not extend further and are therefore Nikolsky sign negative. In contrast to mucous membrane pemphigoid, oral lesions are uncommon at presentation but can be seen as the disease progresses in 10% to 40% of patients.[153-155]



• **Figure 24-8** Pemphigoid ulcers of the gingiva.



• **Figure 24-9** Pemphigoid with Nikolsky sign.

Histopathology

When a patient is suspected of having either mucous membrane pemphigoid or pemphigus vulgaris, a biopsy specimen for histopathologic examination and direct immunofluorescence (DIF) is indicated. Histopathologic examination shows a subepithelial cleft whereby intact surface epithelium is separating from the underlying supporting tissues. Immunofluorescence, which demonstrates the degradation of the vital tissue components, should be used for DIF. In 80% to 100% of patients, DIF will show a linear

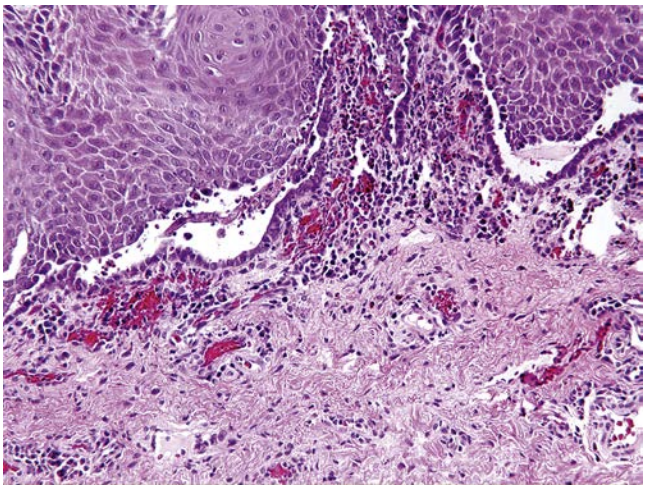
band at the basement membrane zone with IgG and C3 as well as IgA to a significantly lesser degree.[145,156] Studies using indirect immunofluorescent techniques on a patient's serum have had unpredictable results in mucous membrane pemphigoid patients, although IgG basement membrane zone antibodies are seen in 70% of patients with bullous pemphigoid.[156]

Treatment

Patients with mild oral disease, including desquamative gingivitis, can be treated twice daily with gel-based topical corticosteroids such as 0.05% fluocinonide, clobetasol propionate, or betamethasone dipropionate[137,142,145,152,157-159] that should be in contact with the tissues for at least 30 minutes. An adhesive base such as Orabase or vacuum-formed latex trays holding the gel or ointment in contact with the tissues are suggested modalities. Both bullous pemphigoid and mucous membrane pemphigoid patients benefit from topical corticosteroid applications as well as intralesional corticosteroid injections of triamcinolone acetonide 5 to 10 mg/mL every 2 to 4 weeks. Intralesional treatment has shown prompt healing for stubborn lesions. Daily application of topical tacrolimus 0.1% showed resolution and prevented progression of lesions.[160] Dapsone has been considered the drug of choice, although it does not come without adverse side effects such as hemolysis, methemoglobinemia, and hepatotoxicity. The usual effective dose is between 100 and 200 mg/day. Minocycline in dosages between 50 and 100 mg/day has been shown to be effective through its anti-inflammatory and anticollagenase activity but also is known for inducing nausea, photosensitivity, and hyperpigmentation.[152,161] Azathioprine, 1 to 2 mg/kg/day, or cyclophosphamide, 0.5 to 5 mg/kg/day, can be used to treat these diseases, but neither is usually sufficient alone, and side effects such as bone marrow suppression are possible.[146] Their use is in a steroid-sparing role, although initial treatment usually includes concomitant prednisone dosing of at least 40 mg/day. An isolated case of stubborn mucous membrane pemphigoid showed rapid resolution following treatment with infliximab at a dosage of 5 mg/kg at 2 and 6 weeks with maintenance doses every 8 weeks.[162]

Pemphigus

phigus erythematosus, and paraneoplastic pemphigus—although pemphigus vulgaris, vegetans, and paraneoplastic pemphigus are the only forms where oral cavity involvement is common. Paraneoplastic pemphigus has been characterized as a separate disease process due to an underlying lymphoproliferative neoplasm.[163] Pemphigus affects the skin and oral mucosa but also the mucosa of the nose, conjunctiva, esophagus, pharynx, and larynx.[164] The vast majority of



• **Figure 24-10** Photomicrograph of pemphigus.

cases, 90%, present as pemphigus vulgaris, whereas 7% present with pemphigus foliaceus.[165] Incidence rates vary from country to country, but one to six cases per million people per year is the norm.[166] Women equal men in incidence rates with the fifth decade being the mean age of presentation. Ashkenazi Jews and persons of Mediterranean origin have been shown to be especially at risk for pemphigus.[167] As pemphigus vulgaris exhibits an initial mucosal manifestation before cutaneous aspects, the dentist is of paramount importance for initial diagnosis.

Keratinocytes of the skin and mucosa are anchored to the underlying connective tissue as well as one another through multiple mechanisms that include desmosomes. In pemphigus, an autoimmune process disrupts this attachment whereby immunoglobulin G (IgG) but occasionally IgA, IgM, and complement protein C3 are directed against structural proteins desmoglein 1 and 3, leading to epithelial breakdown[163,168] known as acantholysis. Desmoglein 1 is found throughout all layers of the skin but is only minimally present in mucous membranes, whereas desmoglein 3 is found in the two or three deepest layers of the epidermis and is predominantly expressed throughout mucous membranes.[168] As a result, some patients develop mucosal lesions without skin blisters due to circulating antibodies against desmoglein 3 and low titers against desmoglein 1. The preserved function of desmoglein 1 in the skin prevents the development of cutaneous lesions while impaired desmoglein 3 function causes acantholysis in the oral cavity.[168]

Various drugs can act as triggers for the formation of bullae and include penicillamine, rifampicin, and angiotensin-converting enzyme (ACE) inhibitors such as captopril.[164] Other factors can exacerbate pemphigus, such as dental work, radiographs, exposure to sun, stress, and trauma[163] (Figure 24-10).

Clinical Features

Pemphigus vulgaris is the most common form of pemphigus and runs a chronic course with 80% of cases originating

in the oral cavity[163,169] causing fragile blisters which rupture to result in irregularly arranged surface erosions and ulcerations which are quite painful. The palate, buccal mucosa, labial mucosa, gingiva, and ventral tongue are the most common presenting intraoral sites. The lesions of pemphigus vulgaris are slow to heal if, at all. Therefore, with persistent lesions in which viral, bacterial, and fungal causes can be ruled out, pemphigus vulgaris should be considered. Within 6 months of an initial diagnosis of pemphigus vulgaris, 99% of cases also show cutaneous involvement, mainly of the scalp, face, and upper torso[163,169] whereby flaccid blisters filled with a clear fluid arise to leave an eroded base once they are ruptured.

For patients with lesions suspicious for pemphigus vulgaris, a clinical procedure can be performed on normal-appearing gingiva or skin near an existing lesion whereby firm rubbing pressure is exerted which elicits bulla formation. This is termed a positive Nikolsky sign and is highly suggestive for pemphigus, but it is not specific for this diagnosis and may be absent entirely.

Like pemphigus vulgaris, in more than half of cases, pemphigus vegetans initially shows oral lesions months before the formation of cutaneous lesions, although all cases eventually manifest with oral lesions.[152,170] The groin and axilla are also common clinical locations. This rare variant of pemphigus vulgaris is characterized initially by pustules (Hallopeau type) or flaccid bullous lesions that transform into erosions (Neumann type). These pustules or bullae subsequently develop into hyperpigmented vegetative plaques with pustules and hypertrophic granulation tissue at the periphery.[152] An additional characteristic feature of pemphigus vegetans is a cerebriform tongue characterized by a pattern of sulci and gyri on the dorsal surface. Patients with the Hallopeau type have a relatively benign disease with a prolonged remission period, whereas patients with the Neumann type have a course similar to that of pemphigus vulgaris.[171]

Histopathology and Laboratory Findings

As the differential is large and varying, including lichen planus, pemphigoid, epidermolysis bullosa, linear IgA disease, lupus erythematosus, and graft-versus-host disease, among others, additional testing might be required. A biopsy immersed in 10% neutral buffered formalin for routine histologic examination is of paramount diagnostic utility, but DIF of the tissue received in a medium such as Michel solution that does not allow degradation of the vital tissue components is an important adjunct tool. Immunoglobulins, complement, and fibrin are preserved in Michel solution, which is a transport medium that also maintains isotonicity and a pH of 7.0 to 7.2. An assay of the patient's serum can also be performed using indirect immunofluorescence studies in a search for circulating autoantibodies. Immunofluorescence will show a classic "fishnet" pattern within the epithelium. On hematoxylin and eosin staining, the split will be above the basement membrane, with acantholytic "Tzanck" cells being a common feature focally.

Treatment

The goal of treatment is control of the immediate disease activity with continued maintenance at the lowest drug levels possible to prevent new lesions. Although topical corticosteroid application may suffice for a while, oral prednisone at 20 to 40 mg/day initially and escalating to 120 mg/day or more is the universal approach until disease activity is controlled. Long-term use of potent steroids may have deleterious effects, including mucosal atrophy and irritation, secondary candidiasis, poor wound healing, hypertension, hyperglycemia, adrenal suppression, osteoporosis, weight gain, fat redistribution, and increased risk of infection.[172-176]

Plasmapheresis in conjunction with cytotoxic drugs such as azathioprine or cyclophosphamide is effective at decreasing circulating concentrations of pathogenic pemphigus antibodies, but this method is increasingly being replaced by administration of intravenous immunoglobulin to achieve the same result.[177] Additional drugs used as adjuvants to reduce the dose of corticosteroid therapy include immunosuppressants such as cyclosporine and methotrexate, anti-inflammatory drugs such as dapsone and colchicine, and antimalarials such as hydroxychloroquine. Mycophenolate mofetil, a drug used for prevention of rejection in renal allogeneic transplants, has also been shown to provide effective treatment through B-lymphocyte suppression, all with minimal side effects.[176,177]

Linear IgA Disease

Linear IgA disease is an uncommon autoimmune vesiculobullous disease that can involve both cutaneous and mucosal surfaces. Linear IgA disease is characterized by subepidermal blistering with a linear homogenous deposition of IgA antibodies along the basement membrane zone as seen in direct immunofluorescence studies.[178] Originally considered a form of dermatitis herpetiformis, linear IgA disease is now considered a distinct entity.[179,180] Linear IgA disease has a bimodal age of onset with a slight female predilection and usually presents before 5 years of age in children and after 30 years of age in adults.[181,182] In children the disease has been referred to as *chronic bullous dermatosis of childhood*.[182]

Etiology

Idiopathic linear IgA disease is caused by a linear deposition of IgA antibodies at the basement membrane leading to neutrophil chemotaxis and complement activation, which causes a lack of adhesion at the dermal-epidermal interface that eventuates in blister formation. Different target antigens at the dermal-epidermal junction have been described in linear IgA disease, and the mechanism

of the loss of self-tolerance to these target antigens is unknown.[183]

Drug-induced linear IgA disease has been well documented. Although the list of implicated medications continues to grow, historically vancomycin has been a major

Linear IgA disease has been reported in association with various infectious and neoplastic diseases, but their causal role in stimulating linear IgA disease has yet to be defined.[185] Unlike dermatitis herpetiformis, a gluten-sensitive enteropathy is generally not associated with linear IgA disease.[181,186]

Clinical Features

annular or herpetiform configurations resembling a *cluster of jewels* and are highly characteristic of the disease. In children the lesions are typically found on the lower abdomen and around the perineum; in adults the lesions are typically found on the trunk and on the extensor surfaces of limbs.[181,182] Ocular involvement in the form of symblepharon formation from the scarring of ruptured conjunctival bullae can occur.[187]

Oral lesions have been reported in more than 50% of cases and can sometimes dominate the clinical presentation. Oral manifestations of linear IgA disease can precede cutaneous involvement, thereby complicating the clinical diagnosis. Oral ulcerations and erosions resulting from ruptured intraoral vesicles and bullae are a common oral manifestation and can be a source of significant morbidity in patients with linear IgA disease. In contrast to cutaneous lesions, mucosal lesions usually heal with scarring. The gingival and buccal mucosa is frequently involved. When the gingiva is involved, it frequently will manifest clinically as a desquamative gingivitis. An erosive cheilitis is seen when the lip vermilion is involved.[184,188-194]

Histopathology and Laboratory Studies

disease, as clinically linear IgA disease exhibits a phenotype that resembles or overlaps other vesiculobullous diseases.[179,189,195] Direct immunofluorescence of perilesional and adjacent clinically normal tissue will show a homogenous linear deposition of IgA antibodies at the basement membrane zone. A linear deposition of C_3 may also be seen, and a subset of patients with linear IgA disease will exhibit both IgA and IgG deposition at the basement membrane zone.[178,180,183,188,194] Approximately 30% to 50% of patients with linear IgA disease will demonstrate circulating serum antibodies on indirect immunofluorescence studies, but these circulating antibody titers are typically low.[179,196] Tzanck smears of bullae fluid may be helpful to rule out a herpes viral infection.

Treatment

Linear IgA disease is a chronic disease characterized by periods of exacerbation and remission. Consultation with dermatology and ophthalmology is important in the ultimate clinical management of patients with linear IgA disease. Most cases respond to dapsone or sulfapyridine; however, oral lesions can prove to be more persistent and difficult to clear. A combination of dapsone and prednisone may help in controlling mucosal disease.[189,190,194,195,197]

Epidermolysis Bullosa

ever, the clinical aspects of the various diseases also carry

phic varieties. Some clinical types have yet to be defined genetically. In addition, there is an autoimmune-mediated category called epidermolysis bullosa acquisita.[198-203] This

better

within

the epithelium. This is unique among the varieties of epidermolysis bullosa. The genetic defect associated with epidermolysis bullosa simplex relate to genes coding for keratins

or by clinical picture. The signs and symptoms associated with the simplex varieties are rather mild compared to the other varieties.[201]

In the hemidesmosomal category and with the other varieties, the splitting will occur at the basement membrane.

molysis bullosa is generally a somewhat more severe form than the simplex. Genetic defects have to do with type XVII collagen, integrin a6β4, and pectin.[200]

In the junctional varieties the genetic defect is in lamin a3, e3, and gamma 2. The Herlitz type is particularly devastating and often lethal in the neonatal period. There is still a non-Herlitz type of junction epidermolysis bullosa subtype, and this type does often allow for life into adulthood.[200]

In the dystrophic category, the defect is in the *production* of type VII collagen. There is some variability in the severity of the clinical disease, which may be accounted for by the differing chromosomal defects affecting type VII collagen production.

Simplex, hemidesmosomal, and dystrophic categories have both autosomal dominant and autosomal recessive inheritance patterns. If separated from the hemidesmosomal designation, the junctional variety is only transmitted by [208]

be
disorder that is acquired much later in life than the typi-

loss of attachment at the base of the membrane and can result in severe signs and symptoms.[209]

Clinical Features

In the simplex variety, the symptoms are less severe, and thus patients may be diagnosed somewhat later in life. The classical junctional variety of the disease comes in two different varieties. One is termed the Herlitz type and the other the non-Herlitz form. Both of these are autosomal recessive. The Herlitz type is often lethal within the first year of life. The non-Herlitz form is milder and patients may

the patients with longer life span, scarring at points of contact is not unusual. Often the scarring is so severe as to result in loss of eyelashes, fingernail dystrophy, focal alopecia with scarring, eyelash and oral mucosal ulceration, and gingival attachment loss. One of the most characteristic deformities has been termed the "mitten" deformity and is the consequence of sequential loss of digits and may progress to loss of the entire hand or foot. In the dystrophic types of epidermolysis bullosa, the disease is not as life threatening as the Herlitz type of junctional epidermolysis bullosa. That is not to say that the disease cannot be disabling and often cause severe problems with significant scarring and loss of function.[210-214]

Oral mucosa involvement is generally seen as gingival erythema and recession. Loss of gingival attachment may progress, with resultant tooth mobility and tooth loss. There may be some scarring in the buccal mucosal vestibule with resulting loss of vestibular height.[212-215]

Histopathology

studies will not be helpful. However, in the epidermolysis bullosa acquisita cases, immunofluorescence will be positive. Various immunoglobulins and complement can be seen in epidermolysis bullosa acquisita patients. If performed, the immunofluorescence pattern is linear and very similar to findings in cicatricial pemphigoid. However, the immunofluorescence may not be seen on both sides of the split. In epidermolysis bullosa acquisita, the immunofluorescent pattern may be more prominent on the connective tissue side.[25]

Treatment and Prognosis

The main dental problems associated with these patients have to do with gingival trauma secondary to mastication and oral hygiene. A soft food diet and minimization of oral trauma secondary to oral hygiene should be stressed. Plaque can be particularly irritating to the gingival surfaces. Therefore there is the quandary of balancing the trauma secondary to oral hygiene procedures with the plaque buildup if oral hygiene is not properly performed. This is often a fine line that is difficult to consistently control. In addition, enamel defects may be severe enough to necessitate coronal coverage.[199,213,216-222]

The dental practitioner should avoid trauma to the mucosal surfaces as much as possible. If the patient becomes edentulous, wearing standard dentures may be problematic due to the pressure and shearing affect of the dentures.[215] There has been one successful report of the use of dental implant–supported prostheses in patients with epidermolysis bullosa.[223] Our clinical experiences have also shown implants to be possible.

Several clinical notes are important. First and foremost is that if crown and bridge procedures are going to be performed, leaving the margins "high and dry" seems to be much preferred. The irritation associated with subgingival margins has been seen to result in increased irritation and rapid gingival attachment loss. Also of possible concern is use of gingival packing material, which may be problematic in these patients. The clinician should also be aware of possible air emphysemas in these patients. This would be caused by high-speed air-driven handpieces. These handpieces can also create widespread positive Nikolsky sign due to the air pressure generated by the handpieces and dissecting through the tissues. Although this may not be avoidable, awareness of the problem may decrease the effect.

Other preventive dental regimens should also be instituted. Proper fluoridation should be provided to these patients to minimize dental caries and therefore the need for dental care. There have also been increased reports of squamous cell carcinoma of the skin in patients with the recessive dystrophic form of the disease. The dental practitioner should strive to achieve the least traumatic methods of dental health care delivery possible. This would include lubrication of the lips and perioral tissues and use of the rubber dam whenever practical.[25]

In the epidermolysis bullosa acquisita form, immunemodulating and anti-inflammatory agents may be used in the oral cavity. These include but are not limited to steroid rinses, tacrolimus, pimecrolimus, dapsone, and

cyclosporine. In the future, gene therapy may be appropriate for some of these diseases; of particular current interest are those dystrophic types associated with a single defect and type VII collagen.[204,208,224-227]

Erythema Multiforme

Erythema multiforme is an acute self-limiting hypersensitivity reaction of variable severity that is characterized by targetoid skin eruptions with or without mucous membrane involvement. Once considered a disease spectrum that included Stevens-Johnson syndrome and toxic epidermal necrolysis, erythema multiforme is now considered by many [228-230]

cutaneous surfaces alone or in combination with mucous membranes.[231,232] Erythema multiforme affects males more often than females and is seen over a wide age range, with a peak incidence in the second through fourth decades of life.[233]

Etiology

Although the exact pathophysiology of erythema multiforme is not completely understood, it appears to involve a cell-mediated hypersensitivity reaction triggered by a variety of stimuli including viruses, bacteria, or drugs.[228-230,232,233] Herpes simplex virus is the most commonly described triggering agent, accounting for over 50% of cases.[228,229,234,235] *Mycoplasma pneumoniae* is another commonly reported etiology, especially in children. In many cases, a triggering stimulus cannot be elucidated. Although vaccine- and drug-related erythema multiforme have been reported, drugs are a more common triggering agent for Stevens-Johnson syndrome and toxic epidermal necrolysis.[228] Recurrent cases of erythema multiforme are often secondary to herpes simplex virus reactivation, even when the viral reactivation may be subclinical.[235]

Clinical Features

Mild prodromal symptoms consisting of fever, malaise, headache, and joint pain can be found in some cases of erythema multiforme and herald the onset of skin lesions. Cutaneous lesions present as sudden-onset, symmetrically distributed, red to dusky edematous macules or papules that spread peripherally and can fuse into patches. The lesions favor palmar and plantar surfaces, extensor surfaces of extremities, and the face. Characteristic targetoid or iris lesions consisting of concentric circular erythematous rings are commonly found on distal extremities.[228,230,233,236] The oral cavity is commonly involved when mucous membranes are affected. Oral lesions begin as erythematous patches that coalesce into diffuse shallow ulcerations and erosions. A necrotic pseudomembranous exudate covers the ulcerated mucosa that may mimic candidiasis. Hemorrhagic crusting of the lip vermilion is not uncommon.[232-235] In contrast to cutaneous lesions, the diffuse ulcerations in the oral cavity are painful, and patients can become dehydrated because of lack of fluid intake.[198,200,232,234] In the absence of skin lesions, the mucosal lesion of erythema multiforme can present a diagnostic challenge.[232,234,237-240]

Histopathology and Laboratory Studies

No specific laboratory tests are currently available for the diagnosis of erythema multiforme, and the diagnosis is usually driven by the clinical presentation. However, ancillary laboratory studies can be helpful in the management of these patients. In severe cases, complete blood count usually reveals moderate leukocytosis with atypical lymphocytes. Electrolyte values may be abnormal with severe skin and mucous membrane involvement, and these values are useful to guide volume and electrolyte replacement therapy. The sedimentation rate is usually elevated but is nonspecific. Cultures are indicated in severe cases where secondary infection is a concern and should be obtained from blood, sputum, and mucosal lesions. Herpes simplex virus antigens can sometimes be detected by immunofluorescence studies. Biopsy of skin lesions shows mononuclear perivascular infiltrates and edema with subepidermal bullae formation with necrosis of overlying keratinocytes. Direct and indirect immunofluorescence studies of biopsy material are not diagnostically useful but may be important to exclude other vesiculobullous diseases.[233,234,236,241]

Treatment

Most cases of erythema multiforme are self-limiting, with lesions subsequently resolving within 2 to 3 weeks. Supportive and palliative care using analgesics, soothing mouth rinses, and electrolyte replacement therapy when indicated are appropriate. Antibiotic therapy is initiated when clinical evidence of secondary infection exists.[233,241] The use of corticosteroids in the treatment of erythema multiforme is controversial, and they should be used only with caution.[230,242] Prophylactic oral acyclovir or valacyclovir is effective in decreasing the frequency and severity of recurrent herpes and herpes-associated erythema multiforme.[230,243]

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25

Osteomyelitis and Osteoradionecrosis

BRIAN ALPERT, GEORGE KUSHNER

Osteomyelitis

Osteomyelitis and osteoradionecrosis are diseases of bone characterized by necrosis of the bone secondary to bacterial invasion. In the case of osteomyelitis, infectious agents overcome host resistance and progressively involve the marrow, compromising blood supply—resulting in necrosis and ultimate sequestration. For osteoradionecrosis (ORN), the bone is already compromised by a radiation-induced avascular necrosis. With its diminished endosteal and periosteal blood supply, it easily succumbs to this bacterial insult and its sequelae. In the case of osteomyelitis, the endosteal and periosteal blood supply at least began intact. In ORN, it may already be fatally compromised.

Classification

can be defined by type of infected organism involved: luetic, tubercular, actinomycotic, staphylococcal, fungal, herpetic, and so on. We find Hudson's classification[5] most useful, as he defines it by acute or chronic and identifies the various types within this classification. A detailed description of the various types of osteomyelitis and their presentations is beyond the scope of this chapter; we will leave this to the various pathology texts and monographs.

Diagnosis

Classic acute osteomyelitis with swelling, fever, adenopathy, leukocytosis, loose teeth, paresthesia, multiple draining fistulas, and so forth is today a third-world presentation rarely seen in developed countries, presumably because of antibiotic use and more optimal dental care. Such cases were classically managed with removal of the etiology—the infected teeth—and exposure of and decortication of the jaw (sequestrectomy and saucerization) via extraoral approach to allow vascular periosteum to contact the exposed marrow. This was followed by irrigations and antibiotic therapy.

In the developed world, the presentation is more subtle but still with swelling, pain, temperature elevation, adenopathy, leukocytosis, and drainage. The hallmark symptom to distinguish osteomyelitis from long-term or chronic dentoalveolar abscess is often paresthesia. Although at one time this was fairly rare, the incidence is certainly on the rise, presumably due to antibiotic resistance or immune deficiency or suppression. At any rate, we are seeing more now. All too commonly, the scenario of toothache, root canal treatment, extraction, infected socket followed by management with multiple debridements, IV antibiotic regimens, drains, and so on, with continued progressive involvement of more bone, intensifying paresthesia, and, ultimately, pathologic fracture is seen. That is the point when patients are seen in a tertiary medical center.

Microbiology

Osteomyelitis of the long bones has been generally associated with a staphylococcal etiology.[6] Osteomyelitis of the jaw is more likely due to streptococcal and anaerobic bacteria.[7] Most of these infections are mixed and often difficult to define because of contamination from oral flora. Gram stains are often useful in showing various bacterial types as well as the presence of fungi. Proper culture and sensitivities and bone batteries on excised sequestra, although useful in theory, are often unrewarding in actual use.

Laboratory Studies

Laboratory studies would obviously reveal leukocytosis and elevation of the erythrocyte sedimentation rate as well as C-reactive protein. These, of course, are indicators of inflammation and are hardly specific for osteomyelitis; yet they can be used to follow progression of the disease.[8] The absence of these indicators when it seems that all the

hallmarks of osteomyelitis are present should suggest the possibility of neoplasm.

Imaging

Today modern imaging has further defined both what we see and what we do with computed tomographic (CT) images demonstrating circumferential involvement not amenable to the traditional sequestrectomy and saucerization and lateral decortication but requiring full-thickness resection (Figure 25-1).

Panoramic imaging can give an idea, but changes in the bone with a classic "moth-eaten" appearance are late and only reflect demineralization of the cortex. The CT scan will give a much truer picture circumferentially of the cortical erosion so that one can more truly see the extent of the disease. Nuclear medicine in the form of technetium-99, gallium-67, or indium-111 can be used to highlight areas of increased bony activity as well as differentiate areas of infection from other etiologies. Magnetic resonance imaging is said to be useful in identifying earlier stages of osteomyelitis by noting the loss of marrow signal.[9]

Management

Over the past almost 50 years, management has involved sequestrectomy and saucerization—opening up the involved area, removing the sequestrum, and decorticating to allow periosteal and vascular contact in addition to intravenous antibiotics appropriate for the culture and sensitivity.[5] If, as was all too often the case, this was unsuccessful and led to pathologic fracture, skeletal pin fixation was used to maintain mandibular continuity. For a time it was fashionable to place antibiotic-impregnated beads into the defect.[10,11] Reconstruction was accomplished following resolution of the infectio

th

at the time of resection. The current management involves resection with inferior alveolar nerve preservation and primary reconstruction with either autogenous bone graft or tissue engineering, a treatment that has dramatically shortened the course of this condition (Figures 25-3, 25-4, and 25-5).[8]

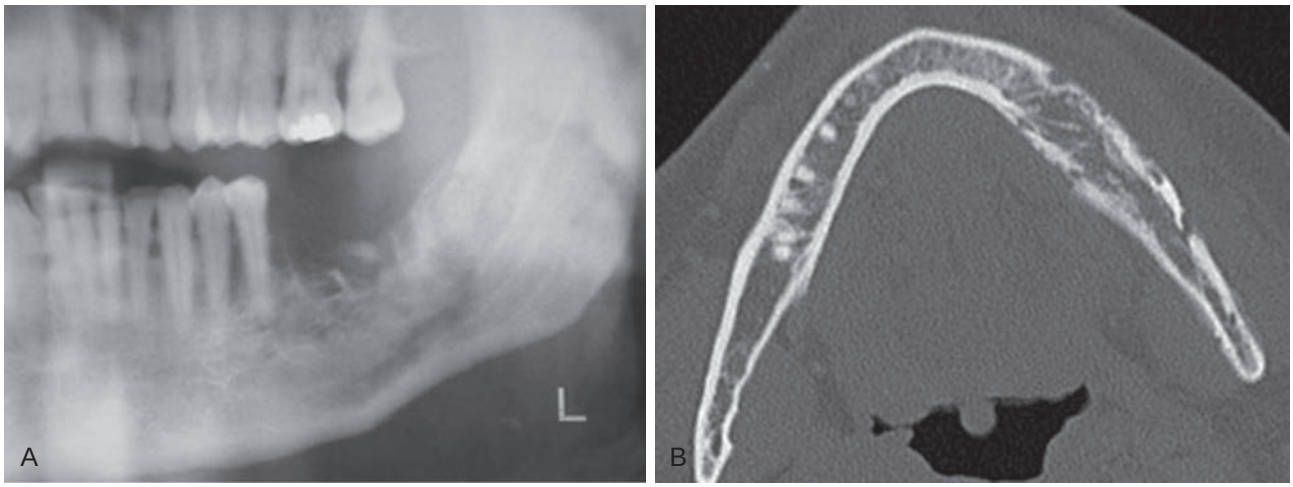
Medical Management

In almost 50 years in tertiary care medical centers, we have never seen a case of mandibular osteomyelitis managed successfully with antibiotics either alone or with "minor surgery." It just does not happen. Perhaps if we were to see condylar osteomyelitis in a neonate—a classic presentation in the first half of the 20th century—antibiotics alone might suffice, but not in adults and certainly not when there is nonvital bone needing to be debrided. This is not to say that chronic disease states such as diabetes should not be optimized. Likewise, antibiotic therapy is certainly a useful adjunct.

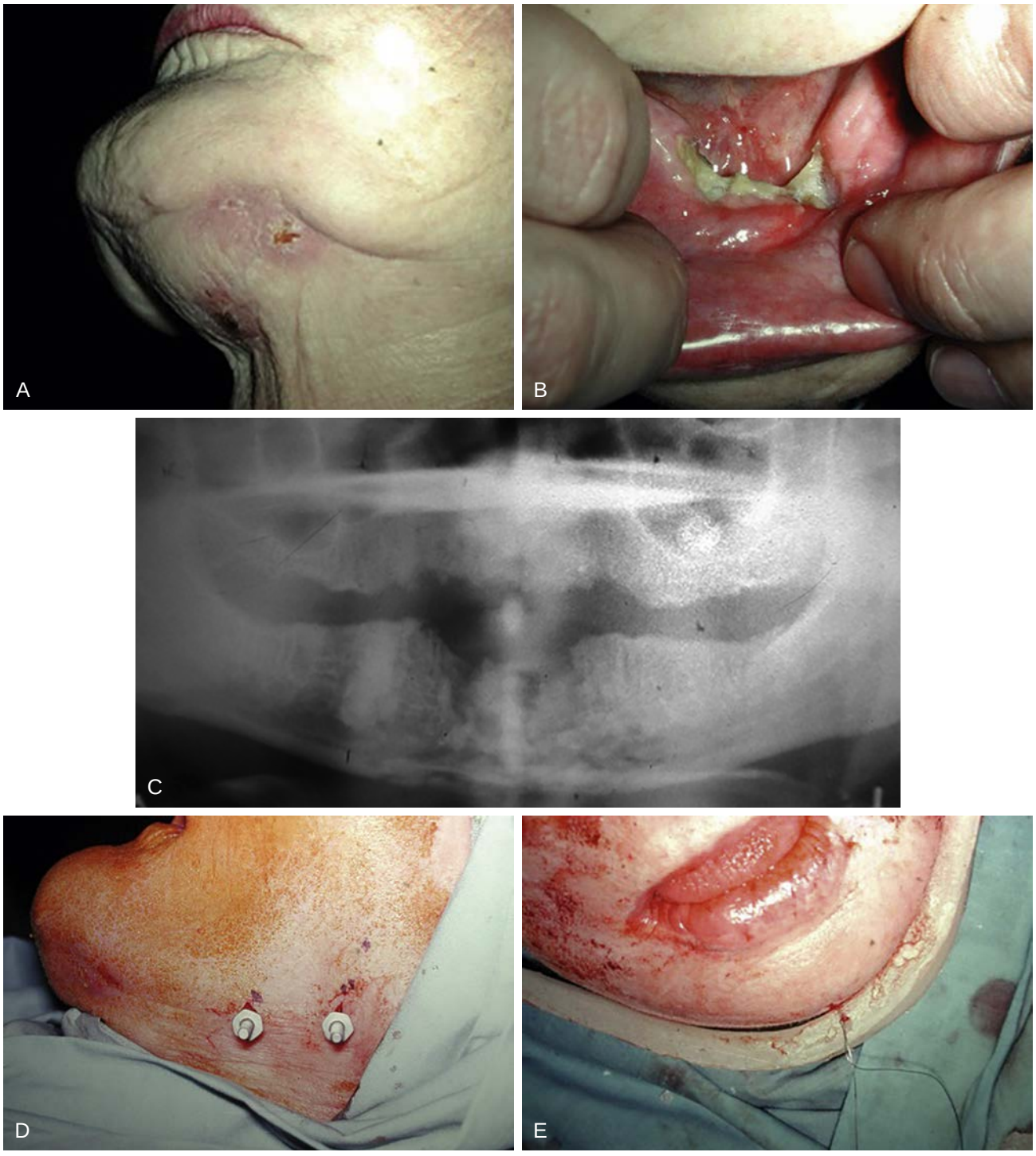
Discussion and Personal Perspectives

There are some fundamental truths regarding osteomyelitis and its management.

1. The presenting symptoms and appearance of osteomyelitis and cancer—primary or metastatic—is often indistinguishable (radiographic appearance, paresthesia, etc.). Tumor must be ruled out.[8]
2. Bone devitalized by infection, the hallmark of which is the "moth-eaten" appearance, must be resorbed by the body (a long process), exfoliated, or surgically removed.
3. The soft tissue is not infected, the bone is—thus there is no reason to delay definitive reconstruction.
4. The resected area does not require tumor resection protocol (in continuity), so there is no reason not to attempt preservation of the inferior alveolar neurovascular bundle by resecting the dead bone in pieces. Although the patient may already suffer from paresthesia, a hallmark symptom of mandibular osteomyelitis, one should still try to facilitate recovery of sensation.

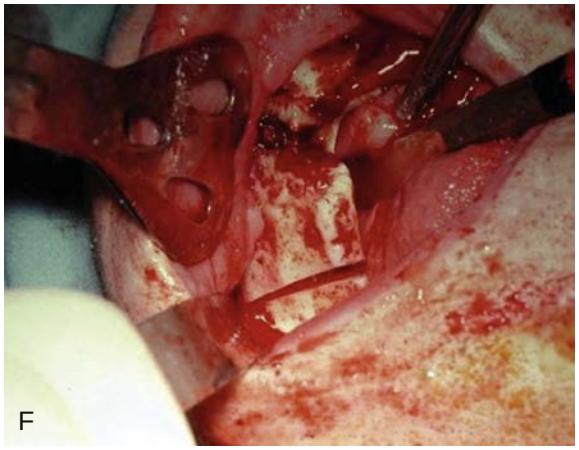


• **Figure 25-1** Panoramic **(A)** and computed tomography (CT) **(B)** images of same jaw demonstrating circumferential involvement seen on CT but not appreciated on panoramic radiograph.

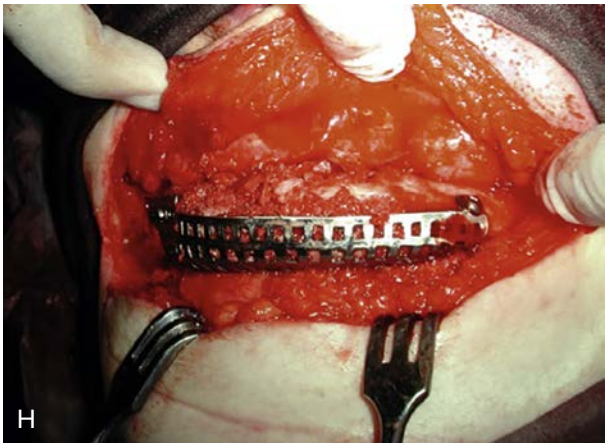


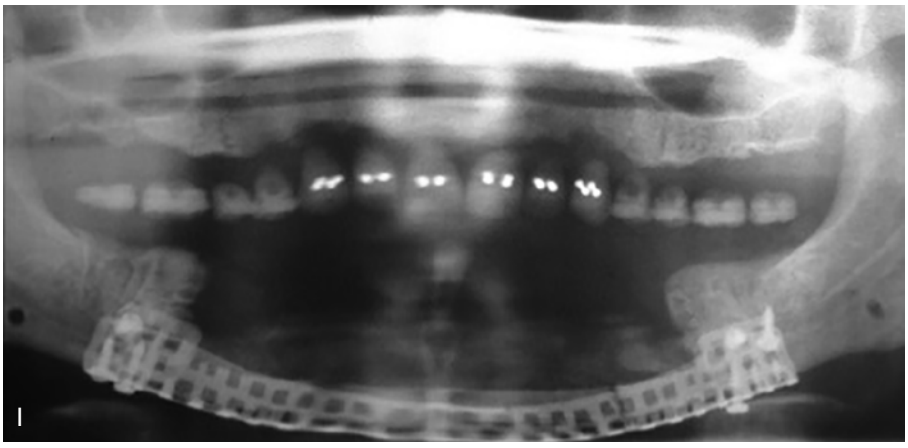
• **Figure 25-2** 55-year-old woman referred by her dentist for treatment of osteomyelitis. She had her remaining six anterior teeth removed 6 weeks prior, followed by exposed bone, multiple debridements, and recently, draining extraoral fistulae **(A)** and obvious nonviable bone **(B).** Panoramic radiograph **(C)** revealed extensive osteomyelitis. Resection of the involved bone was planned. Skeletal pins **(D)** and an external acrylic bar **(E)** were applied. The anterior mandible was resected via an intraoral approach

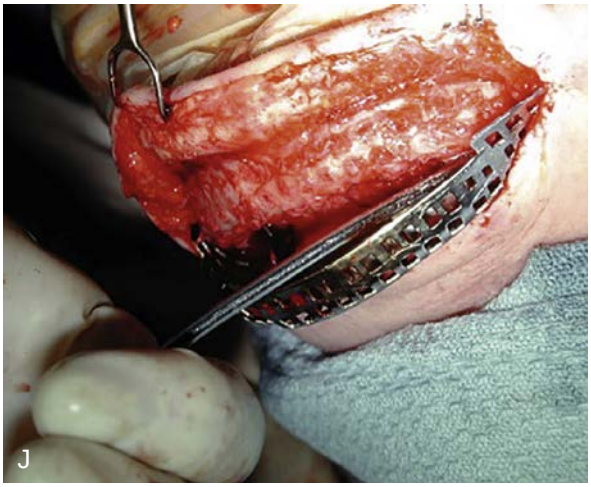
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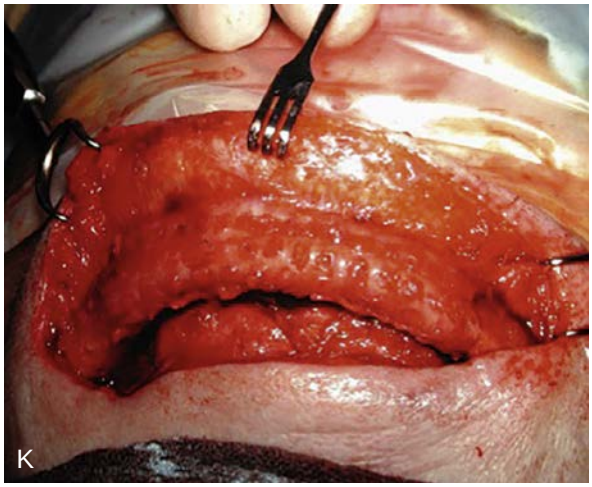




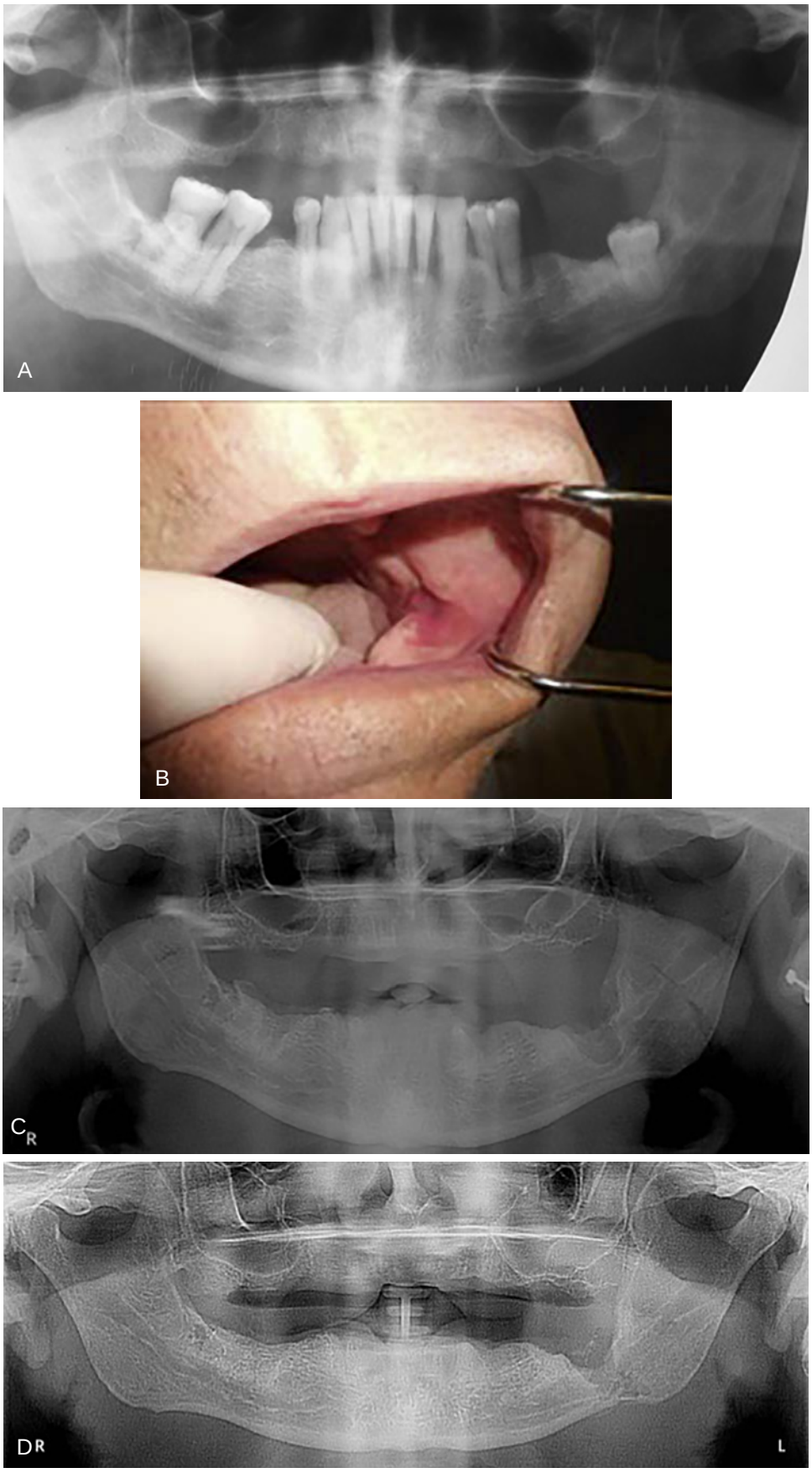






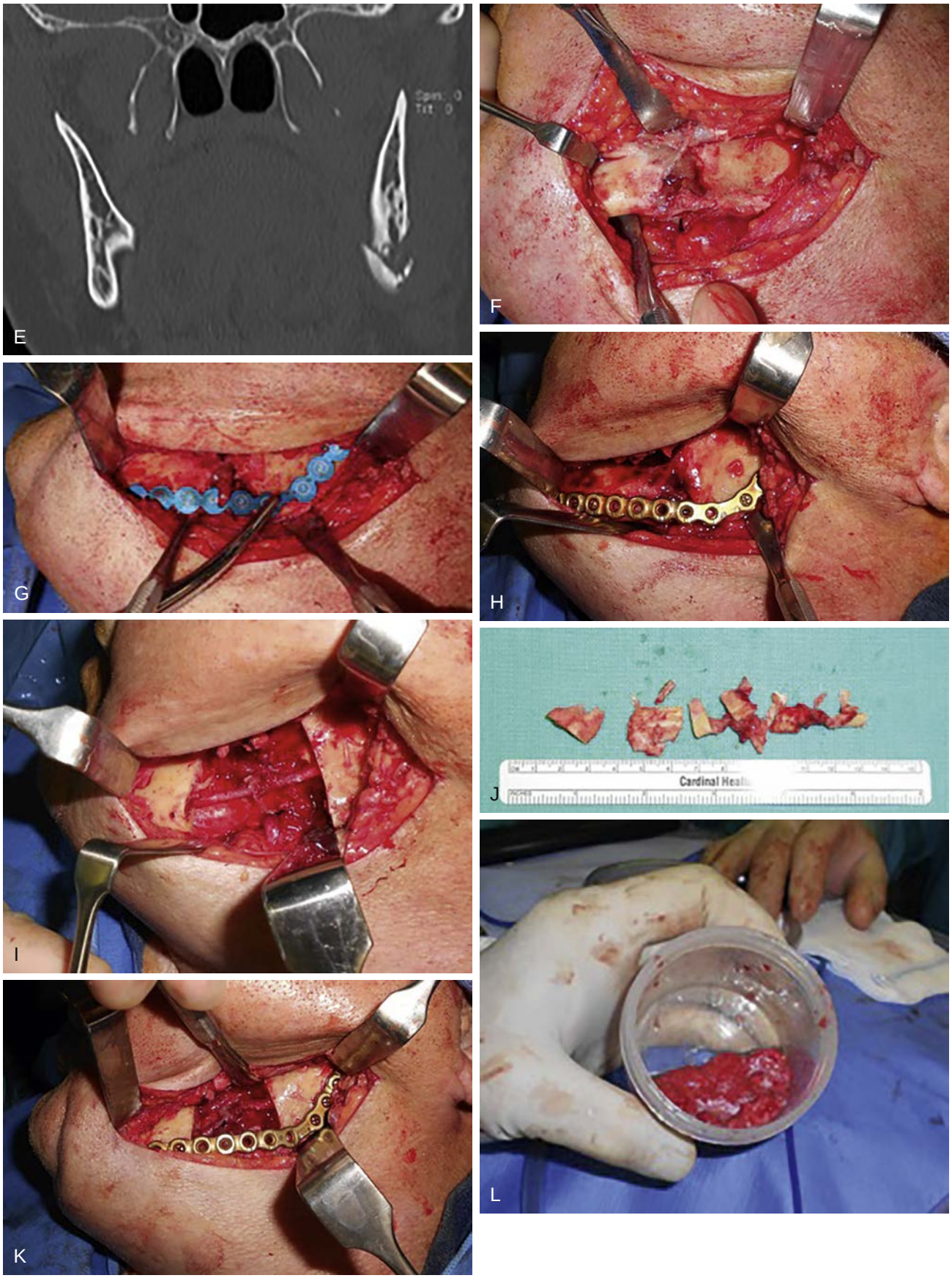


• **Figure 25-2, cont'd (F, G).** Following healing of the intraoral wound and closure of fistulae, the anterior mandible was reconstructed with "mesh and mush" via an extraoral approach **(H).** Panoramic radiograph **(I)** demonstrates the reconstruction. Four months later, the mesh was removed **(J)** leaving a nicely reconstructed anterior mandible **(K).**



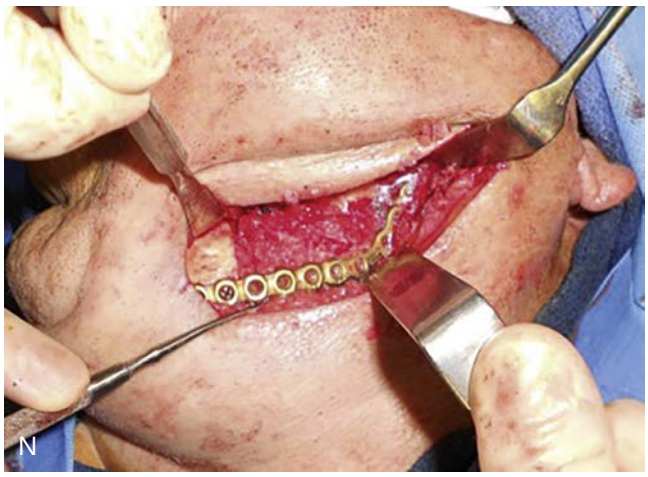
• **Figure 25-3** Panoramic image of a 73-year-old man prior to removal of remaining teeth in preparation for a denture **(A).** The #17 wound failed to heal **(B)** leading to progressive bone loss and pathologic fracture **(C-E).** Extraoral exposure

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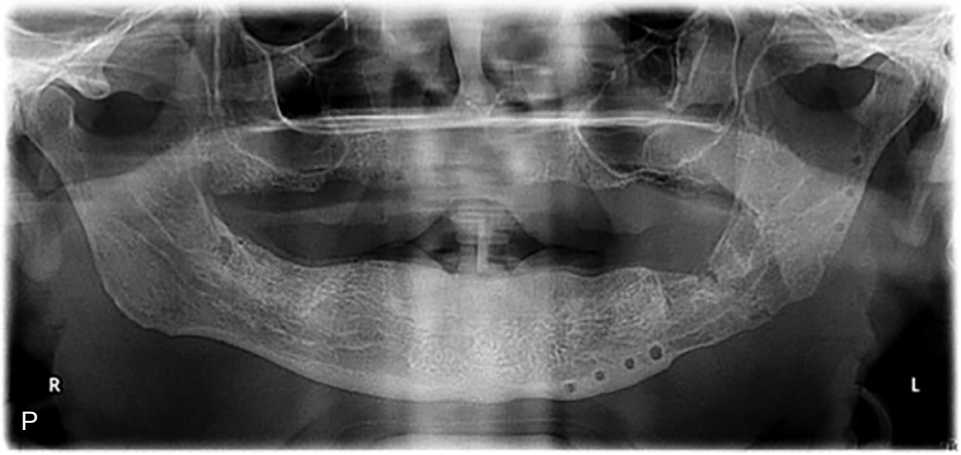


• **Figure 25-3, cont'd** **(F)** revealed the extent of destruction. A template was applied **(G)** allowing adaptation of a reconstruction plate **(H)** temporarily prior to resection of the area of osteomyelitis with neurovascular bundle preservation **(I).** Note that the bone was not resected in continuity **(J).** The reconstruction plate was adapted **(K)** and the oral wound closed in two layers. A particulate graft was harvested from the tibia **(L),** compressed in a modified large bone bore syringe





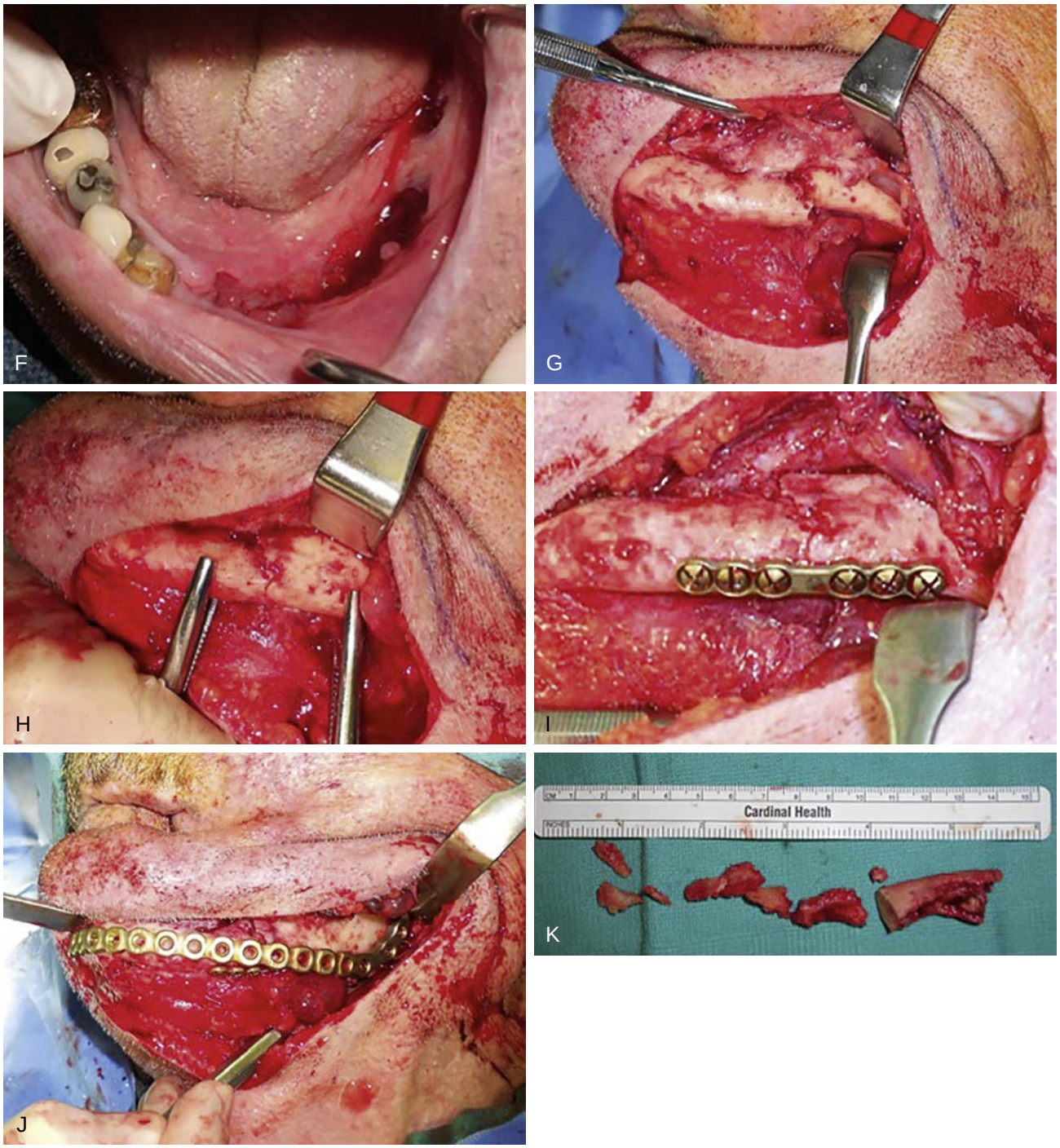




• **Figure 25-3, cont'd** **(M),** and placed into the defect **(N).** Immediate postoperative three-dimensional computed tomography **(O)** demonstrates the resection and reconstruction. Panoramic x-ray at 7 months, following removal of the reconstruction plate, demonstrates bone fill **(P).** Note the formation of a new mandibular canal in the grafted section.

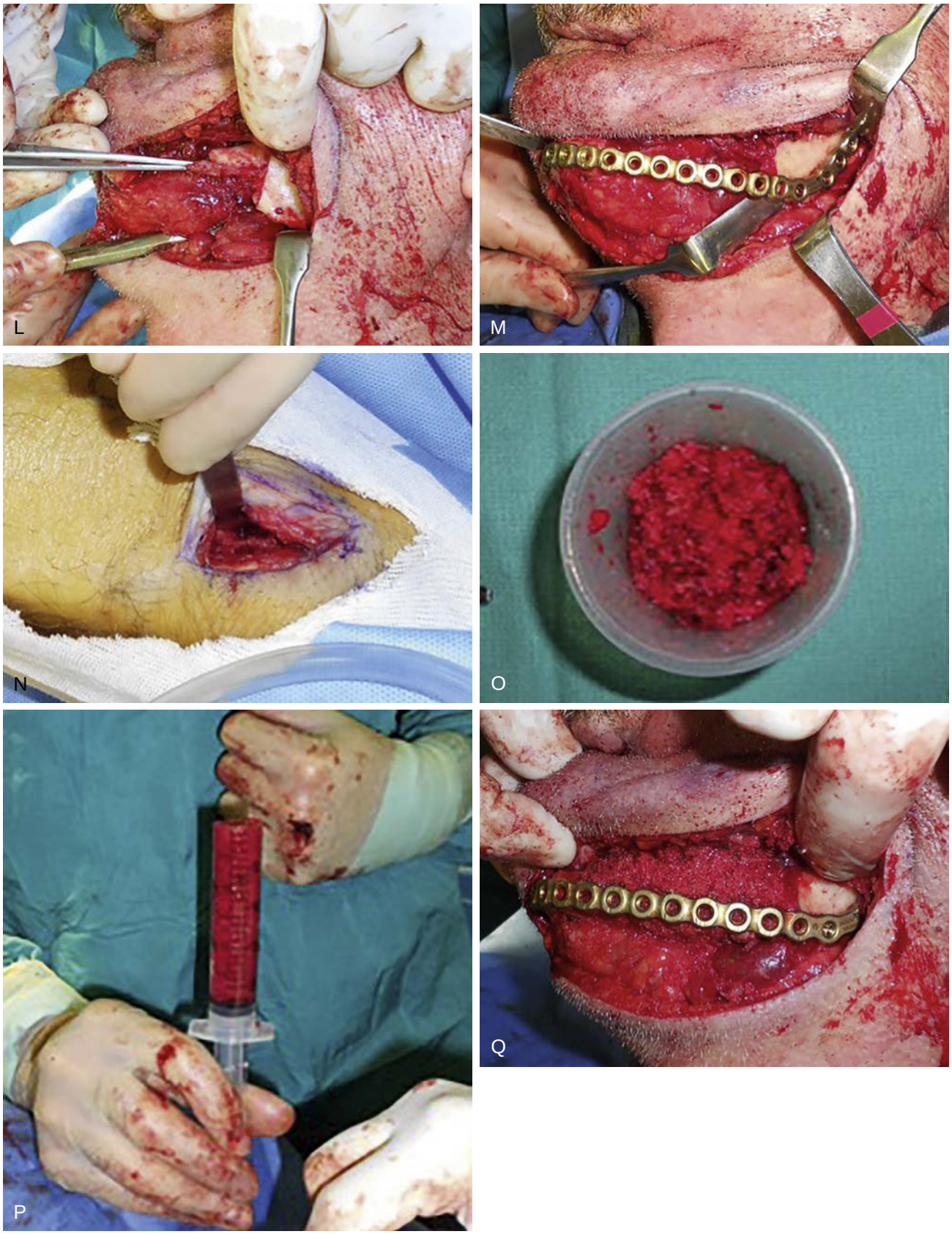


• **Figure 25-4** A 72-year-old man following a 3-month history of herpes zoster of V-3. The skin eruptions have resolved **(A)** but there is exposed alveolus **(B)** and a pathologic fracture evident **(C).** The exposed alveolus was lifted off **(D, E)** revealing a bed of granulation tissue present

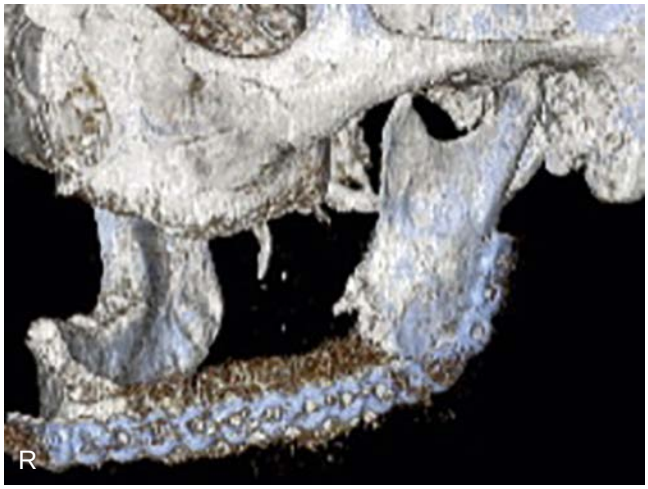


• **Figure 25-4, cont'd** **(F).** Exposure through the neck revealed the fracture **(G),** which was reduced **(H)** and temporarily stabilized with an inferior border miniplate **(I).** A locking reconstruction plate (LRP) was fitted and temporarily applied **(J).** The area of osteomyelitis was now resected in pieces **(K)** with

Continued



• **Figure 25-4, cont'd** preservation of the inferior alveolar neurovascular bundle **(L).** The LRP was reapplied and fixed with multiple screws **(M),** and the oral wound was closed. A particulate marrow graft was harvested from the tibia **(N, O)**, compressed with a modified large-bore syringe **(P),** and placed in the defect **(Q).**

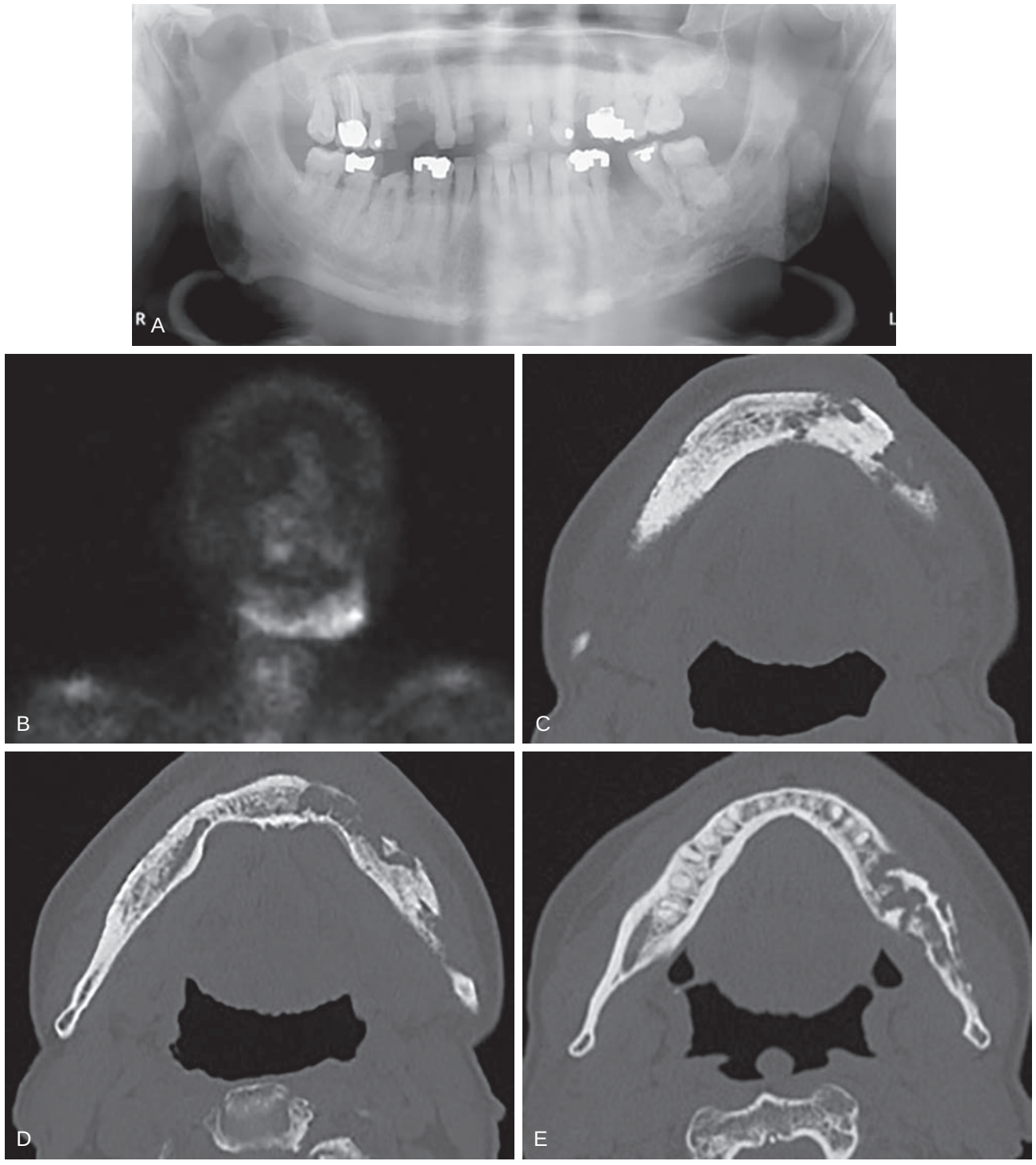








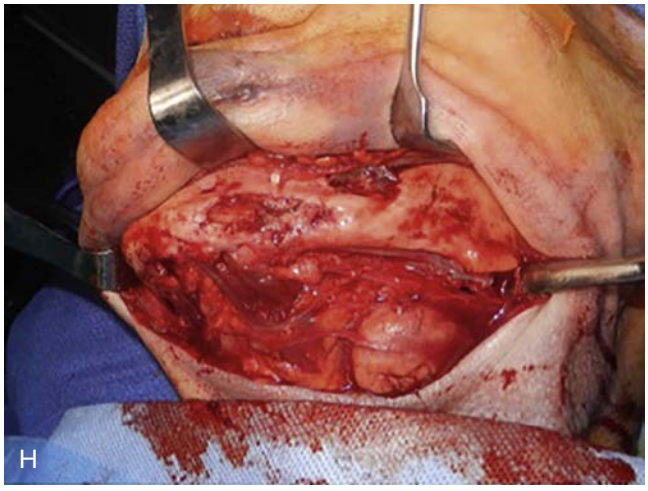
• **Figure 25-4, cont'd** Three-dimensional computed tomography **(R)** demonstrates the reconstruction. Healed oral **(S)** and neck **(T)** wounds and the panoramic radiograph at 6 months **(U)** following dental implant placement (two in grafted area).



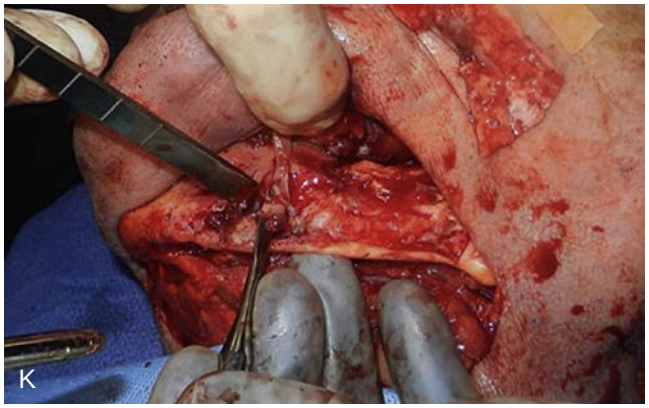
• **Figure 25-5** Panoramic radiograph **(A)** of a 75-year-old diabetic man with a 3-month history of pain, swelling, intraoral drainage, and paresthesia of his left mental distribution. Technetium-99 scan **(B)** demonstrated "hot" left mandible. Computed tomography scans **(C-E)** demonstrate moth-eaten appearance. An intraoral biopsy was consistent with osteomyelitis. It was scheduled for resection with neurovascular bundle preservation and immediate reconstruction.







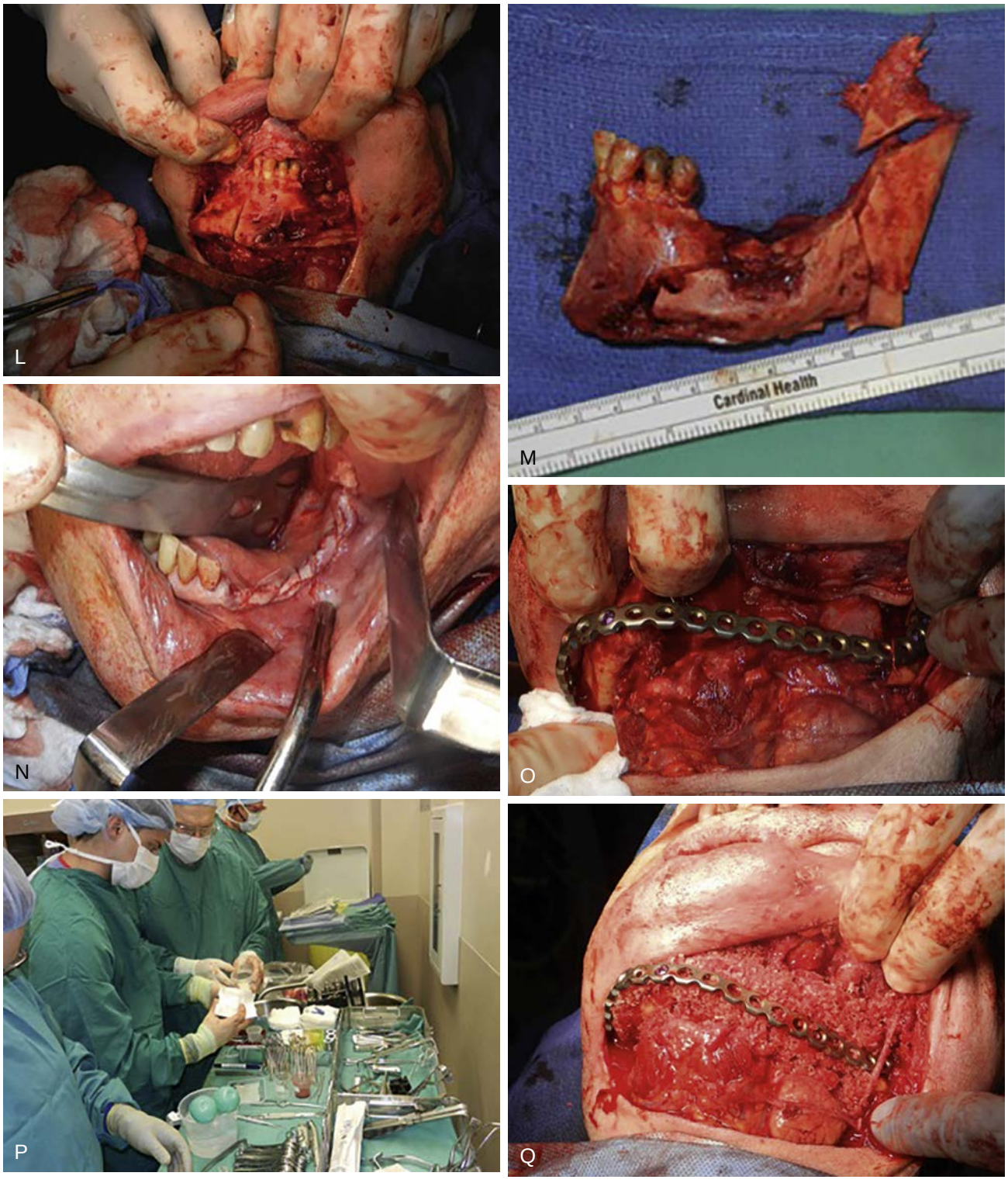






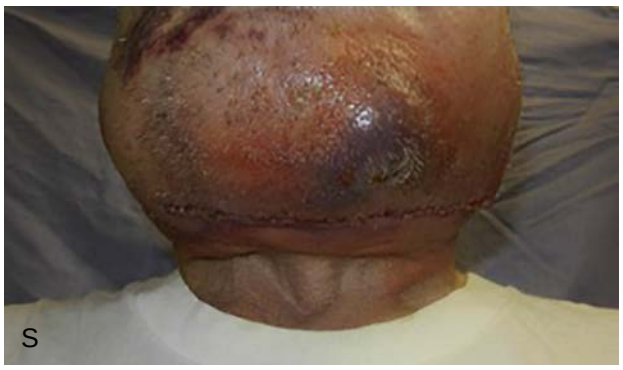
• **Figure 25-5, cont'd** In preparation, a stereolithic model of his mandible was obtained **(F, G)** to aid in locking reconstruction plate (LRP) adaptation in advance of surgery. An approach through the neck **(H)** reveals the destruction. The preadapted LRP was temporarily applied **(I)** and then removed. Lines of outer cortical osteotomies were made **(J),** the outer cortex removed, and the neurovascular bundle dissected free **(K).**

Continued



• **Figure 25-5, cont'd** The anterior osteotomy was completed **(L)** and the specimen delivered **(M).** Two-layer intraoral closure was accomplished **(N)** following application of the LRP **(O).** In view of the size of the defect to be grafted, it was decided to utilize a combination of particulate marrow from the tibia, bone morphogenetic protein (BMP), and freeze-dried allograft held together with platelet-rich plasma. **P**, Graft preparation on the back table. The mixture was packed into the defect **(Q)** and the wound closed.













• **Figure 25-5, cont'd** The use of BMP is noted for impressive edema **(R, S)** which ultimately resolves. Two-year follow-up **(T-W)** reveals good bone formation, facial form, and complete oral healing.

5. Infected mandibular fractures are not true osteomyelitis with fever, leukocytosis, adenopathy, and so on. They are areas of dead bone that need to be resorbed or removed for healing to take place. They are treated by rigid internal fixation, debridement, and primary reconstruction as well.[12]
6. A word on graft systems when there is oral contamination: Modern implant dentistry and the use of transoral bone grafts in support thereof have changed the way we view bone grafts.

For reconstruction of significant segmental defects with through-and-through exposure, an adequate tension-free oral closure with healthy tissue is necessary. Likewise, block grafts or costochondral grafts, which are slower to revascularize, should be avoided because if they become exposed in the mouth to wound breakdown, the entire graft may be lost. Particulate marrow grafts are more quickly revascularized, so that if the intraoral wound breaks down only a few flakes are lost.

In cases where there is inadequate healthy tissue for tension-free oral closure (most unusual in mandibular osteomyelitis) or the patient is immunocompromised, delayed reconstruction should be considered (Figure 25-6).

Osteoradionecrosis

Malignancies of the maxillofacial region continue to plague our patients and often occupy a large portion of our practices. In 2014, more than 41,000 new cases of malignancies in the oral cavity and pharynx were diagnosed in the United States.[13] Treatment of these malignancies involves surgery, chemotherapy, radiation therapy, or a combination of these modalities. Radiation therapy plays a valuable role in treatment of maxillofacial malignancies, but it also has well-known and very real complications. Short-term complications include mucositis, altered taste, and xerostomia. Longer-term complications include radiation fibrosis of the muscles of mastication, which leads to trismus. Radiation caries are also commonly seen with longstanding xerostomia.[14] The most dreaded complication of radiation therapy to the jaws is the development of osteoradionecrosis (ORN).

Osteoradionecrosis is defined by exposed bone through the oral mucosa that persists for greater than 3 months in the radiated field. There should be no other contributing factors such as bisphosphonate therapy. The definition of osteoradionecrosis has been modified, as early ORN has radiographic changes that are visible before the clinical symptoms of exposed bone arise.[15] The incidence of ORN is variable, ranging from a low of 2% to a high of 40%.[16] Osteoradionecrosis is more common and predominantly seen in the mandible (Figures 25-7, 25-8, and 25-9). Despite considerable efforts, no universally accepted treatment protocol has been determined. Osteoradionecrosis is commonly caused by dental procedures, such as extractions, in the radiated field. Any oral surgical procedure involving manipulation of bone can be a causative factor in the development of ORN. Poorly fitting dental prostheses that cause sore spots (mucosal breakdown) have also been identified as an etiology of ORN. Spontaneous ORN has been reported in the radiated field without an identifiable etiology.

Osteoradionecrosis has been well studied and there is extensive literature devoted to the subject. Marx, in the early 1980s, developed a theory that radiation caused hypoxia, hypocellularity, and hypovascularity. This triad could lead to osteoradionecrosis of the jaws.[17]

Marx theorized the main etiology was hypoxia in both hard and soft tissues, which led to the use of hyperbaric oxygen (HBO) in managing osteoradionecrosis. Recent advances have brought forth new explanations for ORN, such as the radiation-induced fibroatrophic theory. Impaired healing results from endothelial cell injury, release of cytokines, and abnormal fibroblast activity.[16] Clinicians will gain a better understanding of this complex disease process as research and evidence-based science improves.

Prevention of osteoradionecrosis can be very important in the overall care of the patient. Once the diagnosis of malignancy has been established and radiation therapy has been planned, the patient should be referred for dental evaluation, preferably by a dentist who is accustomed to treating oncology patients. There are established guidelines for dental management of the cancer patient during all aspects of radiation therapy treatment.[14] Emphasis is placed on removing potential sources of infection before radiation therapy has been initiated. Teeth with poor prognoses related to periodontics, endodontics, or restorability should be extracted before radiation therapy, and adequate time for the soft tissue healing is preferred. Dental prostheses should be inspected for potential irritation areas. Dentate patients undergoing radiation therapy to the jaws should be evaluated for fluoride carriers, as the caries index generally rises secondary to xerostomia. All patients receiving radiation therapy to the jaws should be counseled with regard to its effects on soft tissues (mucositis and pain) and the importance of oral hygiene and dental care during and after treatment.[14] The principle is to minimize invasive dentistry after radiation therapy has been delivered to the jaws. Dental extractions in the post radiation therapy period have a higher incidence of developing osteoradionecrosis.[18]

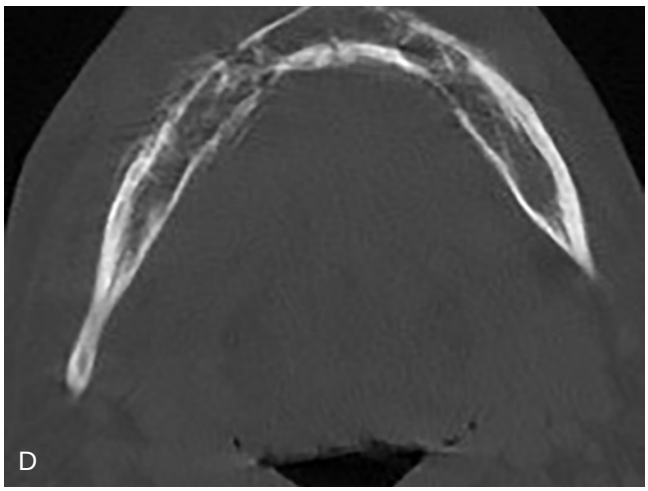
Advances in radiation therapy have also improved care for the oncology patients. Intensity-modulated radiation therapy (IMRT) allows for high doses of radiation to be given directly to the tumor and lower doses to the surrounding normal tissues. The overall effect is tumoricidal doses to the cancer and decreased radiation exposure to the jawbones, soft tissues, and salivary glands.[14] The lower dose of radiation to the surrounding tissues allows for decreased xerostomia, and the increased salivary flow equates to a lower chance of radiation caries. The lower incidence of radiation caries can mean fewer dental extractions in the radiated field and a lower chance of osteoradionecrosis.

Despite the advances in managing osteoradionecrosis, there is no universally accepted treatment protocol. Early-stage ORN, with small areas of exposed bone, can be managed conservatively with observation and chlorhexidine









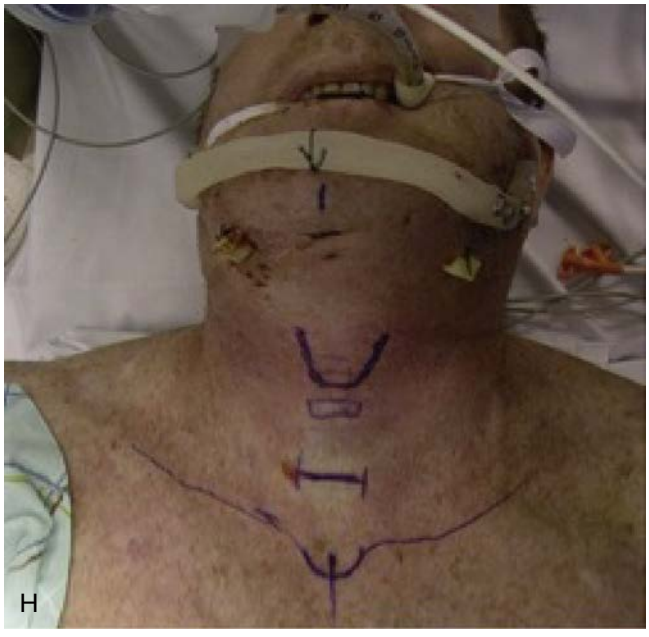


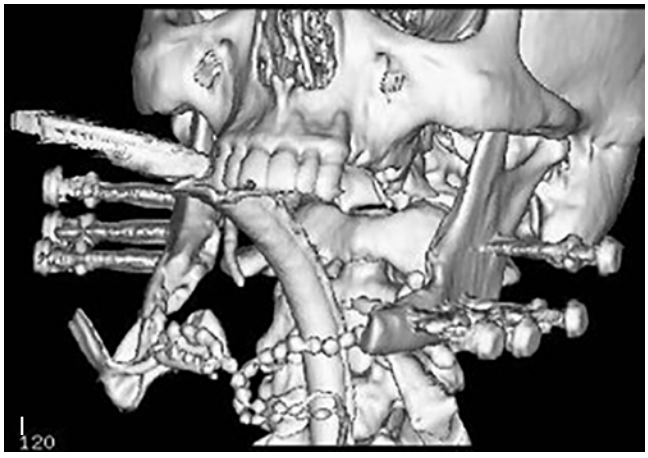
• **Figure 25-6** A 45-year-old man afflicted with AIDS **(A).** Three months prior he had undergone removal of three teeth and excision of mandibular tori in preparation for a mandibular removable partial denture. Incision and drainage was performed multiple times, along with minor sequestrectomies and multiple courses of intravenous antibiotics. He now presents with draining oral wounds **(B)** and moth-eaten appearance on panoramic radiograph **(C).** The computed tomographic (CT) scan **(D)** reveals the process to be bilateral. A phase I biphasic appliance **(E)** was applied and the mandible resected from right posterior

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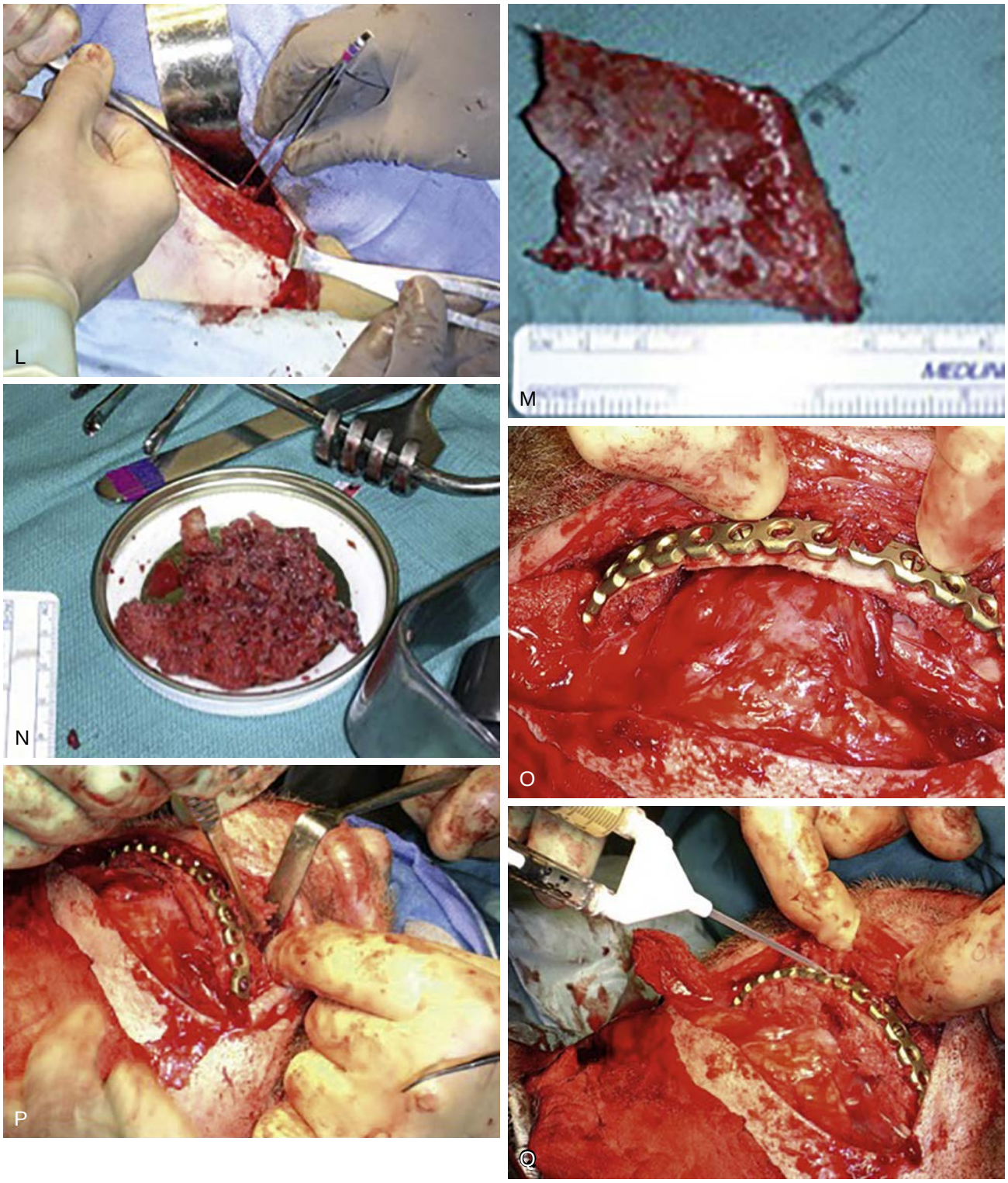






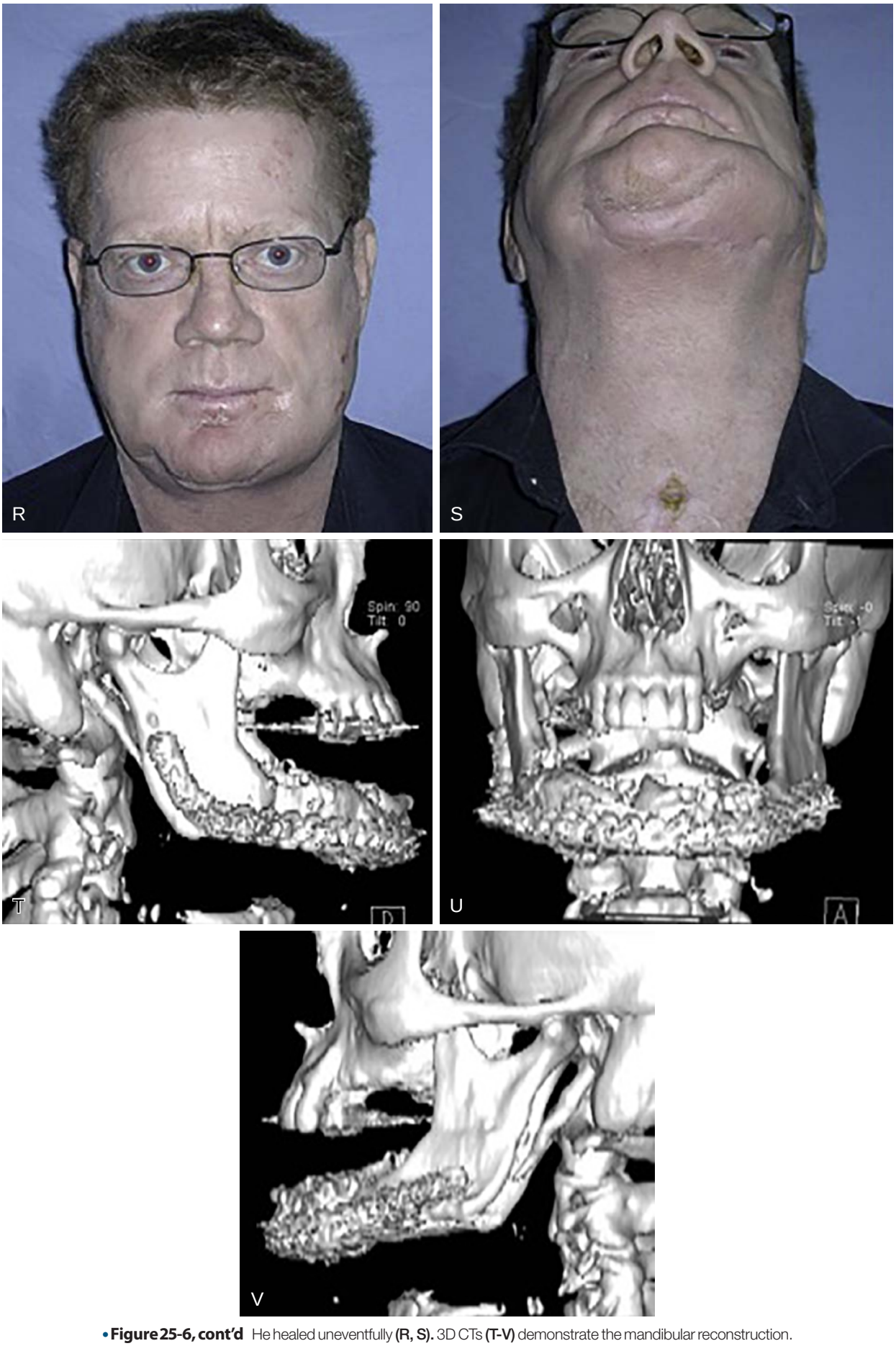


• **Figure 25-6, cont'd** body to left second molar region **(F).** The phase I biphase was converted to phase II by placing an acrylic bar **(G, H).** The three-dimensional (3D) CT **(I)** demonstrates the skeletal view of the defect and remaining jaw. Note the antibiotic bead chain in place. A fungal etiology for the osteomyelitis was discovered in the resected specimen. The patient was not considered to be a suitable for a free fibula reconstruction by two separate microvascular surgeons although his CD4 count was in the 950 range. Reconstruction was accomplished with a combination of tibia **(J, K)**



• **Figure 25-6, cont'd** and iliac crest **(L-N).** Three separate teams harvested the grafts and performed the mandibular reconstruction with a locking reconstruction plate and a combination of corticocancellous strips and particulate marrow **(O-Q).**

Continued



• **Figure 25-6, cont'd** He healed uneventfully **(R, S).** 3D CTs **(T-V)** demonstrate the mandibular reconstruction.

gluconate rinses. Early-stage ORN often has very few clinical symptoms other than intraoral exposed bone. Sharp bony edges can be smoothed or gently debrided. Antibiotic therapy is generally saved for acute episodes or "flare-ups." The patient should be counseled to stop smoking and maintain good oral hygiene.

Mid-stage ORN has larger areas of exposed bone and more extensive disease. Often this will present with symptoms of pain and swelling. Sequestrectomy or debridement of necrotic bone becomes increasingly indicated. Chlorhexidine gluconate rinses and systemic antibiotics play a larger role in patient management. HBO can play a role in the management of osteoradionecrosis. During HBO therapy, patients breathe 100% oxygen at pressures of 2 to 3 atm. The patient's tissue oxygen levels increase, and the overall effect is better wound healing. HBO treatment can be used in a variety of conditions other than osteoradionecrosis to augment wound healing. Marx's HBO protocol calls for both preoperative and postoperative HBO sessions in conjunction with the surgical intervention. HBO has also been recommended for extraction of teeth in the radiated field, often as seen with radiation caries, in an attempt to decrease or eliminate the chance of osteoradionecrosis. HBO treatments are given as daily treatment sessions of approximately 2 hours over a 30- to 40-day time period.[17] The HBO treatment protocol can be both time-consuming and expensive for the patient. HBO has conflicting scientific evidence of efficacy in the treatment of osteoradionecrosis. There are numerous conflicting studies in the literature. The debate continues today, with no universally accepted treatment protocol.



• **Figure 25-7** Clinical photograph of early osteoradionecrosis of anterior mandible after dental extractions in the radiated field.



• **Figure 25-8** Clinical photograph of more extensive osteoradionecrosis of anterior mandible after dental extractions in the radiated field.

Other treatment modalities have been advocated for the management of ORN. Ultrasound has been used to treat earlier stages of ORN. Ultrasound increases angiogenesis and stimulates wound healing and has been used to treat other chronic wound problems in the human body.[19] Pentoxifylline and tocopherol have been proposed in the management of ORN. Pentoxifylline is a vasodilator that increases blood flow to the area of healing. Tocopherol or vitamin E scavenges oxygen radicals. Patients were given results. Platelet-rich plasma has also been used to treat osteoradionecrosis. It has added growth factors that augment soft tissue healing[22] and has been throughout the body to aid in healing of both hard and soft tissue. A universally accepted



• **Figure 25-9** Panoramic radiograph of same patient. Notice lytic bony changes in the anterior mandible.

treatment protocol has yet to be scientifically validated and generally adopted.

Late-stage ORN is very often debilitating. Chronic pain, invasion into adjacent anatomic areas, extraoral fistulae, and pathologic fractures are commonly seen. The late-stage presentation of ORN is often treated with resection of the involved tissues (Figures 25-10 and 25-11). Options for reconstruction can include no reconstruction, local tissues such as myocutaneous flaps, or distant flaps with their own blood supply. The advent and increasing popularity of "free flaps" and microvascular surgery techniques that bring flaps with their own blood supply to the radiated (hypoxic) field has been a huge advancement in this field. Hidalgo first described the osteocutaneous free fibula flap in 1988.[14,23] The fibula is the most commonly used donor site for microvascular reconstruction in the maxillofacial region (Figures 25-12, 25-13, and 25-14). The fibula provides adequate bone and a soft tissue flap to reconstruct both hard and soft tissue defects. It can be osteotomized to curve and follow facial contour. Dental implants are possible in the fibula to support dental rehabilitation in these patients (Figure 25-15). The fibula has been a reliable free flap with an excellent survival rate of 95%.[14,24] Nonvascularized grafts have traditionally not performed as well in the radiated field. Other options for microvascular reconstruction in the maxillofacial region include the iliac crest, scapula, and distal radius. Microvascular surgeons are becoming very creative in their reconstructive efforts to restore patients to their premorbid state. The future of designer flaps that are crafted for very specific needs holds great promise for the patients.

Radiation therapy provides a vital role in the treatment of oral and maxillofacial malignancies. The most dreaded complication of radiation to the jawbones is osteoradionecrosis. Clinicians forge onward to prevent and treat this complication, which has caused significant morbidity and even mortality in our patient population. Despite our best efforts, a definitive and universally accepted protocol to manage the devastating effects of osteoradionecrosis has yet to be found. However, the future is still very bright and hopeful for our maxillofacial oncology patients.



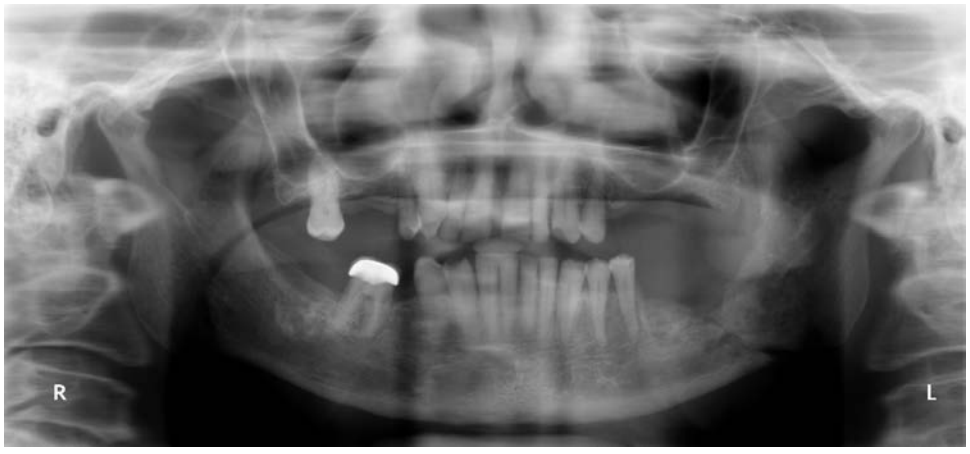
• **Figure 25-10** Panoramic radiograph of a patient with osteoradionecrosis in left mandibular body and angle region. Note lytic bony changes and pathologic fracture.



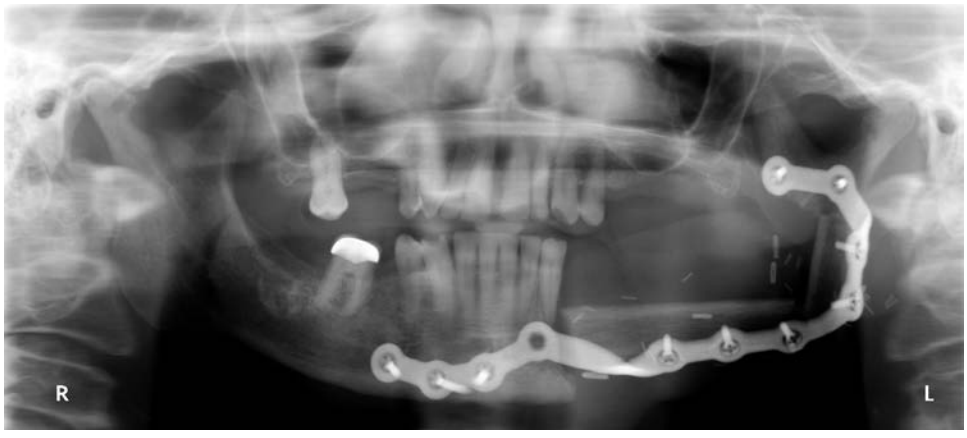
• **Figure 25-11** Resection of osteoradionecrosis in left mandibular body and angle region with *no* reconstruction. Patient was medically compromised and could not tolerate extensive surgery.



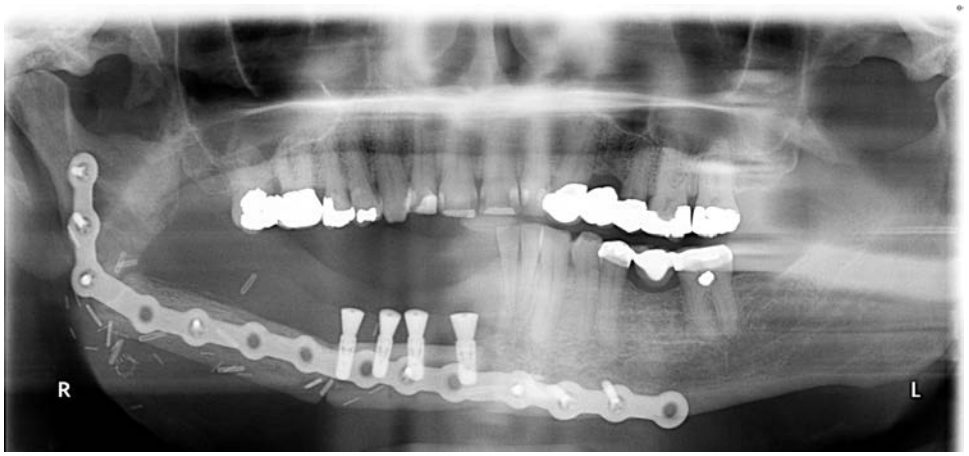
• **Figure 25-12** Panoramic radiograph of patient after dental extraction in radiated field of left posterior mandible.



• **Figure 25-13** Subsequent panoramic radiograph of same patient with osteoradionecrosis and pathologic fracture left posterior mandible.



• **Figure 25-14** Panoramic radiograph showing resection of osteoradionecrotic left mandibular body with



• **Figure 25-15** Panoramic radiograph showing implant placement in fibula free flap for subsequent dental implant rehabilitation.

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26

The Molecular Biology of Cancer

RANDY TODD

Introduction

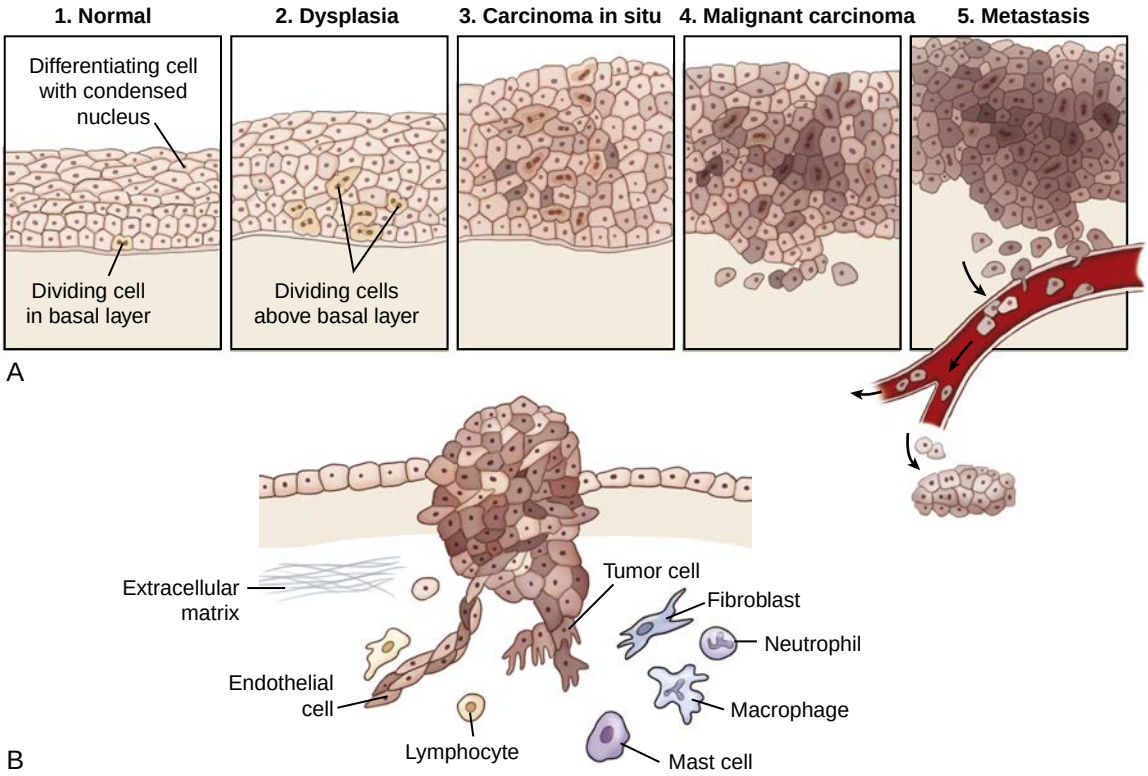
Understanding the molecular biology of cancer is an essential step toward developing a rational approach for the diagnosis and treatment of the oncology patient. Fundamentally, cancer results from a collection of molecular errors that confer increasingly abnormal proliferative and invasive behaviors. Alterations of regulatory molecules lead to a limited expansion of a single cell until the next mutation occurs, and that new mutation, in turn, gives rise to a clonal outgrowth with even greater proliferative potential.[1,2] Therefore, as the cancer cell "evolves," it gains the ability to take advantage of and outcompete its normal neighbors. These changes that define the malignant cell are being investigated as valuable targets to better diagnose and treat cancer patients.[3] This chapter provides a broad overview of the types of molecular alterations that govern cancer cell behavior and discusses some of the approaches using these observations as diagnostic and therapeutic targets.

Cancer remains the second leading cause of death in based on their tissue of origin: epithelial (carcinomas), mesenchymal (sarcomas), or neuroectodermal. The disease is also frequently divided into inherited and sporadic forms. Inherited malignancies occur in the pediatric patient population and/or present earlier than their sporadic counterparts. For example, there are inherited and sporadic forms of retinoblastoma, an eye tumor.[6] Inherited retinoblastoma shows a family predilection and presents early as multiple tumors in both eyes. Sporadic retinoblastoma occur in patients without a family history of the disease, presents in one eye, and occurs at a later stage in life. Therefore, in addition to chemical carcinogens, radiation and viruses, age and genetic background are key risk factors in developing the disease. All five of these risk factors share a common characteristic of altered DNA structure and function. Epidemiologic studies suggest that 80% to 90% of cancers arise from an accumulation of DNA-damaging environmental exposures over time.[7] The histopathologic stages observed during tumorigenesis also reflect the time-dependent accumulation of environmental and inherited genetic damage.[8]

Cancer Histology

Rather than arising de novo, cancers develop through a progression of histologic changes characterized by a breakdown of tissue architecture that is followed by local and distant invasion into surrounding "normal" tissue.[5] For example, squamous cell carcinomas begin as hyperplasia or a thickening of the epithelium (Figure 26-1, *A*). However, cell division is confined to the basal layer of the epithelium, and the more superficial layers remain ordered and show differentiation (see Figure 26-1). As tumor progression continues, the epithelium becomes dysplastic. Cell division is observed above the basal layer, and the structure of the epithelium loses its order. Dysplasia is further categorized as mild, moderate, or severe, based on how superficial cellular atypia occurs within the epithelium. Left alone, dysplasia can remain harmless or can even regress spontaneously. Carcinoma in situ presents with disordered cell division and tissue structure, as well as cells having structural characteristics of cancer cells. However, as the name implies, carcinoma in situ is restricted by the basal membrane and does not invade the surrounding structures. Squamous carcinoma is characterized by underlying connective tissue invasion. Cancers are further graded by their level of differentiation (well, moderately, or poorly differentiated). Following local invasion of the underlying stroma and surrounding normal structures, the cancer metastasizes.

Although it is tempting to think of cancers as a homogeneous cell population, emerging evidence indicates that even early tumors may already contain distinct clonal subpopulations. This heterogeneity is likely due to cancer stem cells (CSCs).[9-11] CSCs are functionally defined by their efficiency in seeding new tumors in mice.[12] Like stem cells in normal tissues, CSCs self-renew and spawn derivatives. Therefore, the plasticity of CSCs allows formation of functionally distinct cell populations. Diversity of cell



• **Figure 26-1 A,** Epithelial cancer progression. Malignancies arise through a series of histopathologic changes. *1,* In normal epithelium, cell division occurs in the basal layer while the more superficial layers show increasing degrees of differentiation. *2,* Dysplastic epithelium shows cell division above the basal layer. In addition, cellular changes characteristic of cancer cells are also observed. Degrees of dysplasia (mild, moderate, severe) are based on the relative thickness of these changes. *3,* Carcinoma in situ is characterized by malignant changes in the full thickness of the epithelium. However, the basement membrane is intact in both dysplasias and carcinoma in situ. *4,* Carcinoma shows disruption of the basement membrane and invasion of cancer cells into the stroma. *5,* Metastasis is the transfer of disease from one organ to another not directly connected with it. **B,** The cancer stroma. Cellular alterations in the stroma invaded by cancer, once believed to be a protective response, may actually support tumor progression and metastasis.

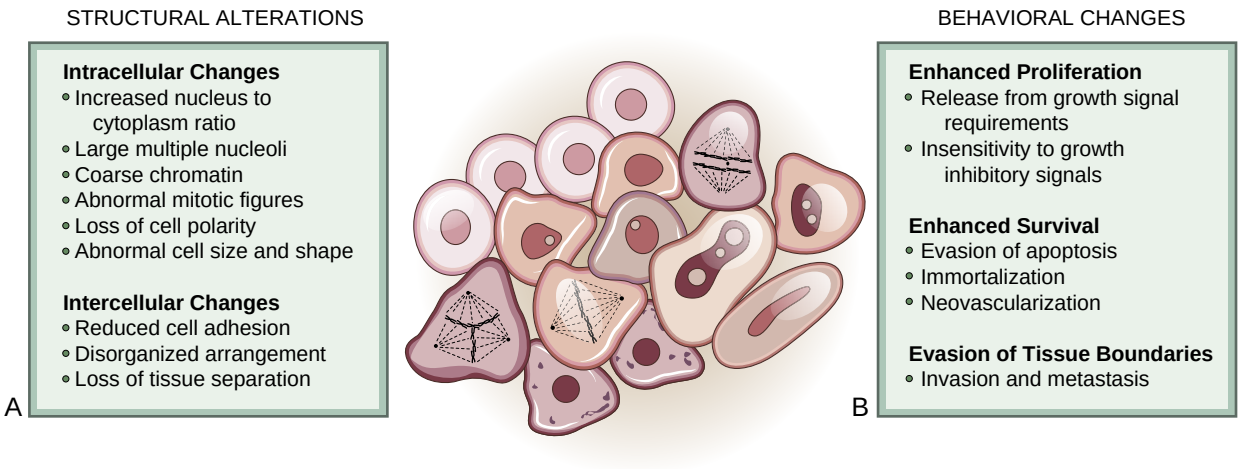
bution or offering complementary capabilities between cell types.[13] To add to the complexity of the anatomy of cancer tissue, the tumor stroma is believed to make important contributions to tumorigenesis.

Several important stromal changes occur during cancer progression (see Figure 26-1, *B*). Recent research has focused not only on the cancer cell, but the cell types found within the "normal" stroma.[14] In essence, the tumor has an organ-like complexity.[9] A microenvironment exists in which the cancer cells interact with tumor-associated fibroblasts, endothelial cells, and immune cells.[15]

The most abundant cell type in the tumor stroma are cancer-associated fibroblasts.[16] Fibroblast proliferation is often referred to as "desmoplasia" and is recognized as a wound response to the cancer.[17] The predominant cell type in this stromal reaction is the myofibroblast, named for the morphologic characteristics of its large, spindle-like shape, indented nuclei, and stress fibers.[18] Myofibroblasts are rare in healthy tissue but are commonly found in chronic wounds. The desmoplastic stroma associated with myofibroblasts is believed to support tumor proliferation, metastasis/invasion, and angiogenesis.[9]

Angiogenesis is an essential requirement for a tumor mass to grow larger than about 1 mm^3. Only 1 in 600 of these in situ malignancies achieves the blood supply necessary to become a clinically detectable tumor.[19,20] Rather than invading and appropriating existing vascular beds, tumors recruit and stimulate endothelial cells to construct a tumor-specific blood supply.[19,20] In fact, vascular density has been used to follow a primary tumor toward its malignant end point.[21] Endothelial cells and pericytes are important components of tumor-associated vasculature. Although a great deal has been elucidated regarding tumor neovascularization ized mesenchymal cells that are related to smooth muscle. In addition to the support of and collaboration with endothelial cells, pericytes may serve as a barrier to cancer cell intravasation.[22]

A pronounced inflammatory infiltrate is present in the stroma.[23,24] Diverse evidence exists whether the



• **Figure 26-2** The cancer cell. In addition to changes in the tissue architecture during cancer progression, the cancer cell accumulates several alterations. **A,** Structural alterations of the cancer cell appear both other cells in the tissue (such as reduced cellular adhesion and loss of polarity). **B,** Important behavioral changes in the cancer cell can be broadly categorized in rapid proliferation (release from growth factor requirements and insensitivity to growth inhibitory signals), enhanced survival (evasion of apoptosis and immortalization), and evasion of tissue boundaries (invasion and metastasis).

tumor-associated inflammatory cells inhibit or promote tumor growth.[9] Likely, both concepts are true. Because immunosuppressed individuals experience elevated levels of certain cancers, it is believed that the immune system surveys and eliminates cancer cells.[25] Although a comprehensive overview of tumor immunology is beyond the scope of this chapter, for summary purposes it can be broadly subdivided into the innate and adaptive immune systems.[26,27] The innate immune system, consisting of macrophages, dendritic cells, and cytotoxic T cells/natural killer (NK) cells, detects and kills cancer cells. Monocytes are recruited early and are later differentiated into macrophages.[28] Cytotoxic T cells recognize and attack cells with tumor-associated antigens (TAAs), releasing factors that inactivate cytotoxic T cells and recruiting regulatory T cells (which also inactivate cytotoxic T cells).[29,30] Dendritic cells are important antigen-presenting cells that can also suppress angiogenesis. However, cancer cells can evade immunosurveillance by downregulating TAAs. The adaptive immune system consists of T and B lymphocytes, key stimulators of both the cytotoxic and humoral anti-tumor responses. However, not only can the immune response be suppressed by cancer cells, but some studies indicate that factors produced by immunocytes can support cancer progression.[31] The contribution to and/or inhibition of tumorigenesis by these stromal cell types is an active area of investigation that will be discussed further. In addition to an accumulation and progression of tissue changes, the cancer cell itself shows important alterations from its normal counterparts.

Cancer Cell Biology

Cancer cells have several structural and behavioral differences from normal cells[5] (Figure 26-2, *A*). Structurally, cancer cells show varying degrees of anaplasia (or degree of differentiation). Both the cytoplasm and nucleus are pleomorphic. Malignant cells may be either much larger or smaller than their normal counterparts. Typically, cancer cells show a loss of cell adhesion between cells and loss of polarity with respect to the overall tissue architecture. The nuclei of cancer cells typically are disproportionally larger (with respect to the cytoplasm) and more dense (or hyperchromatic). Large nucleoli also appear, suggesting high synthetic activity. Normal mitotic spindles are replaced in malignant cells by atypical mitotic figures with tripolar, quadripolar, or multipolar spindles.

In cell culture and in vivo, cancer cells show key behavioral alterations that are often reflected in the structural changes[9] (see Figure 26-2, *B*), Cancer cells often proliferate rapidly and in an uncontrolled manner. In addition, cellular controls leading to apoptosis or cell death are often abrogated. Malignant cells lack the ability to terminally differentiate. Evasion of apoptosis, senescence, and terminal differentiation leads to enhanced cell survival. Most importantly, cancer cells invade the local stroma and induce changes such as angiogenesis. Many malignant cells eventually achieve the ability to metastasize.

Fueling these malignant phenotypes is a metabolic switch in cancer cells (referred to as the "Warburg effect") to glycolysis as the primary energy source.[32-34] To compensate for the lower efficiency for generating energy, cancer cells increase glucose intake (a phenotype that is exploited in positron emission tomography [PET], where radiolabeled glucose is used as a reporter).[9,35] Despite its inefficiencies, the Warburg effect has selective advantages for cancer cells. Byproducts of glycolysis can fuel biosynthetic pathways that generate nucleosides and amino acids.[9] Furthermore, lactate secreted from glucose-dependent cancer cells can be used

by better-oxygenated cancer cells as fuel.[36] In fact, the same molecular determinants governing malignant cell phenotypes also contribute to the metabolic changes within the cancer cell to support these phenotypes.[9]

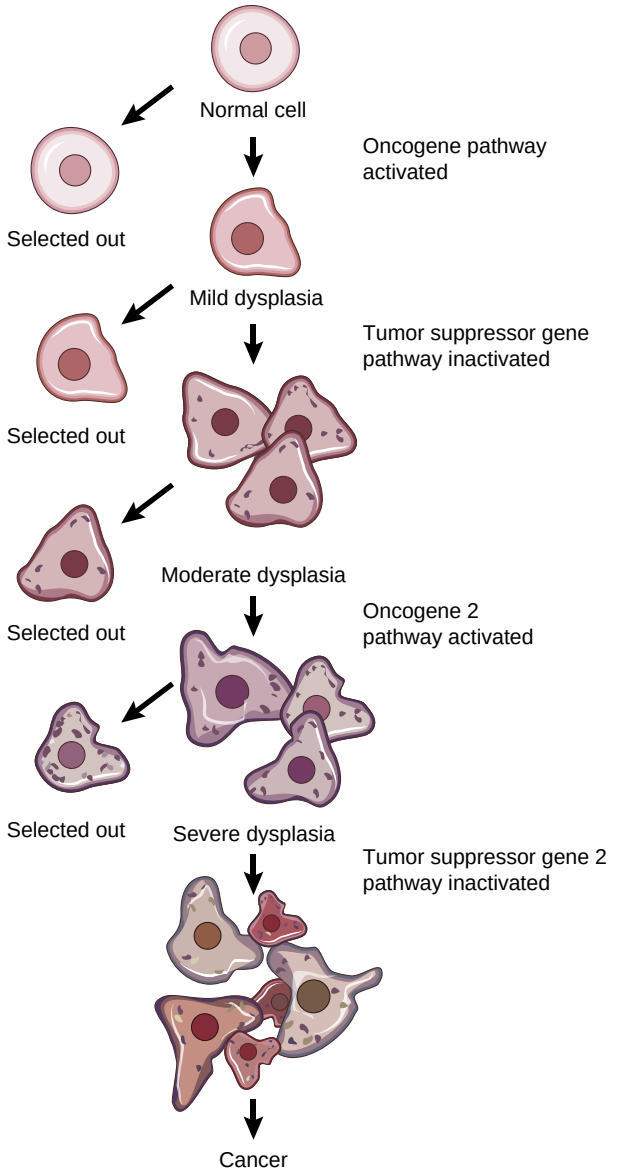
In summary, time and exposure to environmental carcinogens lead to the cellular and histologic progression observed during malignant transformation. It is widely believed that these risk factors lead to an accumulation of underlying genetic alterations that drive the structural and functional traits characteristic of the cancer cell. Molecular biology has provided important insights into the causes of cancer progression. In the next section, the nature of cancer-associated molecular alterations in cancer cells is examined in the context of their influence on cancer behavior.

Signal Pathways Are Altered by Cancer-Associated Molecular Changes

Several observations support a multistage progression during tumorigenesis.[8,37] Epidemiologic studies examining age-specific mortality rates for different forms of human cancer predict that multiple alterations are required for the genesis and outgrowth of clinically detectable tumors. Clinical and histologic detection of "premalignant" lesions and their underlying microscopic changes also suggests that multiple pathways are involved in cancer development. In addition, behavioral differences (such as treatment response) between clinically and histologically identical lesions suggest that distinct subcellular or molecular pathways may be abrogated to account for the observed difference.

Several lines of evidence indicate that the multiple molecular events lead to cancer development are genetic in nature. In the early 20th century, Boveri suggested that chromosomal imbalances lead to cancer development.[38] This observation was supported by the study of inherited pediatric tumors and identification of damaged chromosomes in cancer cells. Furthermore, chromosomal DNA damage was linked to cancer formation. DNA repair defects were linked to ultraviolet (UV) light-induced skin cancers. Muller and Auerbach demonstrated the mutagenic potential of ionizing radiation and chemical carcinogens, respectively. Statistical analysis of human tumor incidence and natural history in sporadic and inherited human tumors suggested that between 7 and 10 genetic events were required in human tumorigenesis (Figure 26-3). These genetic events were thought to be in two broad categories: oncogenes and tumor suppressor genes.

Oncogenes, or altered growth genes that promote cancer formation (proto-oncogenes), were identified early in molecular investigations in the origins of human cancer.[38] Rous suggested that a retrovirus that caused sarcomas in chickens contained a specific oncogenic sequence. Duesberg and Vogt confirmed that a genetic element induced the chicken sarcoma, and Bishop and Varmus identified the specific v-Src oncogene. Weinberg later identified the first human oncogene using nonviral human tumor cells.



• **Figure 26-3** Accumulation of molecular changes in the cancer cell. The cancer cell is a product of a Darwinian selection process. The cancer cell undergoes alterations in molecular pathways that confer a behavioral advantage, causing cells without these changes to be selected out. These molecular alterations principally consist of overactivity of tumor-promoting (oncogene) pathways or inactivation of tumor suppressor pathways.

Because oncogenes could be experimentally added to normal cells to induce a malignant phenotype, oncogenes were initially easier to study.

Tumor suppressor genes, or genetic elements that suppress tumorigenesis, were also postulated early in cancer research.[39] At the cellular level, cancer is a recessive phenotype: normal cellular activity can suppress malignant transformation. Experimentally, fusion of cancer cells with normal cells resulted in a hybrid cell with normal cell characteristics, suggesting that normal cells had one or more elements that could suppress cancer formation.[40] Later, the addition of specific normal chromosomes to certain cancer cells was found to have the same effect.[41,42] Using statistical

analysis of inherited tumors, Knudson compared the difference between the natural history of inherited versus sporadic cancers and suggested a "two-hit" hypothesis in which both copies of a tumor suppressor gene had to be inactivated for cancer formation.[42] Familial cancers, which arose experimentally after the identification of the first tumor suppressor gene.[44] The retinoblastoma (Rb) gene was cloned by Friend from the pediatric eye tumor (discussed earlier) with a biphasic clinical appearance. In patients who presented and presenting later), both inherited copies of the Rb gene were normal.[45,46]

Although an accumulation of genetic events is widely believed to lead to tumorigenesis, the nature and identification of those events continues to be refined. Cell behavior is governed by various molecular pathways. With each oncogene pathway that becomes activated and each tumor suppressor gene pathway that becomes inactivated, the cell acquiring these changes clonally expands because of a behavioral selective advantage over its neighbors. Disruption of these molecular pathways occurs when genetic alterations lead to abnormal numbers and/or function of the protein elements that govern cell structure and behavior. Therefore, in order to understand how cells become malignant, it is important to first understand the nature of gene regulation and how it is altered during human cancer development.

Gene Regulation of Cell Function: A Primer

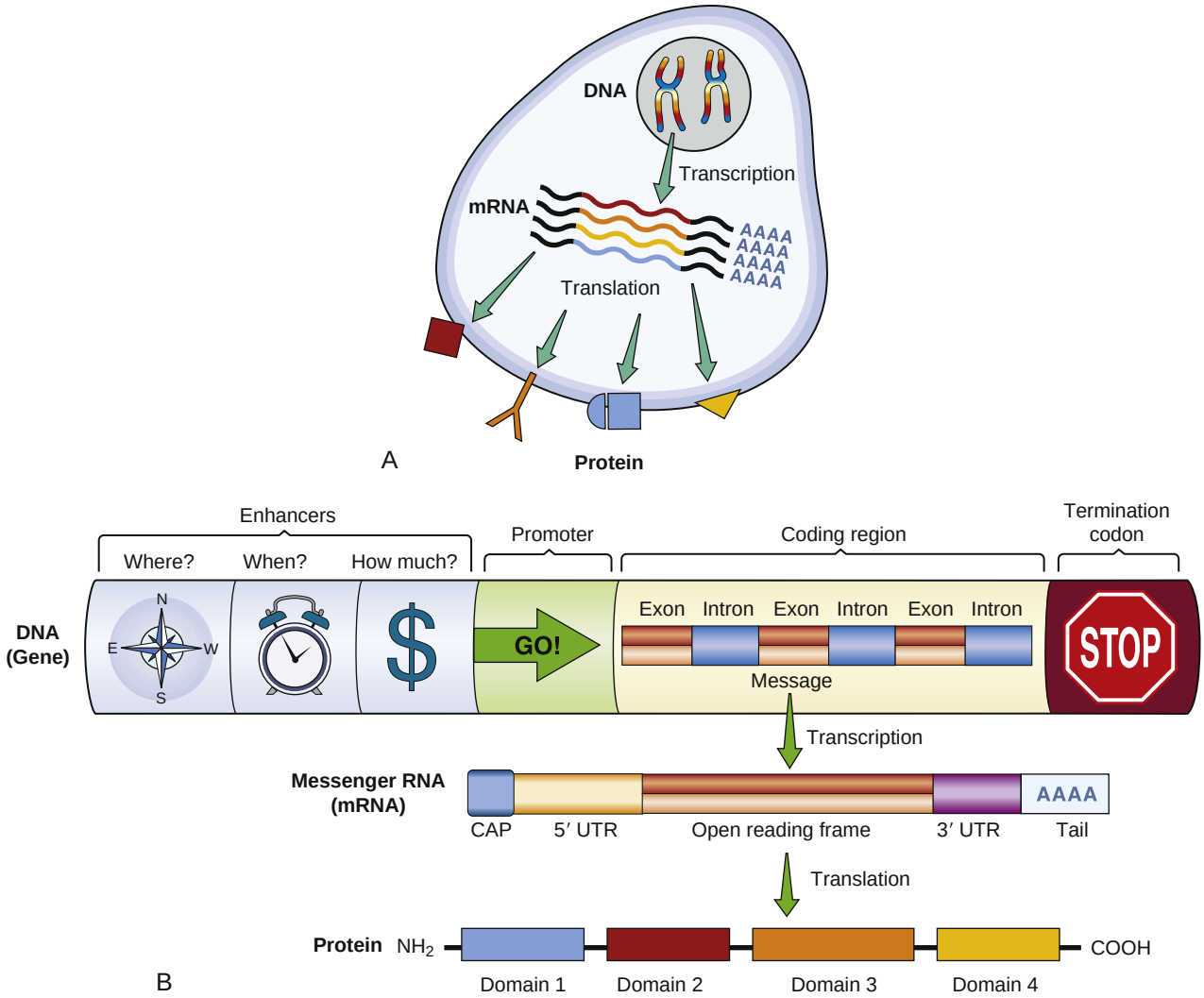
How do genetic alterations lead to cancer cell behavior? Although cellular homeostasis is regulated at many levels, the core of basic cancer research is based on the disruption of the molecular paradigm of gene expression (Figure 26-4). Genes (or coding regions of DNA) are transcribed into messenger RNA (mRNA) that is later translated into proteins. The gene products, proteins, govern much of the structure/function of the cell and are the true determinants of the malignant phenotype.[47] Therefore, to understand the molecular biology of cancer, it is important to understand its key elements: DNA, mRNA, and proteins associated with the malignant phenotype.

DNA (or *d*eoxyribo*n*ucleic *a*cid) is an essential molecule in human health and disease. The 23 pairs of human chromosomes are composed of DNA and protein. Within chromosomal DNA, there are approximately 23,000 paired genes. Therefore, there are two copies of each gene, a DNA region that carries the structural and functional blueprint of the cell.[48] The paired, homologous regions of DNA are called alleles. *Every* cell contains *every* gene that encodes *every* the majority of gene activity and control baseline cell function and structure. Tissue-specific genes are responsible for specific characteristics of differentiated cell types. Whereas about 10,000 to 15,000 housekeeping genes are expressed, fewer than 1000 tissue-specific genes are active in any given cell type.[49] Therefore, a significant portion of genes in a differentiated cell remain inactive. This diversity of genetic activity is the essence of both morphologic and physiologic differences between cell and tissue types.

Genes have three fundamental regions that help govern which sequences are expressed: the enhancer/promoter region, the coding region and the termination region.[50] The gene promoter/enhancer region, which is bound by transcription factors, determines the activity of a gene. Some scribed into RNA and subsequently translated into protein. The message translated is based on the order of the nucleotides: adenine, thymine, guanine, and cytosine. The order of these nucleotides is highly regulated. Although there is a redundancy in the code that allows for a limited number of specific changes, nucleotide insertions, deletions, or exchanges can have far-reaching effects (which are discussed later). To prevent nucleotide sequence changes, DNA mismatch repair genes provide an important mechanism to protect the integrity of the code.[51]

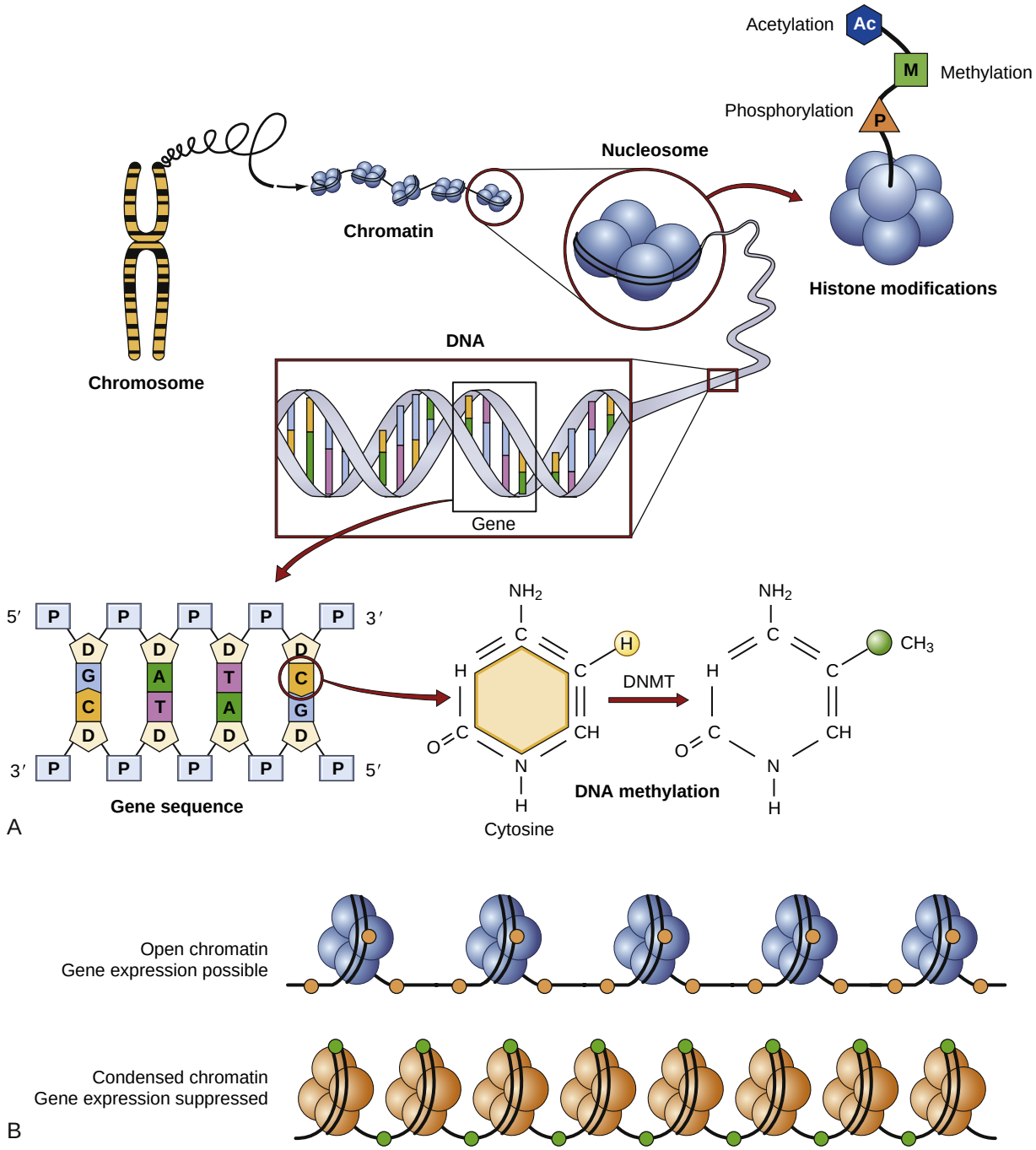
In addition to direct regulation of gene activity, genes are controlled by epigenetic factors.[52,53] The conformation of chromosomal DNA regulates the ability of genes to be expressed (Figure 26-5). Chromosomal DNA packaged with histone proteins is called chromatin.[54] Dense chromatin prevents gene expression; open chromatin allows gene activity.[55,56] The two best-understood means of epigenetic control of gene expression are DNA methylation and his-[57] family associated with chromosomal DNA) though acetylation, methylation, and phosphorylation is another important control of gene activity. These modifications to DNA and histone change the conformation of the chromosome, leading to dense (low gene expression) and open (high gene expression) chromatin (see Figure 26-5, *B*). Therefore, gene regulation is both genetic (or controlled by the promoter/enhancer gene region) and epigenetic (or gene expression control based on chromatin structural conformation near the gene).

The genetic message encoded in DNA is carried by an intermediary molecule, messenger RNA (*r*ibo*n*ucleic *a*cid) or mRNA, from the nucleus to the cytoplasm (see Figure 26-4, *B*) Outside the nucleus, the message is transcribed into protein. Amounts of mRNA are regulated by two primary mechanisms. First, gene activity and post-transcriptional processing influence how much or how little mRNA is produced. Second, the structure and stability of the mRNA molecule



• **Figure 26-4** The molecular paradigm of gene expression. **A,** The cellular location of gene activity. Genes are coding areas found in the DNA of chromosomes. They are transcribed into messenger RNA, which moves from the nucleus into the cytoplasm to be translated into protein. Proteins can be ligands, receptors, secondary messengers, transcription factors, and so on. **B,** Schematic of gene expression. The gene is composed of four primary regions: enhancers (which guide where, when, and how much a gene is expressed), a promoter (which initiates gene transcription), the coding region (which contain the message in regions called exons separated by "spacer" DNA called introns), and a termination codon. The messenger RNA is transcribed and processed from the gene. The message for the new protein is in the open reading frame. The flanking regions (5′ and 3′ untranslated regions) are regulatory regions that govern the transcript stability and translation efficiency. A 5′ cap aids in translation and helps protect the transcript. A polyadenylated (poly A+) tail also helps protect many transcripts from degradation. DNA and RNA are nucleic acids (DNA has thymine, whereas RNA has uracil; both have adenine, guanine, and cytosine). Protein is a chain of amino acids (three nucleic acids encode one amino acid). Domains are distinct functional areas of the protein determined by the amino acid sequence, chemical modifications, and structural conformation of the molecule. *UTR,* Untranslated region.

regulate how much transcript is available for protein production. Messenger RNAs have three primary domains. The open reading frame (or region carrying the protein coding sequence) is flanked by 5′ and 3′ untranslated regions (UTRs). The UTRs play a key role in stability and translation. Many (but not all) mRNAs are further protected by a 5′ cap and poly-adenylated tail that retard transcript degradation. By varying the speed by which mRNA is degraded and/or translated, the cell has another means of regulating itself independently of gene activity. Furthermore, micro RNAs (miRNAs), usually 22 nucleotides in length, can bind mRNA. Thus, miRNA binding further epigenetically alters transcriptional activity by degrading mRNA or prevention of translation.[58] Genes that regulate cell homeostasis ("housekeeping" genes) are often constituently active, whereas genes responding to a stimulus, such as proliferation, undergo increases and decreases in cellular levels. Like DNA, mRNA does not affect cell structure or function directly.



• **Figure 26-5** Epigenetic control of gene expression. **A,** Epigenetic modifications. Human chromosomes are composed of chromatin, DNA wrapped around histone protein octomers. Each DNA-histone octomer complex is termed a nucleosome. The nucleosome can be modified and epigenetically controlled at two sites. The DNA can be methylated at the 5-position of cytosine. The histone can be modified through acetylation, methylation, and/or phosphorylation. **B,** Mechanism of epigenetic control of gene expression. Modification of histones and DNA cause reversible modifications in chromatin organization. Genes are expressed when the chromatin is open. Acetylated histone *(blue)* and de-methylated cytosine *(yellow)* lead to open chromatin. Gene expression is suppressed when the chromatin is condensed. Methylated cytosines *(green)* and deacylated histones lead to condensation of the chromatin. *DNMT,* DNA methyltransferase.

Proteins are responsible for many important structural and functional properties of a cell (see Figure 26-4). Each of three nucleotides in the DNA/mRNA coding region is called domains. For example, the cell surface protein epidermal growth factor receptor contains a ligand binding domain, a transmembrane domain, and a tyrosine kinase domain (to stimulate intracellular signaling).[59] In addition to the presence and amount of protein synthesis, protein

function is further regulated by chemical and conformational modifications that allow the cell even finer (and more rapid) means of regulation.[49] Proteins can be activated by enzymatic cleavage of inactive precursor molecules. Extracellular proteins are frequently modified by glycosylation, or the addition of complex sugar molecules. Intracellular proteins, especially those associated with signal transduction, undergo the phosphorylation of specific amino acids (serine, threonine, or tyrosine). Acetylation is also a major form of chemical modification of proteins. Environmental changes, such as a change in pH, can profoundly affect protein structure and function. Last, protein function can be modulated by feedback inhibition.[49]

Taken together, the constituents of the DNA→mRNA→protein molecular paradigm shows a remarkable amount of efficiency and flexibility. Although the cell contains an estimated 23,000 to 40,000 genes, mRNA and protein processing actually can generate an estimated 1 million separate proteins.[60] Modulation of gene expression exerts a more powerful, albeit slower, response to the cell's needs than protein metabolic and feedback inhibition functions.[49] In addition to structural building blocks, proteins also govern regulatory pathways as ligands, receptors, secondary (or intracellular) messengers, and transcription factors. Proteins act in cascades or pathways. Frequently, proteins producing similar effects within these pathways lead to redundancies that protect and maintain the cellular function governed by the pathway. In short, at each step of the paradigm (DNA→mRNA→protein), cell structure and function can be regulated and modified.

The molecular basis of many human diseases, including cancer, results from perturbations in this genetic paradigm. Therefore, discovery of "disease genes" for conditions such as Alzheimer disease, cystic fibrosis, or breast cancer is an important but preliminary step toward unraveling the molecular basis of the disease pathogenesis. Molecular alterations leading to the aberrant behavior of the cancer cell can be categorized as nucleic acid (DNA/mRNA) and protein alterations. Changes in DNA structure and function (gene expression) lead to important qualitative and quantitative protein alterations that ultimately result in the structural and behavioral characteristics of the cancer cell.

Nucleic Acid Dysregulation in Human Cancer

Complex biologic and biochemical mechanisms protect the integrity of DNA; therefore, there is a low rate of mutagenesis in normal cells. Some genetic diversity must occur to allow for evolution; however, rapid or uncontrolled genomic alterations can lead to cancer or cell death. Biologically, tissue architecture protects stem cells (believed to be the originating cell type of human cancers) from genetic damage.[61] Biochemically, an array of enzymes and low molecular weight molecules neutralizes mutagens before causing any genetic alterations. However, each cell type still undergoes low but significant mutation rates due to a variety of chemically reactive molecules.[62] Cancer-associated DNA signal pathways. Second, nucleotide sequence alterations affect specific genes. Cancer-associated mRNA changes result from either large or small-scale DNA alterations, as well as perturbations in other post-transcriptional regulatory mechanisms.

Genomic Instability Leads to DNA Alterations in Cancer Cells

Because most cancer cells are observed to show at least some DNA alteration, many investigators believe a certain level of genomic instability allows the cancer cell to sustain the necessary genetic damage to lead to the malignant transformation.[63-66] Variability in development and progression between tumors suggests that tumors may differ in their proclivity to accumulate the necessary genetic alterations. Cancer cell genetic alterations can occur at a frequency as high as 100 times that of their non-transformed counterparts.[67] Therefore, in addition to selective pressures on cancer cells, genetic alterations leading to cancer behavior may be due to a failure to survey and repair DNA damage, as well as enhanced sensitivity to mutagens.[65,68,69] "Caretakers" of genome integrity can be arranged into three broad categories: (1) DNA damage detection and repair mechanisms, (2) direct DNA damage molecules, and (3) inhibitors of DNA mutagens.[9,70-72] Genomic instability can be progressive or episodic. Progressive instability results from an inherited defect that leads to new mutations with each successive cell generation. In progressive genomic instability, DNA alterations tend to be widespread in the genome.[73-75] Episodic instability leads to specific DNA alterations that occur in cells that do not inherit a defect in genomic homeostasis.[75] Rather, episodic instability is triggered by a selective pressure, such as oxidative stress. Both large-scale chromosomal alterations and small-scale nucleotide sequence alterations might result from either type of genomic instability during tumorigenesis.[76-78]

Chromosomal Abnormalities in Cancer Cells

Most human cancers show quantitative (aneuploidy) or qualitative (structural) chromosomal abnormalities.[79] Numerical chromosome changes involve either the entire chromosome or one of the DNA alleles (or pairs). Allelic changes often result in the duplication of the remaining allele.[80] Cells within various tissues tend to share the same numerical chromosomal alterations and can lose a significant number of alleles (25% to 50%) during malignant transformation. These alterations may be due to progressive instability through inheritance of mutations to DNA damage repair genes such as MMR and p53.[81-85] Several other events can lead to numerical chromosomal alterations in aneuploid cancer cells. Abnormalities in the number and/or function of the chromosomal centrosome due to STK 15 kinase or p53 inactivation can lead to aneuploidy.[81] Alteration of mitotic spindle checkpoints, such as hMAD2 in breast cancer, can lead to abnormal segregation

of chromosomes during cell division.[86,87] Last, inactivation of genes that respond to DNA damage, such as p53 ATM or BRCA1/2, can also lead to replication of an altered DNA number.[85,88,89] In addition to numerical chromosomal alterations, three forms of chromosomal structural alteration may be critical for malignant progression: gene amplification, rearrangement/translocation, and deletion.

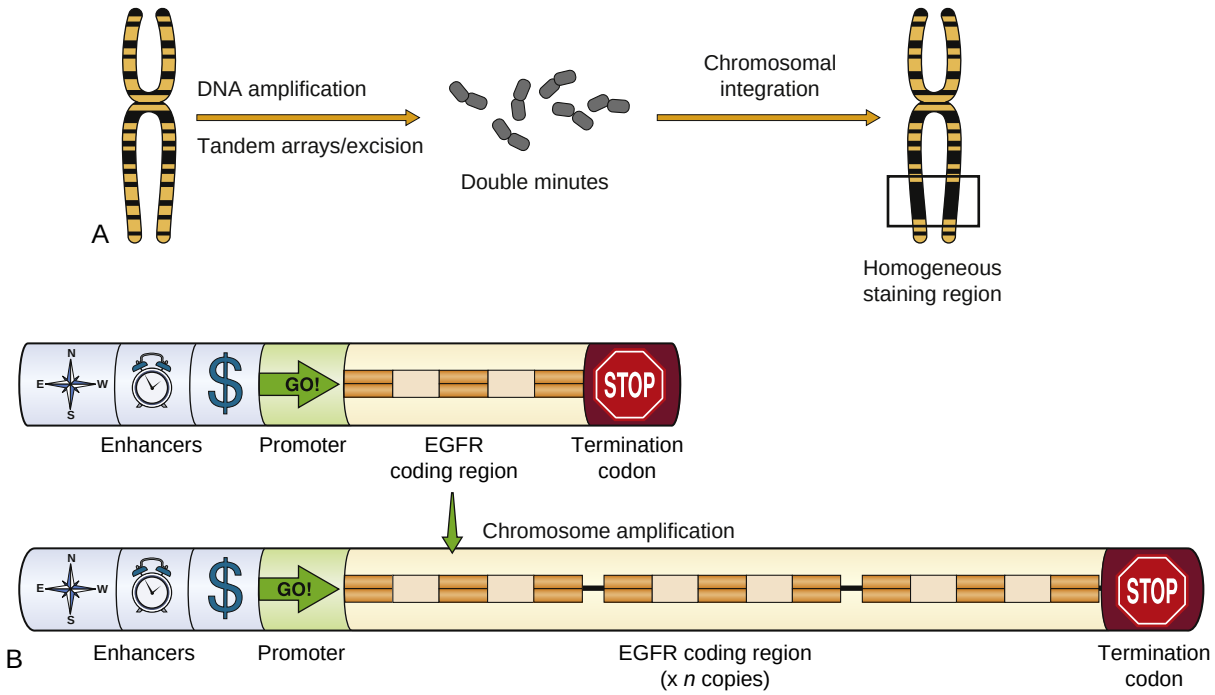
Gene amplification is the repeated duplication of a certain chromosomal region, often 50- to 100-fold[38] (Figure 26-6). There are two distinct structural alterations that lead to amplification. Double minutes are small pieces of chromosome that lack a centromere.[90] They cannot be inherited but are maintained by selective pressures. Homogeneous staining regions are double minutes that are incorporated into chromosomes during cell division. Both double minutes and homogeneous staining regions are frequently observed in chemotherapy-resistant tumors and are believed to harbor genes that confer a selective advantage to the cancer cell.

Chromosomal rearrangements such as translocations have been well described in human cancers[38] (Figure 26-7). Translocations are a transfer of part of one chromosome to another.[94] Translocations are considered reciprocal if two chromosomes trade material. Like gene amplification, translocations can lead to cancer-associated alterations of gene expression.[95] In Burkitt lymphoma, reciprocal translocation of the Myc proto-oncogene to an immunoglobulin promoter in B cells leads to an elevated expression of Myc.[96,97] Therefore, unlike gene amplification, which increases gene expression by increasing template number, this example of reciprocal translocation leads to increased gene expression by changing the transcriptional regulatory apparatus. The Philadelphia chromosome (a translocation from chromosome 9 to chromosome 22) is an important marker for chronic myelogenous leukemia.[98] Rather than alter the expression level of the genes at this locus, a fusion gene product, BCR-ABL, results. Activation of both oncoproteins is important to tumor progression.

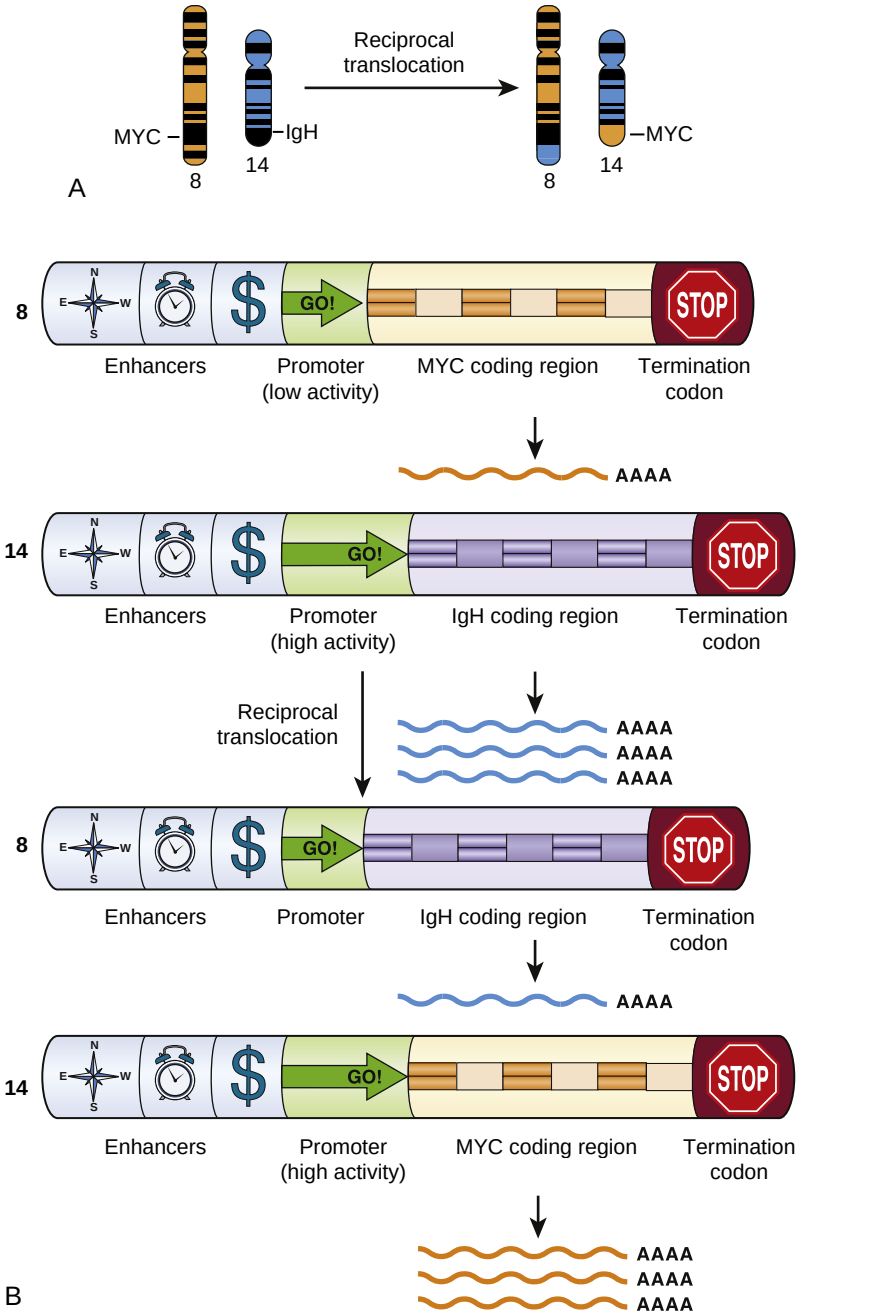
Chromosomal deletions are believed to be an important mechanism of inherited loss of tumor suppressor gene loci[38] (Figure 26-8). Following the sporadic or inherited deletion of one allele, the second can be inactivated by either mutation or epigenetic "silencing" (which is discussed later) in a "two-hit" fashion. In colorectal cancer, deletions of important suppressor gene loci at chromosome 5 (APC), 17 (p53), and 18 (DCC) are important molecular events leading to malignant progression.[99-101] Although translocations and deletions are often linked to genes that promote malignant transformation, chromosomal deletions are primarily associated with loss of genes that suppress cancer formation.

Nucleotide Sequence Abnormalities in Cancer Cells

Rather than large-scale changes in chromosomal DNA, nucleotide sequence alterations affect individual genes.[102-104]



• **Figure 26-6** Cancer-associated chromosomal alterations: gene amplification. **A,** Amplified DNA in tandem arrays is excised as double minutes or reintegrated as homogeneous staining regions. **B,** Cancer-associated gene amplification of a gene such as the epidermal growth factor receptor *(EGFR)* occurs when multiple copies of the same gene come under the control of the same promoter, thereby increasing the number of transcript copies and protein products.

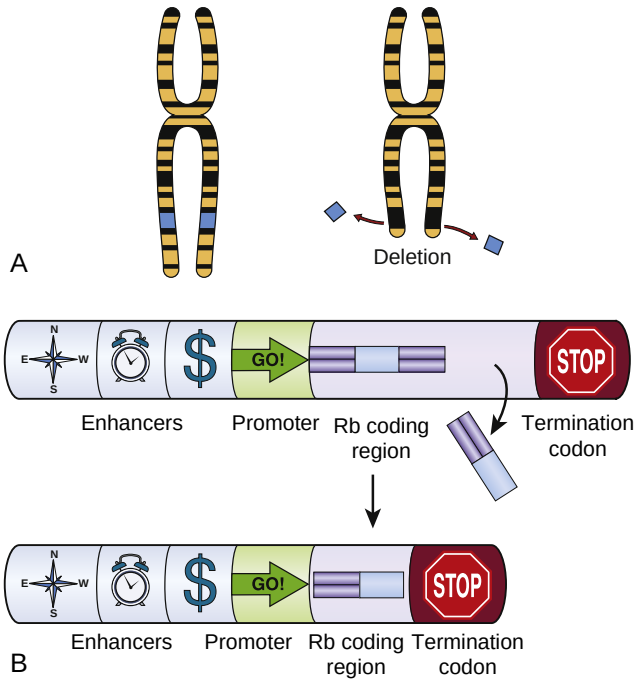


• **Figure 26-7** Cancer-associated chromosomal alterations: translocation. **A,** An exchange of a portion of chromosome 8 containing the Myc gene with that of a segment of chromosome 14 leads to the Myc gene being attached to a highly active immunoglobulin promoter. **B,** The consequence of the reciprocal translocation is that the Myc gene activity is increased because it is now under the control of a more active promoter.

These alterations usually involve a single nucleotide change or insertion/deletion of nucleotides[105] (Figure 26-9). Changes in a single nucleotide (point mutation) can lead to a missense mutation (changing an amino acid) or nonsense

the message is read, leading to a completely altered amino acid sequence. This altered amino acid sequence can lead to profound changes in protein function.[105] A common nucleotide alteration observed in cancer cells is microsatellite instability.

Microsatellite instability (MSI) in cancer cells refers to insertion or deletion of nucleotides in simple repeated sequences that are normally found in DNA.[103] Microsatellites are repeats of four (or more) nucleotides and appear as numerous and randomly distributed regions throughout the chromosomal DNA.[106] The frequency of microsatellite alteration depends, in part, on the type of repeated sequence (mononucleotide repeat, dinucleotide repeat), length (larger



• **Figure 26-8** Cancer-associated chromosomal alterations: deletion. **A,** Portions of a chromosome (or even entire chromosomes) can be lost as a result of genomic instability. **B,** The consequences of the deletion on Rb suppressor activity.

alleles are more frequently altered), location of the sequence, and the type of alteration in DNA repair.[107-109] Alteration of mismatch repair genes such as hMSH1/2/3, hPMS1/2, and hMLH3 is associated with an increased frequency of MSI.[110-119] MMR-deficient cancer calls can show about a 100-fold increase in MSI over MMR-proficient cancer cells.[120] Microsatellite alteration leads to frameshift mutations in important proteins regulating normal cellular homeostasis, such as TGFβRII, BAX, APC, and IGFIIR.

Epigenetic Alteration of Gene Expression in Cancer Cells

Tumor suppressor gene inactivation and oncogene activation can occur through epigenetic manipulation of gene expression.[121,122] The "two-hit" hypothesis (where a tumor suppressor gene functional loss is due to a sequential loss

Hypermethylation of one or both copies of genes encoding important cell adhesion molecules and growth regulatory proteins can lead to loss of gene expression. In addition, DNA hypomethylation can lead to chromosomal instability and oncogene activation.[125-127] Epigenetic alteration of gene expression has been observed in several cancers, including colorectal cancer (MLH1), renal cell carcinoma (VHL), p16/CNKN2A (head and neck cancer), and BRCA1 (breast cancer).[128-131] Epigenetic gene expression alteration is an important target for cancer therapy that is discussed later.

Summary and Consequences of Cancer Cell Nucleic Acid Alterations

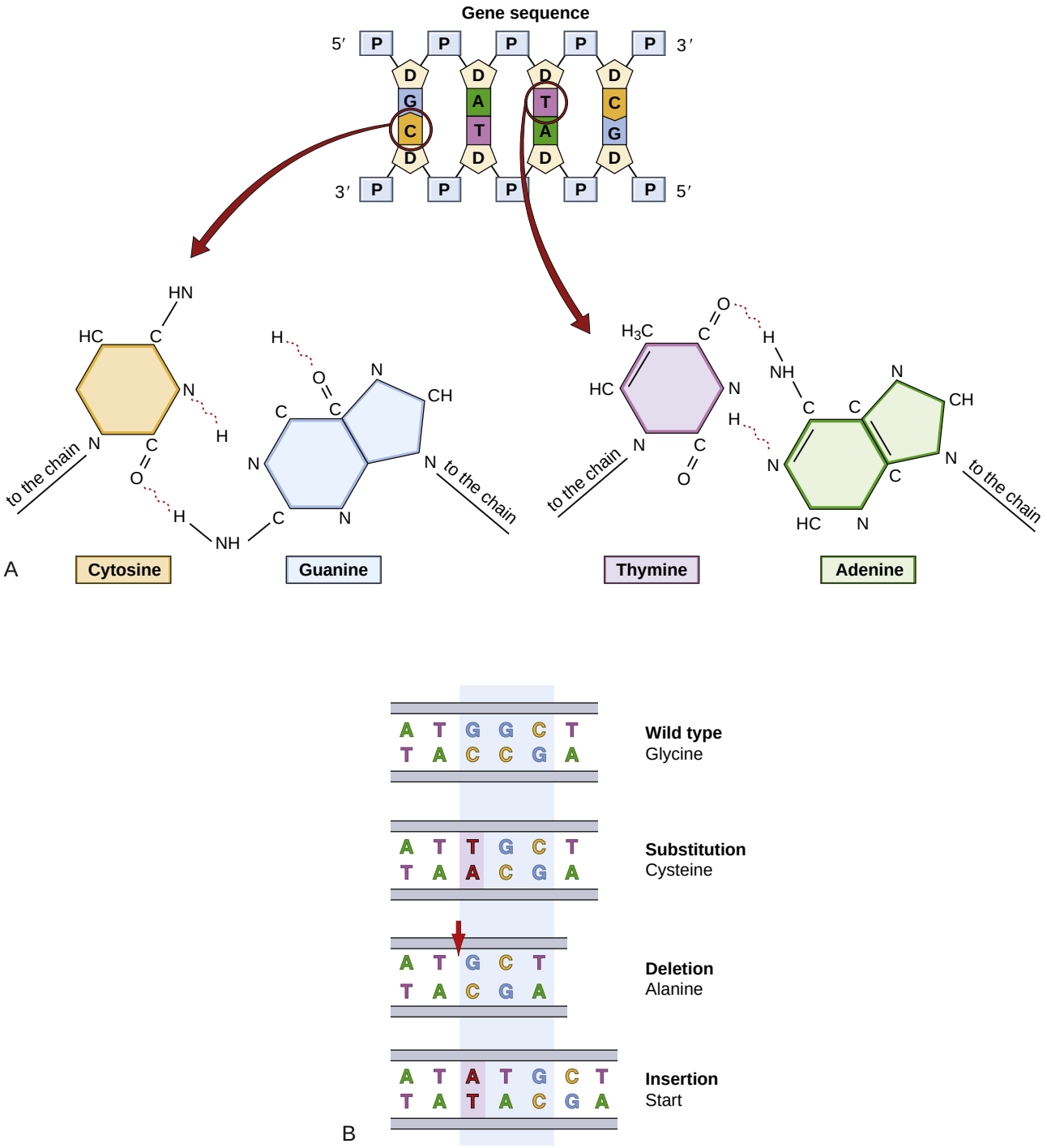
In summary, cancer arises from an accumulation of inherited or environmentally triggered genetic (and epigenetic) alterations. Genes become overactive or silenced by large-scale genetic changes such as chromosome number (aneuploidy) and structure (amplification, rearrangement, deletion) or small-scale genetic changes such as nucleotide point mutation, insertion, or deletion. Gene expression is also affected by epigenetic or conformational changes due to nucleotide or histone modifications. These large- and small-scale alterations, in turn, create quantitative and/or qualitative changes in the encoded mRNAs. Ultimately, the changes in the transcripts lead to either increases/decreases in protein amount or a change (overactivity or suppression) in protein function. These proteins perform crucial roles in normal cellular homeostatic pathways. Abrogation of these pathways leads to the cancer cell behavior that confers a selective advantage over their normal cellular counterparts.

Protein Dysregulation: How Genetic Alterations Lead to Cancer

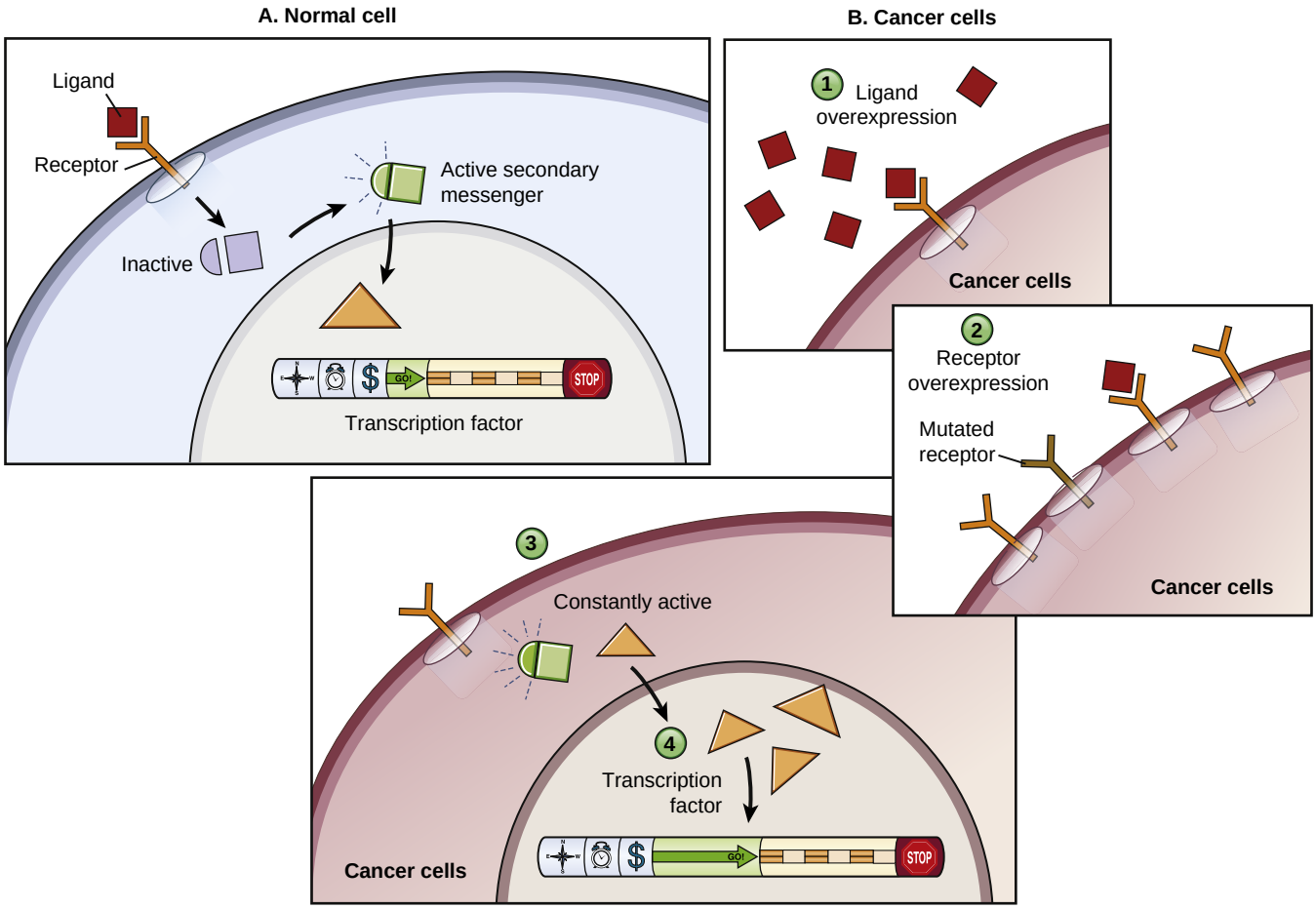
When genes are activated, the products of their expression are proteins. Therefore, when gene expression is quantitatively and/or qualitatively altered, the same changes to the protein product can occur. Proteins govern many of the structural and functional characteristics of the cell and are often categorized by their cellular location and function (Figure 26-10, *A*). In the context of cancer biology, deregulated proteins that support malignant traits are often referred to as oncoproteins; those that inhibit the malignant phenotype are termed tumor suppressor proteins (often referred to as "gatekeepers"). Extracellular proteins refer either to molecules that provide a structural and regulatory framework for the cell or to soluble factors that can provide signals locally or from a distance. Cell surface proteins can

a cell to respond to stimuli. Part of that response can be to signal transcription factors to upregulate or downregulate gene activity. The activated genes can lead to a strong, pluripotent response. Not only do proteins form response pathways, but also they can create networks of pathways. In other words, activation or inactivation of a factor in one pathway can influence the function of several other pathways. These pathway networks may influence a single or several cell traits.[49]

By changing the amount and/or function of a protein, an entire protein pathway or pathway network can become deregulated.[132,133] For example, a cancer cell might carry a gene mutation that leads to production of a growth factor receptor that is activated without needing to be bound to a growth factor. The result is the stimulation of a network of pathways leading to cell proliferation, even though all the other proteins in the pathway are "normal." Accelerated



• **Figure 26-9** Nucleotide sequence mutations. **A,** The nucleotide is the fundamental component of DNA. The components of the nucleotide are phosphorus *(P)*, sugar (deoxyribose, *D*), and four nucleotides cytosine *(C)*, guanine *(G)*, thymine *(T)*, and adenine *(A)*. The two DNA strands have complementary nucleotide sequences based on pairings between G:C and T:A. **B,** DNA sequence changes can result in profound protein alterations. Each three nucleotides encode a single amino acid in the polypeptide chain. For example, GGC is eventually translated as glycine. A G→T substitution changes the code to the amino acid cysteine (TGC). Deletion of G leads to a shift in how the sequence is read; therefore, the peptide chain starts with alanine (rather than glycine) and each amino acid thereafter is incorrect because of the sequence frameshift. Likewise, addition of a nucleotide leads to a frameshift. Instead of glycine, a start codon (ATG) is generated, creating a new (and different) polypeptide chain. A frameshift can also lead to a mistaken stop codon that will prematurely terminate the synthesis of the amino acid chain.



• **Figure 26-10** Release from growth signal requirements. **A,** The signal transduction pathway. Many proteins serve to transmit signals to allow the cell to respond to stimuli. Signals for cell division often are triggered by an extracellular ligand such as a growth factor (GF). Binding of the growth factor receptor (GFR) initiates the activation of secondary messengers that conduct the message from the cell surface throughout the cytoplasm and to the nucleus. Activation of transcription factors can initiate programmed cellular responses. **B,** Growth signal requirements can be negated by alteration of any component of the pathway. *1,* Overexpression or autostimulation produced by cancer cells can eliminate the need to wait for other cellular sources to provide a stimulus. *2-4,* Overexpression or mutation of GFRs, secondary messengers, or transcription factors can make the cancer cell more sensitive to growth stimulation, or mutated forms might remain constituently activated.

proliferation confers a selective advantage on the cancer cell over its neighbors. The cancer cell proliferates without needing to be stimulated by the appropriate ligand; the normal cell must wait for the proper signal(s).[134] In addition, accelerated activity might lead to other genetic mistakes that could generate other mutations to support genetic growth. Several traits are believed to confer selective advantages that form the hallmarks of cancer cell biology.[9]

Several important regulatory pathways are abrogated to allow cancer cells to outcompete their normal neighbors. Molecular alterations at the DNA, mRNA, and/or protein levels disrupt key networks that regulate normal cell appearance and behavior, thereby leading to the common cancer cell traits. However, because different cells may be regulated by different molecules and the alteration of any single molecule within a pathway or network may lead to the same malignant trait, no single molecular alteration is responsible for cancer (or even a single cancer trait) within all malignancies.[134,135] Important molecular growth controls that are deregulated in the process include release from growth signal requirements, insensitivity to inhibitory signals, evasion of apoptosis, immortalization, neovascularization, and metastasis.[9]

Release from Growth Signal Requirement

Hyperactivation of proliferative or mitogenic pathways is a key trait of cancer cells.[15,136] The release of cancer cells from normal growth controls is largely achieved by the overactivity of growth-promoting networks and inactivation of growth-inhibiting networks (discussed in the next section). Normal cells depend on diffusible factors, extracellular matrix molecules, and cell-cell adhesion molecules as growth signals. Therefore, the growth signal starts at the cell surface, is transmitted through the cell membrane, and stimulates intracellular cascades that control the signal response. Without the proper growth signals, normal cells do not divide or remain in a quiescent state.

There are four fundamental mechanisms through which a cancer cell becomes autonomous from growth signal requirements (see Figure 26-10, *B*). First, extracellular growth signals can be altered.[137] A well-described example is autocrine stimulation, a positive feedback loop by which the cancer cell produces its own growth factors.[138] The result is that the cancer cell is no longer dependent on growth factors from the microenvironment to stimulate cell division. Overexpression of growth factors, such as platelet-derived growth factor and transforming growth factor alpha (TGF-α), is also common in solid tumors.[139-141] Alternatively, the tumor stroma can supply mitogenic factors.[16]

Second, cell surface receptors can be altered quantitatively or qualitatively. In normal cells, cell surface receptors have extracellular ligand-binding domains, transmembrane domains, and intracellular domains that transmit the growth signal by phosphorylating target molecules at specific amino acids (primarily tyrosine or serine/threonine).[59,142-144] Overexpression of growth factor receptors, such as the epidermal growth factor receptor and HER2/neu receptor, leads to a hypersensitivity to growth factors in the microenvironment.[145] Receptors also can be truncated, leaving the domains responsible for cellular stimulation active without either the requirement of ligand binding or the ability to inhibit stimulation.[146] In addition, cancer cells can change the receptors on the cell surface to those that promote cell growth. Frequently, cancer cells alter integrins, cell surface molecules that transmit signals from the extracellular matrix.[147-149]

Third, cancer cells may have altered secondary messenger pathways, molecular messengers that receive and process messages from stimulated cell surface receptors.[150,151] Signals generated by receptor-ligand binding are sent through the cytosol and to the nucleus by secondary messengers. A growth signal can be accentuated by disrupting negative feedback mechanisms that inhibit cell proliferation.[9] These pathways have many members and can be altered by changing the structure or function of any one of its members. For example, the SOS-Ras-Raf-MAPK pathway is altered in many tumors.[9,152,153] In normal cells, Ras is activated by binding to GTP.[38] This is mediated by guanine nucleotide exchange factors (GEF) and inhibited by guanine activating proteins (GAP). In cancer cells, Ras can be activated by overactivity of GEF or inactivation of GAP.[154] Other important secondary messenger pathways include the JAK/STAT, Wnt-catenin, and PTEN regulatory loops.[155-157] Ultimately, abrogated secondary messenger pathways can lead to activation of cell proliferation programs.

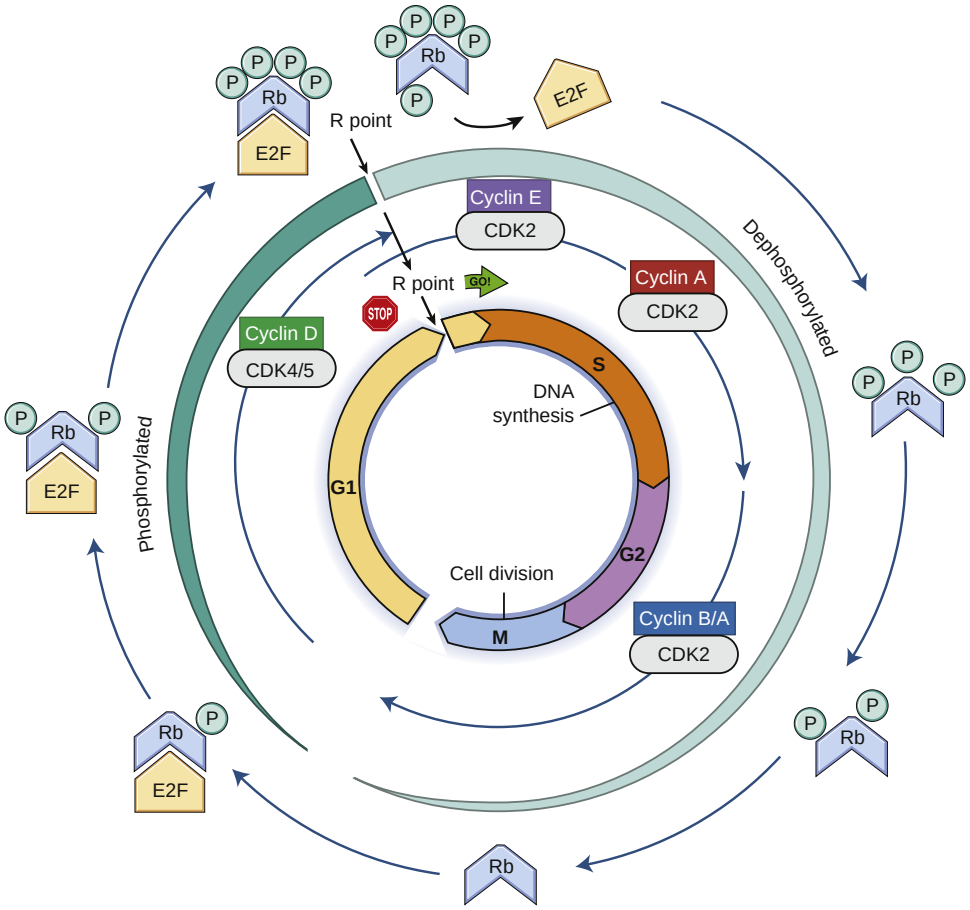
Fourth, overexpression of transcription factors or expression of mutated transcription factors can activate immediate-early and delayed growth programs in conjunction with or independent of upstream stimulation. For example, overexpression of the transcription factor Myc contributes to deregulated cell growth (and is associated with poor prognosis) in many human cancers (the molecular mechanism is discussed in the next section).[158,159] As a transcription factor, Myc controls the expression of several proliferation-related genes necessary to sustain a response to a growth signal.[160,161] Overexpression of transcription factors such as Myc overrides inhibition of gene expression activation by outcompeting transcription inhibitors (such as Mad and Max).[162,163]

What is the selective advantage of growth signal independence for the cancer cell? Rapid cell division helps replace normal cells with other cancer cells within a tissue. In addition, rapid cell division can result in more DNA mutations by decreasing the time in which it is possible to detect and repair replication errors. Therefore, other genes might be mutated, leading to the deregulation of other networks and acquisition of new cancer cell traits. Proto-oncogenes refer to genes that encode for growth-promoting proteins in a normal cell. Oncogenes refer to altered (mutated) proto-oncogenes (normal growth stimulatory genes) that lead to this self-sufficiency from growth signals. These mutations can be both large-scale and small-scale chromosomal alterations. EGFR can be overexpressed through gene amplification or activated through a gene deletion.[164] The Ras gene family is altered by a point mutation leading to an amino acid change. This single amino acid substitution results in GEF overactivity and constituent Ras activity.[165] In some cases, epigenetic forces such as DNA methylation also have a role in oncogene activation.[166] Although hyperactivity of growth-promoting pathways clearly is important to cancer development, the intensity of oncogenic signaling depends on disabling growth-inhibitory and apoptotic pathways.

Insensitivity to Growth Inhibitory Signals

To maintain homeostasis in normal tissues, growth-inhibitory signals modulate and block growth-promoting signals.[136,167,168] These signals (or ligands) also bind cell surface receptors that trigger intracellular secondary messengers and activate transcription factors. Growth-inhibitory signals are either soluble or adherent to adjacent extracellular matrix or neighboring cells. These "gatekeeper" proteins, encoded by tumor suppressor genes, are inactivated during tumorigenesis, leading to a loss of extracellular and intracellular controls to cell division.[136]

Normal cell division is regulated by a complex molecular circuit often referred to as the cell cycle clock.[169] Specific checkpoints in the cell cycle clock are governed by changing the levels of cyclins, a family of regulatory proteins of serine-threonine kinases (known as cyclin-dependent kinases).[170] The levels of cyclins rise and fall depending on the cell cycle stage. Accumulation and destruction of these cyclins ensure that each checkpoint in the cell cycle occurs in its proper order at its proper time. The four checkpoints in the cell cycle clock are G1 (gap 1), S (DNA synthesis phase), G2, and M (mitosis) (Figure 26-11). External signals, such as extracellular mitogenic signals, influence the decision of a cell to replicate in the G1 phase; the progression through the remaining phases of the cell cycle is independent of external signals once the cell division regulatory apparatus passes the restriction point (or R-point).[169] Cyclins D and E are most directly under mitogenic control and G1; the



• **Figure 26-11** Rb-mediated control of the cell cycle. The molecular regulators that govern cell division are referred collectively as the "cell cycle clock." A cell can choose between a quiescent (no cell division or G_0) and proliferative (cell division) state based on upstream signal transduction pathways triggered by transforming growth factor beta (TGF-β), integrins, the microenvironment, tyrosine kinase receptors, and G-proteins. The cell cycle is divided into four phases: G1 (or gap 1), S (DNA synthesis), G2, and M (mitosis or cell division). In G1, the cell is responsive to upstream signals promoting and inhibiting cell division. Restriction or R point is the moment in G1 where the cell decides to commit irreversibly to cell division. The cell cycle phases are controlled by the pairing/activation of cyclins with cyclin-dependent kinases (CDKs). Rb is hypophosphorylated during G1 until the cell progresses through R-point. Subsequently, Rb becomes progressively more phosphorylated until the M/G1 transition (it then becomes dephosphorylated). Rb is an inhibitor of cell division. Phosphorylation inactivates Rb and allows cell division. The cyclin-CDK complexes phosphorylate Rb, thereby guaranteeing that cell division is completed. In cancer, mutation/deletion of the Rb gene, Rb promoter methylation, or Rb sequestration by tumor viruses perpetually inactivates Rb control of R-point, thereby eliminating an important restriction of cell division.

remaining cyclins (A and B) regulate the remaining cell cycle phases.[168,171-173] The key regulatory point in G1 between cell division (entrance into the cell cycle) versus differentiation/senescence (cell cycle block) is the R-point.[174-177] Therefore, a critical step to achieve unconstrained proliferation in tumorigenesis is to deregulate the proteins that govern R-point.

Most signals that regulate cell division at R-point modulate the retinoblastoma (pRb) pathway.[178-183] G1-phase moves irreversibly to S-phase based on the activity of the transcription factor E2F. pRb inhibits proliferation by binding/inactivating E2F transcription factors. E2Fs control genes necessary for cell division.[184] When phosphorylated, pRb can no longer bind E2F; therefore, cells progress through R-point into S-phase. In normal cells, pRb is dephosphorylated by antigrowth signals, such as transforming growth factor beta (TGF-β), and the pRb-E2F complex blocks cell cycle progression from G1 to S.[185] Cell proliferation occurs when cyclin D (complexed with either cdk4 or cdk6) and cyclin E (with cdk2) phosphorylate pRb, overcoming its inhibitory effects on the cell cycle by causing E2F to be released.[186-190]

In cancer cells, pRb activity often is blocked or lost, leading to a loss of R-point regulation and uncontrolled cell proliferation.[178] In some tumors, such as retinoblastomas, osteosarcomas, and small-cell lung carcinomas, pRb is inactivated directly through gene mutation/deletion or promoter methylation.[9] Viruses, such as the human papillomavirus in cervical cancers, also produce proteins that bind and inactivate the pRb protein.[191,192] However, like

the SOS-Ras-Raf-MAPK pathway, the pRb circuit more often is inactivated by disrupting other members of the pathway.[9,193] For example, cancer cells might lose TGF-β responsiveness through downregulation of the receptor or production of dysfunctional receptors.[194,195] Intermediary messengers in the pathway, such as Smad4 and $p15^{INK4B}$, also might be mutated. In breast cancers, cyclin D1 is overexpressed, causing hyperphosphorylation of pRb.[196,197] Therefore, inactivation of any member of the pRb pathway can lead to the same trait of uncontrolled proliferation that is characteristic of cancer cells. In addition, oncoproteins that can deregulate cell differentiation can affect pRb cell cycle regulation. Hypophosphorylated pRb is required to halt cell division to allow differentiation.[198] Oncoproteins such as Myc inhibit cell differentiation in human cancers by ov

pr
that blocks reentry into the cell cycle.[163] Differentiated cells contribute to tissue function (in contrast to nondifferentiated cells), which supports tissue renewal by replacing lost cells. Cancer cells often vary in their degree of differentiation. The significance and underlying mechanism of cellular differentiation is poorly understood. At the molecular level, two transcription factors, Max and Mad, bind and stimulate genes involved in differentiation.[158] Normal proliferating cells produce Myc, which binds preferentially to Max, allowing the expression of proliferation genes.[199] In cancer cells, Myc is overproduced, leading to displacement of Mad for Myc and a switch from differentiation programs to proliferation gene programs. As mentioned earlier, Myc is overexpressed in Burkitt lymphoma.[159] The coding region of the Myc gene is translocated or swapped to the highly active promoter of an immunoglobulin gene in B cells. Normally, the immunoglobulin gene/gene promoter is very active in B cells and the Myc gene/gene promoter is not. By replacing the immunoglobulin coding region with Myc, the affected B cell fails to perform its differentiated task (to produce immunoglobulins), instead overproducing Myc, which leads to increased proliferation. Increased Myc protein binds to and sequesters transcription factors that promote differentiation and bind to/activate the promoters of proliferation genes. Therefore, Myc overexpression not only accelerates growth promoters (as addressed in the previous section) but inhibits growth suppression (through differentiation).[200]

What is the selective advantage to the cancer cell of inhibiting growth suppressors? The genetic basis of the loss of inhibitor or "gatekeeper" protein function probably is more common in human cancers than oncogene activation but is experimentally more difficult to identify because it is a negative phenotype (or an event no longer present in a cancer cell). Dozens of tumor suppressors that inhibit cell proliferation through a variety of mechanisms have been identified in a wide range of human cancers.[9] Classically, the inhibitor proteins are completely inactivated. By the strictest definition of tumor suppressor genes, a chromosomal loss of heterozygosity (LOH) must be identified in many different tumors, where one allele (often due to a dele-

sor gene function can be reduced by other mechanisms. The function neurofibromatosis-1 gene (NF-1) product is

eliminates the normal or wild-type protein product of the unaffected gene. Loss of p53 function is one of the most common molecular events in human cancer, and the biologic consequences are far-reaching, especially with respect to apoptosis.[204] In short, virtually every cancer involves some genetic and/or epigenetic perturbation of cell cycle regulation/the Rb pathway. Furthermore, in human cancers, inactivation of the growth inhibitors is likely a more common and important event leading to uncontrolled proliferation than is overactivity of oncoproteins.

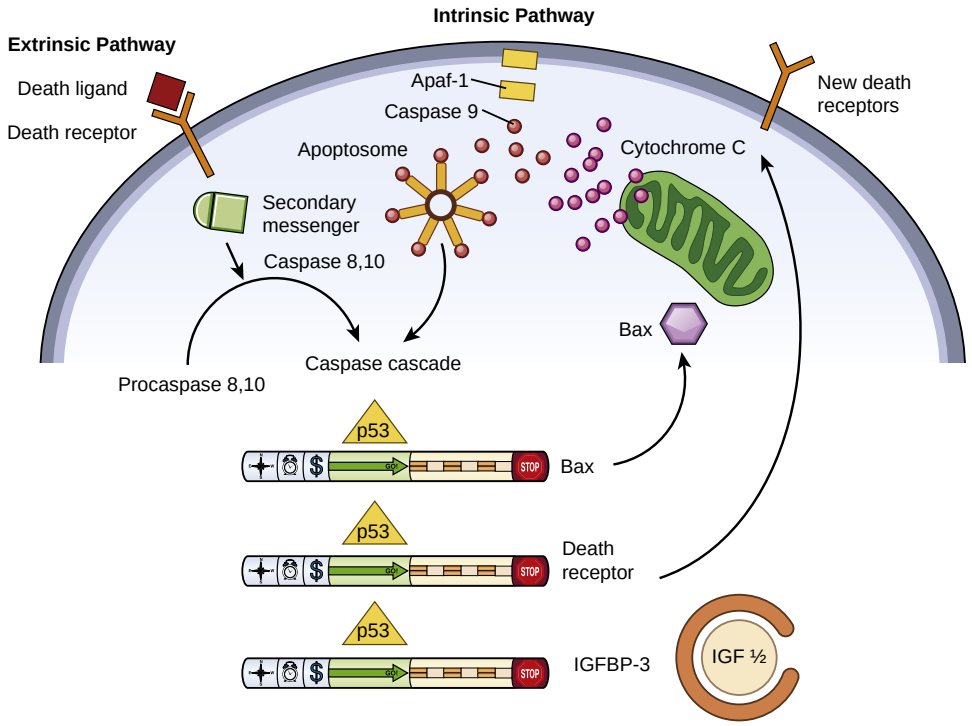
Evasion of Apoptosis

Thus far, the protein products (ligands, receptors, secondary messengers, and transcription factors) of proto-oncogenes and tumor suppressor genes have been discussed in the context of pro-mitogenic and anti-mitogenic regulators. However, there are key regulators abrogated in tumorigenesis that control a cell's exit from the cell cycle.[205,206] Cells leaving the cell cycle (like differentiated cells) are termed quiescent or post-mitotic. Quiescent cells can reenter the cell cycle. Post-mitotic cells undergo several processes including terminal differentiation, senescence, or apoptosis.[207,208]

Resistance to apoptosis is a critical hallmark of cancer cells.[9,209] Tissue homeostasis balances renewal (through cell division) against attrition (through cell death). Apoptosis (deriving from the Greek term for the falling of petals from

chemotherapy cytokine exposure, high calcium concentrations, nitric oxide, or oxidative stress[210,211] (Figure 26-12). Once initiated, apoptotic cascades systematically dismantle a cell to a condensed mass of its sum parts that is engulfed by neighboring phagocytic cells. Left in place, apoptosis eliminates the "precancer" cells that have begun the succession of genetic changes conferring growth advantages by detecting, among other things, DNA damage and oncogene activation. Like the cell cycle, apoptosis is regulated by pro- and anti-apoptosis pathways; therefore, apoptosis is tightly regulated and a function of the severity of the stimulus rather than simply the specificity or a single apoptotic stimulus.[209]

The process of apoptosis proceeds through three phases: initiation phase, effector phase, and degradation



• **Figure 26-12** Apoptosis and cancer. Initiation of apoptosis occurs with extrinsic and intrinsic pathways. *Above:* Extrinsic pathways *(left)* are triggered by death ligand–receptor binding and secondary messenger activation that leads to cleavage of procaspases 8 and 10 to activated caspases. The intrinsic pathway begins with cytochrome C release from the mitochondria. Apaf-1 combines with cytochrome C and caspase 9 to form the apoptosome, which also activates the executioner caspases. *Below:* p53 activates several pro-apoptotic gene programs. Cell death receptor genes are activated to make the cell more sensitive to additional cell death signals. IGF-binding protein-3 (IGFBP-3) is activated. IGFBP-2 sequesters IGF 1/2 and blocks their anti-apoptotic activities. p53 also upregulates Bax, the pro-apoptotic protein that contributes to cytochrome C release.

phase.[210,211] The initiation phase triggers apoptosis and is governed by the extrinsic pathway (receptor-mediated) and intrinsic pathway (mitochondria-dependent).[212,213] The extrinsic pathway is initiated by extracellular ligands that bind to the tumor necrosis factor-alpha receptor (TNFR) superfamily.[214-219] Ligand-receptor binding leads to activation of the secondary messengers: death domain adaptor proteins FADD and TRADD.[220-222] However, there are other extracellular ligands/pathways that prevent apoptosis. For example, colony stimulating factors block hematopoietic stem cells from undergoing apoptosis. These secondary messengers lead to caspase (8 and 10) activation through a death-inducing signaling complex (DISC).[220-222] The intrinsic pathway (which responds to intracellular stress, such as DNA damage, growth factor withdrawal, and some chemotherapeutic drugs) results in increased mitochondrial membrane permeability and release of cytochrome C (which causes apoptosome formation and caspase [3 and 9] activation).[212,223-227] The Bcl-2 family (including Bcl-x_L, Bcl-w, Mcl-1, and A1) inhibits apoptosis by stabilizing the mitochondrial membrane and preventing cytochrome C release through binding (and suppressing) proapoptotic proteins such as Bax and Bak.[228-231]

The effector phase leads to the activation of the caspase cascades that control destruction of the cell. Caspases are a act simultaneously, but as a cascade. Although structurally similar, caspases are very specific in their substrates, and that specificity allows them to function in a highly orchestrated manner, controlling the specific stages of cellular breakdown (degradation phase).[233,234] Although both the extrinsic and intrinsic pathways of the initiation phase trigger different initiator caspase activation, the caspase cascades tend to converge at the effector caspases.[235] An important family of caspase inhibitors, the inhibitors of apoptosis (IAPs), play a central regulatory role in blocking apoptosis initiated either by the extrinsic or intrinsic pathways.[236,237]

The final stage, the degradation phase, results in the byproducts of the cellular suicide.[210] The cell nucleus fragments, and double-stranded DNA is broken down into nucleosomal segments. The cytoplasm condenses and protrusions appear in the cell membrane. Finally, the cell collapses into membrane-bound apoptotic bodies that are ultimately engulfed by phagocytes. The entire process spans between 30 minutes and 2 hours.

What is the selective advantage for the cancer cell with an inactive apoptosis program? Escape from apoptosis allows for unstable cell populations, (that normally would be eliminated) a key survival advantage, that provides the

opportunity to generate increasingly aggressive clones.[238] Dysregulation of a variety of protein factors in apoptosis pathways can lead to apoptosis escape. Receptors of the TNFR superfamily are mutated and/or downregulated in several lymphoid and solid tumors. Bcl-2 is overexpressed in over half of non-Hodgkin lymphomas.[238,239] IAPs have been shown to be overexpressed in breast, colon, and pancreatic cancers.[240-243] The nuclear factor κB (NFκB), an important transcription factor in apoptosis, is frequently deregulated in lymphomas.[244] However, perhaps the most important and best-described molecular event leading to apoptosis is the deregulation of p53.

The p53 tumor suppressor gene regulates many functions, including growth arrest and DNA repair, senescence, terminal differentiation, and apoptosis.[245] The function of p53 is lost in 50% of all cancers.[246,247] More than 85% of p53 mutations result in a single amino acid substitution. Under normal conditions, p53 is short-lived and appears in small amounts unless otherwise stimulated.[248] p53 is controlled by regulators such as Mdm2 and $p19^{ARF}$ that increase p53 levels in response to DNA damage, UV radiation, ionizing radiation, oncogene signaling, hypoxia, and transcriptional abnormalities.[246,249-251] Wild-type p53 upregulates Bax, Apaf-1, and caspase 9, upstream regulators of the intrinsic apoptotic pathway. In cancer cells, the mutant p53 binds and inactivates the wild-type p53 in a dominant negative fashion. In addition, mutant p53 is not subject to the same control by regulators such as Mdm2 as is wild-type p53.[249,252] Loss of p53 function supports malignant progression by allowing cells harboring aggressive mutations to clonally expand, preventing a halt to cell growth and allowing a rapidly growing cell population to expand uninhibited by hypoxia.[211]

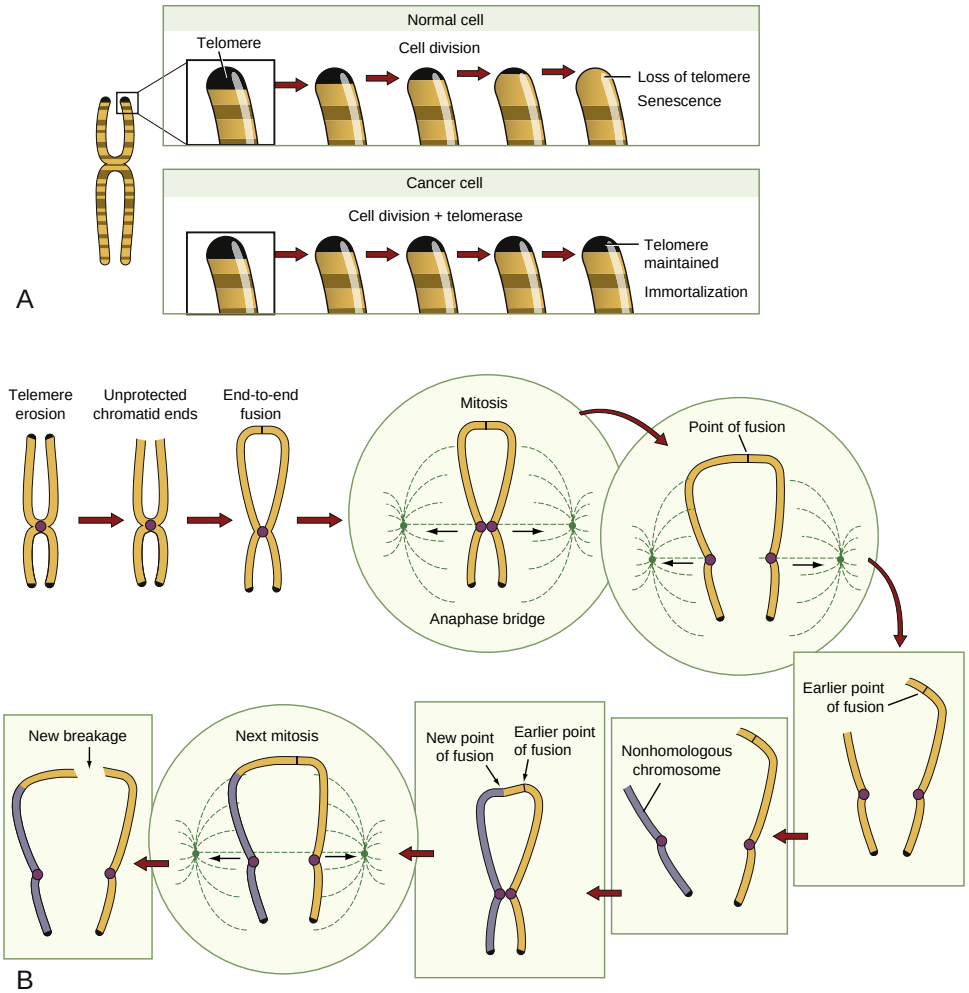
Recently, other genetic programs for cell death have emerged that are subverted by cancer cells. Autophagy, a response to stresses such as nutrient deficiency, leads to organelle breakdown.[209,253] Catabolites from the organelles are then used to support the cancer cell's energy demands. Cell stress–induced signals, such as PI1-kinase, AKT, and mTOR kinases, that attempt to induce apoptosis are also upstream regulators of autophagy. Stress induction of autophagy allows the cancer cell to survive by achieving a dormant state. Necrosis is another genetically based program that paradoxically benefits cancer cells.[209] Pro-inflammatory signals produced by the breakdown of necrotic cells attract inflammatory cells through bioactive mediators such as IL-1α.[27] The inflammatory cells, in return, produce cytokines such as growth factors that promote cancer cell growth. In addition to evading and/or taking advantage of

Immortalization

After a fixed number of doublings, a cell senesces or stops proliferating. In cell culture, limited replicative potential is referred to as the Hayflick limit.[254] Unlike the traits discussed earlier, senescence is largely independent of environmental cues.[255-257] The number of times that a normal cell can replicate is based on the length of its telomeres (from the Greek *telos* meaning "end" and *meros* meaning "part"), serving as a generational clock.[9] These protective G-rich DNA-protein terminal ends of the chromosomes prevent fusion with other chromosomes[258] (Figure 26-13, *A*). Because of inefficiencies in the enzyme that copies DNA, each time a cell replicates, it loses a portion of its telomere.[259] Complete loss of the telomere cap threatens a cell's genetic stability, as the uncapped chromosomal ends can fuse and subsequently rebreak to bind with other chromosomal ends (see later discussion).[260] Therefore, to prevent DNA replication errors, the cell reaches a crisis and stops undergoing mitosis. Other triggers of senescence include oncogene activation (Ras, BRAF), DNA replication stress, and cellular insult (DNA damage, high oxygen levels).[261]

The cancer cell avoids the consequences of crisis and achieves a limitless replicative potential or immortalization.[262-264] Two molecular primary events allow a cancer cell to overcome senescence/crisis and become immortal. First, a defective apoptotic pathway must exist; otherwise, the chromosomal damage generated during crisis would lead to the autodestruction of the cell.[263] The loss of the protective telomere cap leads results in prolonged breakage/fusion/bridge (BFB) cycles, allowing chromosomes to stick to one another[265] (see Figure 26-13, *B*). The loss of a single telomere can result in ongoing genomic instability involving multiple chromosomes, leading to rearrangements commonly associated with human cancer. BFBs lead to aneuploidy, abnormal chromosome number and structure due to amplifications, rearrangements, and deletions.[266,267] Gatekeeper pathways, such as p53 and p16, must be abrogated, or the cell would undergo senescence.[261] DNA damage, dysfunctional telomeres, and genotoxic stress activate p53/p21 gene expression that leads to growth arrest. Mutant p53 prevents the arrest. Oncogene activation and cellular stress induce p16, an upstream regulator of pRb. Activation of pRb leads to chromatin reorganization and E2F target gene repression. Unlike the p53 pathway, once the pRb pathway is activated, it cannot be reversed. By avoiding senescence, these cells can undergo mutations of other oncogenes and tumor suppressor genes.

For cells to clonally expand long enough to accumulate enough mutations to become malignant, a second critical step must be achieved for immortalization: abrogation of the generational clock through renewal of the telomere.[267] Most immortal cells maintain their telomeres using two strategies.[268] First, an enzyme called telomerase can add DNA to the ends of chromosomes.[269] Telomerase is absent in non-immortalized cells in vitro as well as most premalignant tissue in vivo. However, 85% to 90% of immortalized cells, including cancer cells, have abundant telomerase activity. Recently, telomerase has been found to support malignant transformation through telomere-independent pathways, such as Wnt pathway signal amplification, apoptosis evasion, and enhancement of cell proliferation.[270,271]



• **Figure 26-13** Telomerase and cancer. **A,** Telomerase function. In normal cells, a fraction of the chromosomal telomere is lost with each cell division. When the entire telomere is lost, the cell undergoes senescence. Cancer cells produce telomerase, an enzyme that maintains the telomere, thereby allowing progeny of the precancer/cancer cells to divide indefinitely. **B,** Chromosome rearrangement through breakage/fusion/bridge (BFB) cycles. Chromosomes with eroded telomeres can fuse end-to-end. When the chromosomes separate in mitosis, an asymmetric break can occur in the DNA. A different (nonhomologous) chromosome can fuse with the new DNA end. In the next mitosis, chromosomal rearrangement occurs.

Second, the remaining 10% to 15% of immortalized cells use a mechanism termed ALT (alternative lengthening of telomeres), which maintains the telomere by swapping sequences between chromosomes.[260,272]

What is the selective advantage of immortalization for the cancer cell? Accumulation of genetic events leading to malignant phenotypes requires clonal expansion beyond the replicative limit of normal cells.[267] Furthermore, a clinical cancer is composed of a large number of cells. A tumor is first visible by imaging at 10^8 cells, first palpable at 10^9 cells, and lethal at 10^{12} cells. Both intracellular and extracellular mechanisms leading to attrition prevent sufficient clonal expansion through immortalization, a release from senescence.[9] The telomerase/ALT pathways undermine the generational clock that halts proliferation.[210] Abrogation of the apoptotic pathways allows expansion of these clones carrying altered DNA. Immortalization is a difficult trait to achieve (approximately 1 in 10 million "precancer" cells acquires the trait) and a critical hallmark for a precancerous/cancer cell to obtain.[37]

Whereas immortalization is triggered independently of environmental cues, tumorigenesis can be supported by stromal cells (which are genomically stable) undergoing senescence.[16] Senescent fibroblasts can change the microenvironment of precancer and cancer cells that supports growth and tumor progression. Senescent fibroblasts disrupt the functional and morphologic differentiation of epithelial cells by altering the extracellular matrix and secreting growth factors that induce a supportive environment for tumor progression. Furthermore, a mass of cancer cells without replicative restraint requires a robust nutritional supply.

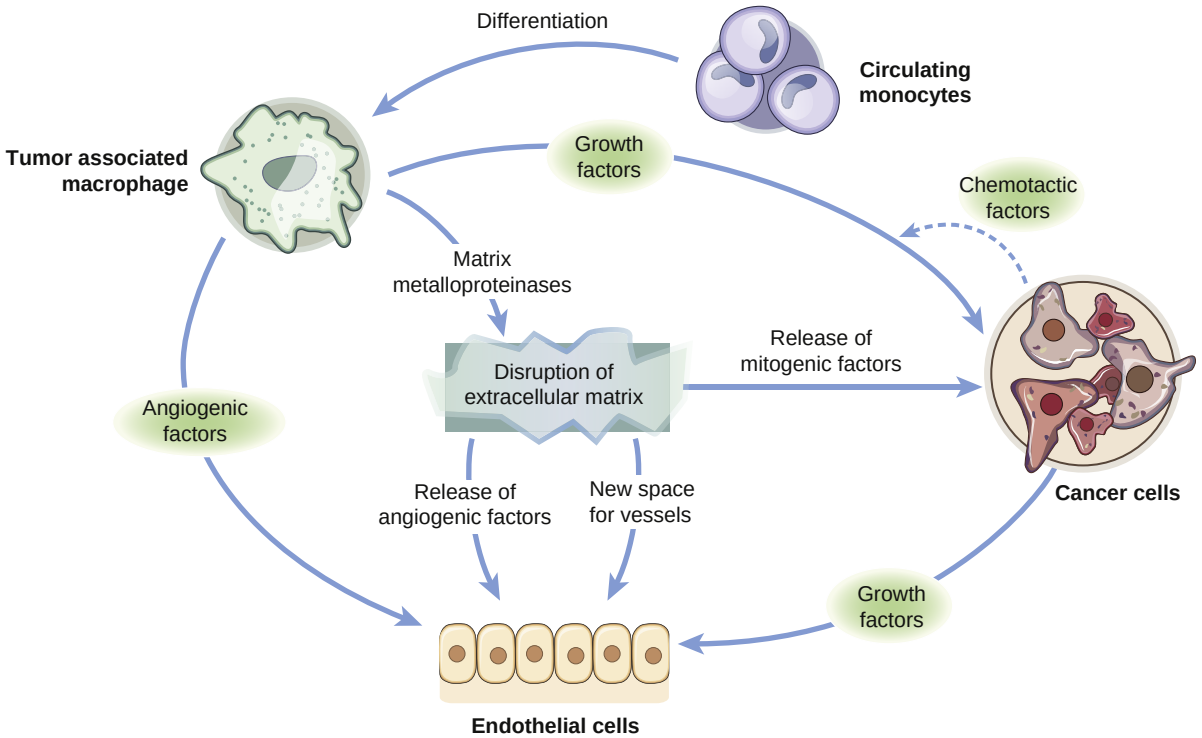
Neovascularization

New blood vessel formation or angiogenesis is a pivotal process in human health and disease.[273] Angiogenesis plays

a crucial role during development, particularly organogenesis.[274] In adults, angiogenesis occurs primarily during wound healing, reproductive functions, or the development of compensatory collateral blood vessels for oxygen/nutrient-deprived tissue. During tumor progression, angiogenesis is a critical and growth-limiting step.[21] The growing tumor mass is supported by enhanced cell proliferation, blockage of senescence, and escape from apoptosis. However, the ability of the tumor mass to expand is profoundly limited by the risk of outstripping its nutrient supply. Nutrients can diffuse three to four cell lengths (or approximately 100 μm) from a capillary.[275] Cells, even cancer cells, beyond that distance die. Therefore, the generation of a vascular network to feed the tumor is critical. Without a sufficient vascular supply to provide nutrients and oxygen to the rapidly dividing cancer cells, a tumor would grow little more than 2 mm in diameter.[276] Cancer cells must acquire the ability to create new vessels or their progression is limited severely. Accordingly, cells in premalignant or incipient lesions must be able to undergo neovascularization to progress to larger neoplasias.

There are two phases in tumor neovascularization. In the prevascular phase (the "angiogenic switch"), cancer cells accumulate changes that support vessel growth to meet the metabolic demands of the growing tumor.[277] Only 1 in 600 incipient tumor masses develops this switch. In the vascular phase, the tumor undergoes rapid growth and metastasis.[19] Angiogenesis arises from a collaboration of cancer cell signaling, matrix support/modification, and endothelial cell proliferation.[278] The process is regulated by pathways that support and inhibit endothelial cell growth. In most normal situations, the homeostatic balance is tipped in favor of angiogenesis inhibition.[21] In addition to increased production of pro-angiogenesis factors, tumor neovascularization is achieved by reduced activity of anti-angiogenic pathways.[279]

Pro-angiogenesis pathways involve a complex interaction between the cancer cells and underlying stroma[280,281] (Figure 26-14). Fibroblast growth factors sustain tumor angiogenesis when constituently overexpressed by cancer cells.[282,283] Vascular endothelial growth factors (VEGFs) are also expressed by cancer cells in response to hypoxia and oncogene signaling.[284] Of the approximately 200 human cancers, about 60% overexpress VEGF.[275] Much of the VEGF released is sequestered by the extracellular matrix (ECM) and becomes inactivated.[285,286] Therefore, the cancer cells must recruit myeloid cells (macrophages and mast cells) that, in turn, secreted matrix metalloproteinases (MMPs) that degrade the ECM and release VEGF.[287] There are gradations of the angiogenic switch that stimulates



• **Figure 26-14** Tumor-stroma interactions in angiogenesis. To meet the metabolic needs of the growing tumor mass, cancer cells must establish a dialogue with cells within the underlying stroma. For example, cancer cells secrete chemotactic factors, such as MCP-1, which recruit/differentiate circulating monocytes into macrophages. The macrophages "talk back" by generating directly and indirectly (through degradation of the extracellular matrix [ECM]) mitogenic factors for the tumor cell. In addition, the macrophage also supports tumor neovascularization by secreting angiogenic factors (such as vascular endothelial growth factor [VEGF]), liberating angiogenic factors from the ECM and remodeling the stromal matrix in order to support new vessel formation. Stromal fibroblasts, the inflammatory infiltrate, and other cell types also participate in heterotypic interactions that support both tumor growth and angiogenesis.

tumor neovascularization.[9] Some tumors are highly vascularized, whereas others are associated with largely avascular stroma. How intensely the pro-angiogenic factors tip vascular homeostasis probably depends on both the biology of the cancer cells (such as activation of dominant oncogenes like Ras) and inductive signals produced by the stroma (such as by immune inflammatory cells). Other important angiogenic factors include angiogenin, TGF-α, TGF-β1, RhoA/Rho Kinase, and platelet-derived growth factor (PDGF).[288,289]

Antiangiogenic pathways also involve the interplay between malignant cells and "normal" stromal cells. For example, after being secreted by a variety of cells into the ECM, thrombospondin-1 (TSP-1) forms a homotrimer that binds to CD-36 and halts endothelial cell proliferation.[290] TSP-1 also binds the pro-apoptosis Fas receptor that is displayed on proliferating (but not nonproliferating, mature) endothelial cells.[291] Both p53 and Myc function downregulate angiogenesis inhibitors, such as TSP-1.[292] Angiogenesis inhibitors have been found to be products of the proteolytic cleavage of structural proteins within the ECM or factors released in the circulation.[293] Endogenous matrix anti-angiogenesis factors include endostatin, anastellin, and arrestin; non-matrix vascular inhibitors include interferon-α, interleukin-1β/-12/-18, angiostatin, antithrombin III, TIMP-2, and vasostatin.[293] In health, these factors limit angiogenesis to a transitory event during wound healing. Circulating anti-angiogenic factors may serve as an intrinsic barrier to expansion of incipient neoplasias.[9]

There are six mechanisms leading to tumor neovascularization.[275,294,295] First, sprouting angiogenesis involves the proliferation and migration of endothelial cells from preexisting blood vessels.[294] Overproduction of VEGF induces endothelial cell proliferation and increases extracellular matrix degradation permissive for endothelial cell migration.[296] Second, intussusceptive vascular growth may account for 50% of tumor neovascularization.[297-299] Rather than sprouting, intussusception involves the partition of adjacent vessels. Therefore, angiogenesis can be achieved rapidly and with more metabolic economy because no endothelial cell proliferation is needed. Intussusception is supported by TGF-β, cell adhesion molecules, VEGF and PDGF. Third, angioblast recruitment, precursors to endothelial cells, can contribute to tumor neovascularization.[300,301] Again, VEGF induces MMP9, mobilizing progenitor cells and inducing differentiation to mature endothelial cells. Fourth, cooption occurs in certain tumors such as gliomas.[302] Ang 2 is activated and induces endothelial cell apoptosis, leading to hypoxia.[275] VEGF production is induced by the hypoxia, and sprouting angiogenesis is induced. Fifth, mosaic cell formation, accounting for approximately 15% of tumor neovascularization, are vessels lined with both endothelial cells and tumor cells.[303-305] Angiogenic factors such as FGF2, VEGF, and MMP2 lead to increases in basement membrane degradation and permeability. Last, vascular mimicry occurs, where vessels are formed that are lined with laminin instead of endothelial cells.[280]

In short, the ability of the tumor cell to induce a supporting vasculature confers a major selective advantage. Although a cancer cell might accumulate the molecular machinery for deregulated growth, clonal expansion cannot occur without the nutritional support to fuel the metabolic requirements. Furthermore, tumor neovascularization is important for the spread of the primary tumor to other anatomic sites. And, like the molecular events supporting metastatic spread, tumor neovascularization depends on an interplay between the genomically unstable cancer cells and genomically stable cells in the underlying stroma.

Tissue Invasion and Metastases

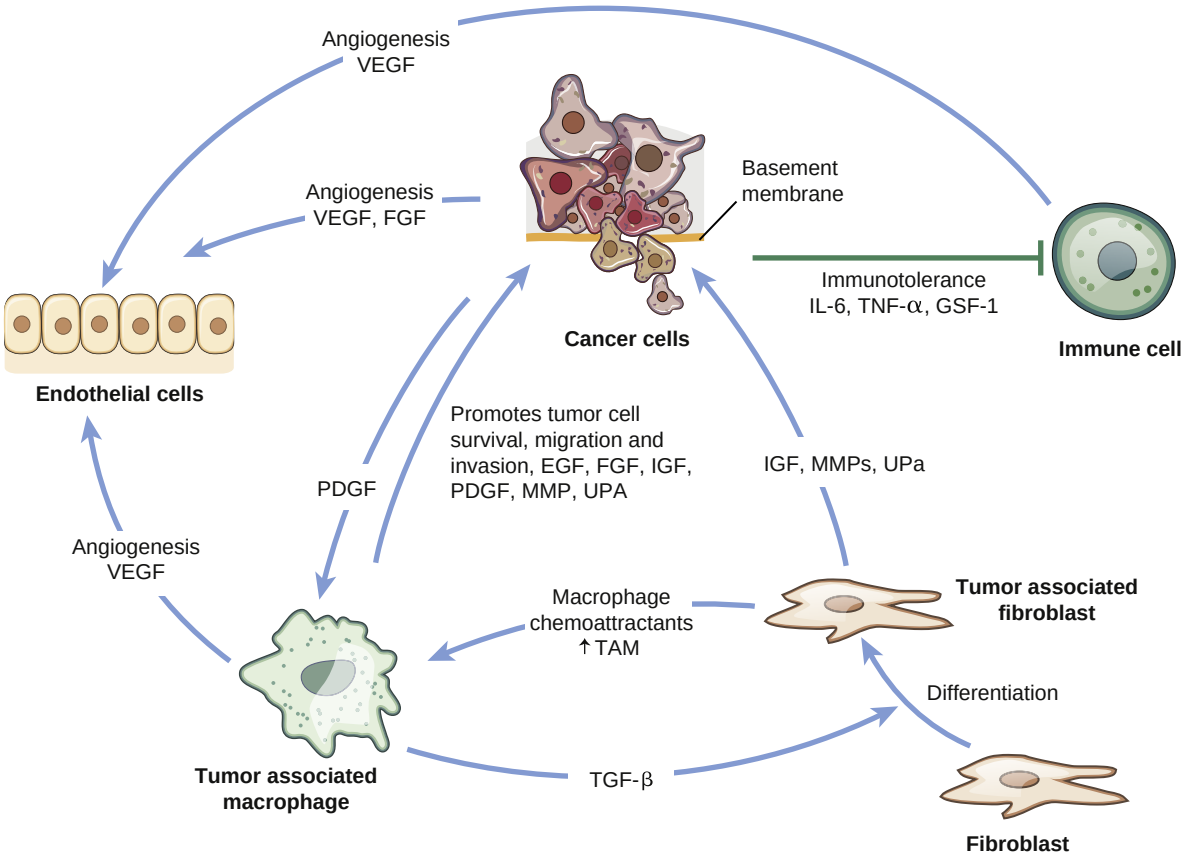
Rather any molecular or biochemical marker, invasion of neoplastic cells into surrounding "normal" tissues is the key event that separates malignant from benign tumors.[306] Metastasis, the cause of approximately 90% of cancer deaths, is the transfer of disease from one organ or tissue to another not directly connected with it.[307] The cellular processes observed in the histopathology of metastasis are beginning to be understood at the molecular level. Like tumor neovascularization, metastasis is the result not only of intrinsic genetic changes in the cancer cell, but of a series of complex alterations with the tumor microenvironment.[9]

Metastasis follows a series of rate-limiting histopathologic steps often referred to as the invasion-metastasis cascade.[307-309] After the cancer cell detaches from the primary tumor and invades the host stroma, it intravasates into either lymphatic or blood vessels, spreads to the capillary bed of distant organs and extravasates from the capillary lumen back into the stroma. The metastatic cell then proliferates in the receptive organ parenchyma. Having undergone further genetic selection, the metastatic cell has proliferative, survival, migratory, and invasive abilities beyond those of its malignant counterparts. Hence, the molecular alterations intrinsic to the metastatic cell confer, in part, the ability to activate the tumor microenvironment to undergo changes at the primary and secondary sites to support invasion and metastasis.[306,309]

Tumor invasion is initiated by fundamental changes to the cancer cell. Referred to as the epithelial-mesenchymal transition (EMT), the cancer cell undergoes functional and anatomic changes that shed static phenotypes in favor of those that promote detachment and mobility (Figure 26-15).[9,310-312] Several phenotypes are lost in EMT cells, including intermediate filament expression, cell polarity, differentiation gene programs, and E-cadherin expression (a key regulator of adhesion junctions linking the cell's cytoskeleton to neighboring cells).[313-316] In turn, the EMT cell acquires several traits, including a fibroblast-like shape, increased mobility, upregulation of transcriptional programs supporting stem cell–like phenotypes, and expression of N-cadherin.[317] Several pleiotropically acting transcription factors have been implicated in supporting the stem cell–like properties and driving malignant progression toward metastasis, including Snail-1/-2, Slug, Twist, Zeb-1/-2, Goosecord, and E12/E47.[9,318-322] In addition to loss

of static cell adhesion molecules, the invading cancer cells have acquired other traits that support motility. [323] Factors that induce locomotion in cancer cells include HGF, scatter factor, and EGF.[324,325] Activation of Rho, small ras-like GTPase molecules, also transforms cell shape, adhesion, and motility.[326,327] The invading cells generate lamellipodia, extensions of their cytoplasm/cell membrane toward the direction of movement.[328,329] Cell surface proteases degrade the ECM at the edge. During this process, new adhesion molecules are formed while others along the trailing edge are released. Last, space needs to be made into which the invading cancer cell will travel. At the lead edge of the cancer cell, MT1-MMP cleaves proenzymes such as pro-MMP2, collagen type IV (in the basement membrane), and collagen type I (in the ECM).[330] Furthermore, the cancer cell secretes factors, such as epithelial growth factor, to induce fibroblasts and endothelial cells in the stroma to synthesize metalloproteinases that degrade the basement membrane and extracellular matrix.[315,331] Disruptions of the basement membrane and extracellular matrix allow the tumor cell to transmigrate into the stroma and intravasate into blood or lymphatic vessels. A key family of molecules altered in this process is the integrins.[332-334] Integrins, cell surface receptors linking the extracellular matrix to the cell's cytoskeleton, regulate signaling cascades that modulate proliferation, survival, polarity, mobility, and differentiation.[335] Activation of oncogenes and loss of tumor suppressor gene function in cancer cells not only allow the cells to survive and proliferate in the absence of normal cell-matrix adhesion, but often cause the cancer cells to overexpress the integrin subunits that promote migration and metastasis.[336-338] In addition, integrins can recruit metalloproteases to degrade the extracellular matrix, supporting cancer cell migration and invasion into the stroma.[339] Although the EMT changes in the cancer cell are critical for invasion through the basement membrane, as well as intravasation into and extravasation out of the endothelial lumen, the EMT phenotype would be impossible without support from the tumor-associated reactive stroma.[340]

Cancer and stromal cells generate growth factors, cytokines, and chemokines that mutually benefit each other and support metastasis (see Figure 26-15). Key stromal cells include the endothelium, fibroblasts, and the immune system. Angiogenesis was reviewed in the previous section. The tumor-associated vasculature not only provides the nutritional support for the expanding tumor mass, but



• **Figure 26-15** Invasion and metastasis. Interactions between the cancer cell and the tumor stroma support invasion and metastasis through secreted ligands. The cancer cell secretes cytokines that cause tumor-associated macrophages (TAMs) to secrete TGF-β (that, in turn, causes fibroblasts to differentiate into myofibroblasts. Cancer cells also secrete factors that suppress the immune system. The myofibroblasts and TAMs, in turn, secrete ligands that promote tumor survival, invasion, and metastasis. Cancer cells, myofibroblasts, and TAMs all secrete factors that support angiogenesis.

mass and potential escape routes (for the tumor cell with the intrinsic invasive properties) and has a distinct morphology (large, tortuous, and leaky vessels due to an incomplete pericyte lining and fragmented basement membrane) that is compatible for tumor cell intravasation. Stromal fibroblasts transdifferentiate into myofibroblasts shortly before tumor invasion.[342-344] Myofibroblasts promote invasion and metastasis by secreting factors that degrade the basement membrane and extracellular matrix (by secreting serine proteases, promoting angiogenesis, and stimulating cancer cell proliferation).[345,346] Last, the immune system, although it clearly surveys for and kills cancer cells, paradoxically can promote tumor invasion and metastasis.[347] For example, tumor-associated macrophages (TAMs), differentiated from monocytes at sites of tumor invasion, are attracted to the invasive edge by cytokines such as IL-4 and CSF-1.[348,349] TAMs can repress tumor growth and progression by killing cancer cells and presenting tumor antigens to other members of the immune system.[350,351] However, TAMs also secrete factors that promote tumor cell proliferation and support angiogenesis.[352-355] In summary, the stroma's contribution to invasion and metastasis is multifactorial and essential. The stroma secretes numerous factors that support the EMT phenotype, including TGF-β, TNF-α, EGF, HGF, Wnt, and IGF. TGF-β's activity promoting cell stasis is inactivated when the Rb pathway is lost (an event common to most cancer cells); therefore, TGF-β stimulates cell proliferation and secretion of lytic proteins.[356-359] MMPs secreted by fibroblasts, mast cells, and macrophages dissolve the ECM, providing space for cancer to invade and release of growth factors to support growth. MMP-9 supports local invasion, as well as intra- and extravasation, by dissolving collagen IV, V, XI, XIV, laminin, and fibrinogen.[15] Vascular endothelium is believed to have organ-site specific "docking" molecules supporting the tropism of cancers to certain sites.[360]

Cancer dissemination occurs in many forms.[9] A mesenchymal type of invasion describes the EMT program of cell spread.[361,362] Collective invasion refers to cancer cells pushing directly into adjacent tissue but rarely metastasizing. Cancer cells showing amoeboid invasive patterns use cell plasticity to insinuate themselves through cell matrices rather than clearing a path.[363] Cells disseminating remotely from the primary tumor initially reverse the EMT program. In the mesenchymal-epithelial transition (MET), circulating cancer cells extravasate into a stroma ill-prepared to support cancer growth.[364] With no cytokines, MMPs, and so on to support invasion, the cancer cell reverts to a more static cellular program (return of a basement membrane, cell polarity, certain differentiated cell structure/functions) that forms nests of cells (<2 mm) called micrometastases.[365] The molecular mechanisms governing suppression of micrometastatic growth, the switch from dormancy of micrometastases to metastases, and the success of metastatic spread are poorly understood. Adaptation of the micrometastatic colonies to the microenvironment of the end-organ parenchyma is probably highly inefficient.[309] In fact, dissemination may be a much earlier step in tumorigenesis than previously believed: The successful adaptation of a micrometastatic colony to its environment may simply require so much time it appears to be a late event.[9] Furthermore, the mechanisms of metastatic tropism are also incompletely understood.[366] Like the mechanisms of invasion, the factors supporting metastatic colonization likely will be a combination of cancer cell metastatic gene signatures and permissive biologic programs specific to individual organs.[9]

Putting It All Together: How Molecular Changes Govern a Cancer Cell

The cancer cell has undergone a Darwinian selection that has conferred cellular characteristics that allow it to exploit and outcompete its normal neighbors.[367] There are several hallmarks of cancer cell behavior.[9] The cancer cell proliferates in the absence of normal growth signals and without the normal inhibitory controls. Therefore, the cancer cell can out-replicate its normal counterpart. In addition, senescence and apoptosis, normal traits that cease cell division and lead to elimination of defective cells, are evaded in cancer cells. Rapid cell division, immortality, and apoptosis evasion all enhance a cancer cell's chance of undergoing more mutations that may result in greater selective advantage. However, intracellular traits leading to an expanding tumor mass are insufficient alone to result in a clinically detectable tumor mass. Cancer cells must undergo an "angiogenic switch" that allows them to feed this growth by exploiting normal stromal cells to generate a neovascular network. In turn, that vascular network not only provides nutrients to allow the tumor mass to expand but is an essential step in allowing the cancer to invade beyond the local stroma to other anatomic sites: metastasis.[9]

These cancer cell traits are controlled by complicated regulatory pathway networks subverted by critical errors accumulated during tumorigenesis.[38] The networks are composed of cooperating and competing pathways that stimulate or suppress cell behaviors. Each pathway contains proteins: cell surface ligands/receptors, secondary messengers, and transcription factors. Normal regulatory functions of pathways are abrogated by abnormalities in these proteins. Enhanced protein activity can be due to such mechanisms as overproduction, overactivity, or presence at an ectopic site/time. Reduced protein activity can be the result of absence of protein production or dominant negative suppression of wild-type function by a mutant protein counterpart.

In the previous section, the mechanisms leading to altered protein activity were reviewed. Large- and small-scale changes in chromosomal structure (or epigenetic alteration of gene activity) lead to a qualitative and/or quantitative change in gene expression and protein production. Changes in genomic stability/DNA repair enhance and accelerate these critical genetic changes that lead to cancer. Furthermore, epigenetic events, as well as signals from the

tumor microenvironment, also affect cancer cell behavior. This understanding of the cumulative factors that govern malignant cell behavior is the basis for creating a rational, individualized clinical approach to the diagnosis and management of the oncology patient.

How Molecular Biology Can Affect Clinical Oncology: Toward the Rational Treatment of Cancer

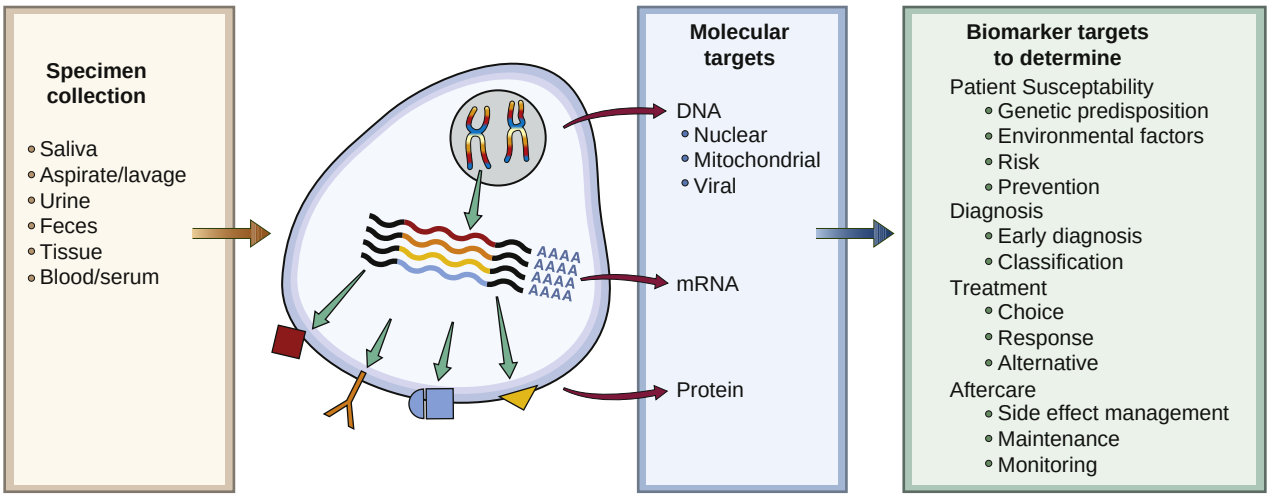
A 2004 survey of the cancer literature revealed almost 300 genes that have been implicated in the genesis of human cancers.[368] Identifying and understanding the molecular events governing the behavior of the cancer cell will, it is hoped, lead to a more precise diagnosis of the disease and a better-targeted (and less toxic), individualized therapeutic protocol.[369,370] Clearly, a comprehensive review of molecularly based diagnostic and therapeutic agents is beyond the scope of this chapter. However, based on the themes reviewed here, we can survey some of the approaches by which molecular biology may transform clinical oncology.

Molecular Diagnostics in Oncology

Understanding the biology leading to cancer progression can lead to a more sensitive and precise diagnosis of [371,372]

the potential of identifying divergent cellular behavior in histologically and clinically identical lesions.[368] There are many potential benefits to these biologically based markers[373] (Figure 26-16). Disease susceptibility will be better assessed with respect to cancer predisposition, influence of environmental factors, risk, and prevention. Cancer diagnosis can be improved both through better early diagnosis and through more precise disease stratification.[374] Conventional and alternative treatment should be more easily selected by better predicting therapeutic response and alternatives.[369] Last, aftercare of the cancer patient will be improved by better disease monitoring, predicting/mitigating treatment side effects and preventing disease recurrence.[60] At present, these cer biomarkers to serve as the basis of an efficient screening program.[377] Most importantly, these biomarkers will need to have a high sensitivity and specificity, especially with low disease volume such as early-stage or precursor lesions.[378] The tests must be easy and minimally invasive, as well as cheap, rapid, reproducible, and cost-effective.

DNA is a promising target for new cancer markers. DNA is a stable molecule and readily detected by a number of robust methods.[48] However, DNA alterations do not always directly contribute to the cancer phenotype. At present, several DNA-based approaches are being explored. Both gross (chromosome translocation, deletion, and amplification) and fine (mutation, microsatellite instability, and single nucleotide polymorphisms [SNP]) alterations are being tested. Perhaps the most famous example is the chromosomal translocation known as the Philadelphia chromosome, a hallmark in the diagnosis of chronic myelogenous leukemia.[379] Double minutes/gene amplification have been shown as a reproducible marker of poor prognosis.[90] For example, Myc amplification is strongly correlated with stage III and IV neuroblastomas, known to have a 10% to 30% 2-year survival.[380] Chromosome number was shown to be a more powerful predictor of the transformation of



• **Figure 26-16** Molecular diagnosis in oncology. Our understanding of the molecular basis of cancer will translate into improved diagnosis in the cancer patient. Advances in collection techniques now allow molecular targets to be detected in a myriad patient specimens. Marker panels based on DNA, mRNA, and protein targets will generate molecular "signatures" of an oncology patient's disease. Based on the diagnostic signature, important determinations can be made regarding susceptibility, diagnosis, treatment, and aftercare that is individualized to the patient.

"premalignant" oral lesions than was histologic assessment of the degree of dysplasia.[381] Mutations in the p53 gene are being used not only for cancer detection, but in the prediction of prognosis and assessment of resection margins.[382] Promoter methylation studies are identifying cancer-associated functional changes in the gene.[383] SNP and methylation studies of various metabolic enzymes, such as glutathione-S-transferase, have been used to explore cancer risk.[375] Last, in addition to human nuclear DNA, mitochondrial and viral DNA are being tested as potential cancer markers. Mitochondria, organelles that contain DNA separate from nuclear DNA, are sensitive to carcinogens and, therefore, readily undergo mutation.[384] Because each cell carries hundreds of copies of the same mitochondrial gene, and all copies of that gene undergo mutation, alterations in mitochondrial DNA are easier to detect than are changes in nuclear DNA. The Epstein-Barr virus (EBV) is being explored as a biomarker for nasopharyngeal carcinomas. EBV DNA is being used to assess tumor burden, monitor for recurrence/metastasis, and predict prognosis.[375,385]

The full potential of DNA as a diagnostic target is being realized through whole genomic sequencing (WGS), a means of analyzing chromosomal changes throughout the entire cancer cell DNA.[386] These advances have been realized through improved automated sequencing that has reduced costs by a factor of 10 billion while increasing experimental efficiency by 10 millionfold since the early automated sequencers of the 1980s.[387] WGS has identified important targets, such as BRAF, isolated important mechanisms of cancer chromosomal rearrangements (chromothripsis), and generated genomic signatures, such as CONEXIC in human melanomas, that aid in tumor diagnosis.[388-390] To more effectively target a personalized diagnostic approach, various arrays, SNP arrays, and molecular inversion probes deep tion and acetylation arrays, is also available.[392,393] Although DNA biomarkers have proven most useful in determining cancer predisposition, recent advances in mRNA analysis may provide another robust means of diagnosing/classifying cancers.

Messenger RNA is a more difficult biomarker to target because it is often rapidly degraded and therefore more difficult to isolate/identify from patient specimens. With improved detection techniques, mRNA has been found more easily in biopsy specimens and all body fluids.[375] More importantly, emerging methods of high-throughput analyses (and statistical analysis to interpret the data) have led to advances in mRNA-based cancer diagnosis based on mRNA splicing form detection and gene expression profiling.[394] Both exon junction arrays and genomic tiling arrays are available but expensive and of limited diagnostic application.[391] Using microarray analysis for gene expression profiling, investigators have been able to separate and identify histologically identical but clinically (and prognostically) distinct malignancies, including lymphoma subtypes and pediatric "blue cell" tumors.[395] Investigators are using primarily three different strategies to correlate gene expression "signatures" to the clinical behavior of cancer.[396] The simplest approach is to correlate gene expression patterns to known clinical features that have an impact on outcome, such as local invasion, node status or metastasis. For example, investigators have been able to establish expression profiles from normal colonic epithelium; adenomas; Dukes-B, -C, and -D adenocarcinomas; and liver metastases.[397] Another approach is to identify gene expression profiles that correlate with treatment response. For example, a signature of 21 genes was identified to predict which breast cancers would be refractory to tamoxifen treatment.[398,399] Last, expression profiles are being tested that identify long-term prognosis/relapse. For example, a 70-gene signature was identified that correlated with recurrence within 5 years in patients with node-negative breast cancers that was able to identify 90% of the poor-outcome patients.[400] This poor prognosis signature was developed into a molecular diagnostic test (MammaPrint; Agendia, Amsterdam).[401] Similar tests, such as the 76-transcript Rotterdam signature or the 21-transcript Oncotype DX assay (Genomic Health, Redwood City, CA), identify distal recurrence in node-negative, estrogen receptor–positive breast cancer patients.[402] The early promise of high-throughput analysis of gene expression has prompted investigators to suggest that a "cancer chip" eventually might be used to individualize the diagnosis, treatment, and post-therapeutic monitoring of the cancer patient.[403] However, before high-throughput analysis of gene expression profiles reaches the bedside, a standardization of intra- and inter-laboratory methods and statistical analysis has to be established. In addition, specimen acquisition methods, handling, and experimental "noise" must be resolved.[396] In short, mRNA, although a biologically fragile molecule, may serve as a more precise method of identifying cancer-related gene activity and a valuable surrogate measure of protein production/activity.

Today, cancer-associated proteins are the most commonly used tumor biomarker and have met with limited success. Because of transcriptional regulation and post-translational modifications, it has been estimated that the 23,000 to 40,000 genes have the potential to produce about 1 million different proteins.[60,391] Although this might provide a greater pool of candidate biomarkers, protein identification is a technically more cumbersome process than nucleic acid identification. Most of the cancer-related protein markers to date suffer not only from the difficulties discussed earlier of using a single marker approach, but also from biologic limitations related to protein biochemistry. For example, the presence or absence of the estrogen receptor (ER) in breast cancers is part of every diagnostic workup of a breast cancer patient to determine candidacy for endocrine therapy. The gold standard to assess ER status is immunohistochemistry (IHC). Although major diagnostic

decisions depend on the results of ER IHC, the reliability [404]

laboratories.[405] Interpretation of the data varies due to reading variability between pathologists and image analysis settings. The prostate-specific antigen (PSA) is a routine test for prostate cancer screening, although more than one third of patients who have an elevated PSA level have benign disease.[406] Moreover, PSA sensitivity and specificity depend on the amount of protein produced by the cancer cell, the amount of tumor mass, and covariables such as inflammation and tissue manipulation.[377] Similarly, the carcinoembryonic antigen (CEA), used to monitor disease progression and therapeutic response of colorectal cancers, is expressed in only a fraction of cancers.[375] Similarly, the use of tumor markers such as CEA, Ca 72-4, or Ca 19-9 to detect stage I gastric cancer is successful in less than 25% of cases.[377] For many other cancers, there are no tissue-specific markers. To better the clinical application of protein biomarkers, investigators have combined known protein biomarkers with assays for proliferation-related gene expression.[404]

Rather than target a single protein, proteomic analysis surveys the entire complement of polypeptides in a cancer cell.[407] Traditional western blotting, IHC, and enzyme-linked immunosorbent assays can be used to assess only a limited number of proteins and are unable to map signal transduction events.[391] Furthermore, post-translational modifications of the cancer proteins can be examined (such as phosphorylation, ubiquitination, glycosylation, methylation, and acetylation). Proteomic analysis is primarily per-

examined to identify biomarkers used for screening, surveillance, and prognosis in colorectal cancer.[411] Proteomic analysis the "secretome," extracellular proteins excreted into the tumor microenvironment, has been applied to a variety of human cancers (lung, breast, prostate, colorectal, and pancreatic) to better understand the tumor microenvironment and identify circulating biomarkers.[412] To date, identification of robust biomarkers using proteomics has proven elusive.[413]

Last, target proteins and the functions they govern are being used to advance diagnostic imaging.[392] Smart contrast agents, such as conjugated gadolinium that binds to proteins associated with apoptosis, are showing promise as earlier indicators of therapeutic response.[414] Positron emission tomography (PET) and single photon-emission computed tomography (SPECT) target tumor metabolism and protein function to differentiate between normal and malignant tissue, especially for cases of detection and surveillance in Hodgkin disease, non-Hodgkin lymphoma, and head and neck, lung, and pancreatic cancers.[415,416]

In summary, multiple DNA, mRNA, and protein cancer-related biomarkers are being identified. The molecular assessment of the cancer patient will likely involve multiple markers and possibly multiple types of biomarkers (DNA, mRNA, protein).[377] Several challenges remain for biomarker research. While many target markers and pathways have been identified, continued research is necessary to identify novel molecules and order the priority of those

Cancer biomarkers likely will vary not only between cancer types and subtypes, but also with respect to the time point of disease progression.[417,418] Therefore, a biomarker important in early detection might not be useful to iden-

robust, more affordable, and amenable to automation/high-throughput analysis. Several collaborative efforts are underway to meet the challenges of molecular oncology. For example, to categorize molecular profiles of various tumors and identify common events, the National Cancer Institute has collaborated with the National Human Genome

technical, economic, and ethical challenges of translating

DNA/mRNA/protein high-throughput analysis, systems biology/bioinformatics, health policy/ethicists, and so on) will be necessary to convert the multidimensional data sets into useful biomarkers to advance the management of the cancer patient.[391] Ultimately, the technical challenges raised

cancer-related biomarker panels will likely yield easy, cheap, minimally invasive, reproducible, and rapid results with a high sensitivity and specificity. These cancer-related molecular events will also lead to target-specific therapeutic options.

Molecular Therapeutics in Oncology

Although better assessment of the cancer patient through the use of biomarkers might improve the efficacy of current tumor therapies, the molecular differences between normal and cancer cells can be exploited to supplement current treatment protocols and to develop novel, target-specific approaches.[9,419,420] Designer treatments based on

cancer-related molecular changes represent an important improvement over the majority of cancer therapies today that distinguish poorly between the biology of normal cells/tissues and those that are malignant cells.[421] Although a comprehensive review of the current clinical trials of these new biologic targets is beyond the scope of this chapter, it is helpful to consider the rational treatment of cancer in two broad categories. First, it is important to understand the strategies used to target cancer-related molecular changes: DNA alterations, changes in gene expression, and aberrant protein products. Second, rather than simply attacking the cancer cell, investigators are targeting specific cancer cell behaviors: uncontrolled cell proliferation, evasion of apoptosis, tumor neovascularization, and invasion/metastasis.

Strategies of Cancer-Related Molecular Therapeutics

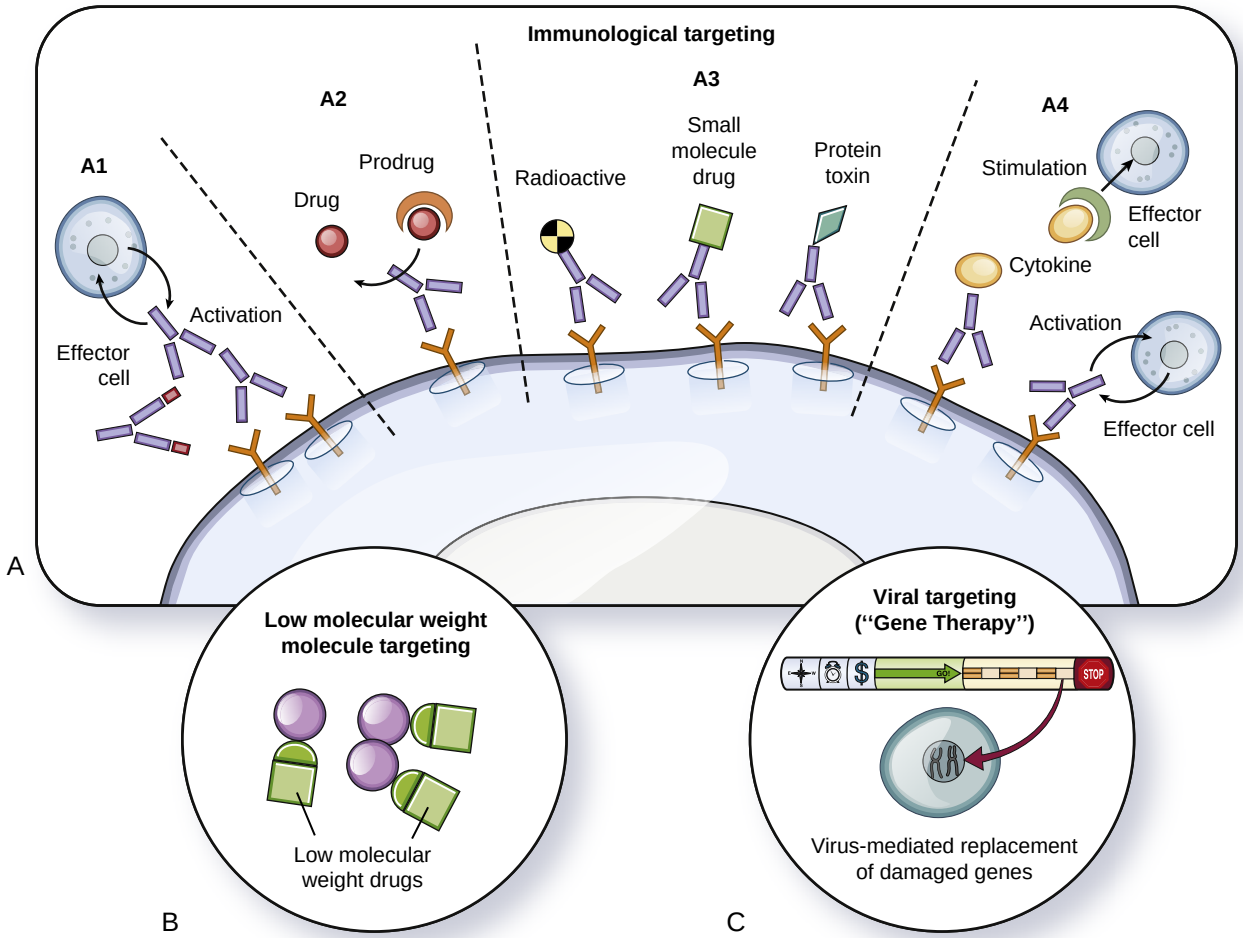
Earlier in this chapter, the molecular alterations leading to cancer cell behaviors were reviewed. Large and small genomic alterations (as well as epigenetic mechanisms) lead to quantitative or qualitative changes in gene expression and protein production. Therefore, it is helpful to consider cancer-related therapeutic strategies based on how the cancer cell deviates from the normal DNA→mRNA→protein paradigm.

DNA-based strategies attempt to override genetic alterations accumulated during cancer progression (Figure 26-17).[422,423] New genetic material is introduced into cancer cells to either directly replace damaged genes or counteract the biologic effects of that genetic damage. Approaches include direct loss or gain of gene function, as well as cancer cell–clearing immune activation, drug resistance gene inactivation, augmentations of DNA repair enzyme activity, angiogenesis inhibition, or enzymatic destruction of viral/cancer genetic material.[422,424,425] Genes are introduced into cancer cells using microorganism and nanocarrier methods. Microorganism vectors include viruses (retroviruses, adenoviruses, and adeno-associated viruses), bacteria, yeast, and parasites.[426] Nanocarrier methods include nanotechnologic methods, including polymerid and magnetic nanoparticles, dendrimers, lipid-based carriers (liposomes/micelles), and carbon nanotubes.[427] Although several different target genes and methods of gene delivery are under investigation, perhaps the most studied is adenovirus p53 gene therapy.[428,429] Mutation of the p53 gene occurs in over 50% of all cancers. Functional loss of the p53 protein contributes to uncontrolled cell proliferation and escape from apoptosis.[430] Therefore, the addition of a normal p53 gene should restore important growth arrest and apoptosis in the cancer cell. The most successful method of p53 gene delivery is the adenovirus, though retroviruses and other nonviral carriers have also been successfully used.[431,432] Infection of the cancer cell by the p53 adenovirus allows delivery of the normal p53 gene to the cancer cell genome. Not only has restoration of p53 function led to reduction of the tumor mass, but, because important growth arrest and apoptosis controls are reactivated, transfer of the tumor suppressor gene in combination with conventional DNA-damaging treatments restores sensitivity to radiation and chemotherapy.[428,433] Several important limitations of this approach remain, including efficient gene delivery and gene regulation. In addition to introducing genetic material to restore "normal" gene expression, cancer therapeutic strategies are targeting restoration of native gene activity.

Cancer-related gene expression is another potent target in molecular cancer therapeutics. Two major approaches are RNA interference (RNAi) of gene expression and reversal of epigenetic gene silencing.[434-437] RNAi is an emerging approach that checks gene expression.[438] Short interfering RNA (siRNA) can be introduced into cells directly using nanocarriers such as liposomes or produced in the cells by introducing DNA-based vector systems.[439] A target of RNAi-based approaches, Bcl-2 and related proteins are overexpressed in a wide variety of cancers.[440,441] Like p53, Bcl-2 is an important regulator of apoptosis. The siRNAs bind complementary portions of the overexpressed Bcl-2 mRNA, leading to degradation of the transcript and effectively silencing the oncogene.[442] Limitations of the RNAi approach to be addressed include chemical modification of siRNAs to increase stability, improved tissue targeting, and selection of siRNA design.[438,439] The last aspect is important because the siRNA must be able to target the cancer-related gene expression but have enough flexibility that different mutations of the same gene will not render the approach ineffective. In addition to RNAi approaches, treatments that inhibit DNA methylation and histone acetylation can reactivate epigenetically silenced genes (or silence epigenetically activated genes).[437] Drugs such as azacitidine and decitabine have been shown to have therapeutic potential in myelodysplastic syndromes, hematologic malignancies, and solid tumors.[443,444] Therefore, rather than replacing structurally damaged DNA (such as using an adenovirus to deliver normal p53), low molecular weight drugs restore DNA function/gene activity of important, structurally intact, but chemically inhibited tumor suppressor genes (and other regulatory genes) to induce growth arrest and apoptosis in the cancer cell.

Gene product (or protein) targeting can be subcategorized into two approaches: monoclonal antibodies and low molecular weight drugs (see Figure 26-17) Anticancer agents targeting cell surface or extracellular space proteins are usually antibody-based.[445,446] Enzymes with catalytic clefts and pathways relying on protein-protein binding are usually targeted by low molecular weight drugs. Thus oncoprotein ligands, receptors, secondary messengers, and transcription factors are all potential therapeutic targets.[447-450]

Cancer-specific protein changes provide a means of differentiating normal from malignant tissue.[451] Cell surface and extracellular matrix proteins are excellent targets for unconjugated antibody and immunoconjugate therapy.[452] Several mechanisms of action have been described using unconjugated antibodies.[445] Strategies include using antibodies to (1) crosslink cell surface receptors and initiate apoptotic signaling, (2) coat cancer cells and initiate an



• **Figure 26-17** Biologically based cancer treatments. Several treatment strategies are under investigation. Cancer-associated molecular alterations are combated at the cell surface using antibodies and low molecular weight drugs. Intracellular alterations are targeted using low molecular weight drugs and transmembrane carriers (such as viruses). **A,** Several antibody-based approaches are under investigation, including *(A1)* growth/survival receptor blocking, *(A2)* delivery of pro-enzyme/drug therapy, *(A3)* targeting cytotoxic effectors, such as radionuclides, small-molecule drugs, and toxins, and *(A4)* stimulation of the immune system. **B,** Low molecular weight drugs have been successful in blocking the kinase activity of activated receptors and their secondary messengers such as Ras. **C,** Gene therapy has been explored to restore the function of damaged genes, such as p53, thereby inhibiting cancer cell proliferation and enhancing apoptosis. In addition, pharmacologic agents that interfere with epigenetic gene expression modulation and RNAi targeting cancer-associated gene expression are important nucleic acid–based anticancer approaches (*not shown*).

immune response, (3) activate the caspase cascade, and (4) neutralize ligands (such as angiogenic growth factors).[453] Specific targeting of immunoconjugates has the potential of reaching high concentrations at the tumor site without the dose-limiting side effects of nontargeted systemic therapies.[454,455] Cytotoxic payloads conjugated to antibodies include radionuclides (yttrium-90, iodine-131), small chemotherapeutic drugs (doxorubicin, calicheamicin), toxins (ricin, gelonin, diphtheria toxin), immunostimulatory cytokines (IL-2, IL-12, GM-CSF), and liposomes carrying anticancer drugs (paclitaxel, vincristine, siRNA).[455] In general, unconjugated antibody and immunoconjugate therapy is well tolerated with a minimum of side effects.[456] However, there can be some bystander tissue damage with some of the antibody strategies, such as radionuclide immunoconjugate therapy.[457,458] Other limitations on clinical success include immunogenicity, insufficient tumor localization/tissue penetration, and failure to trigger the intended biologic effect.[459] Like other biologically based approaches (such as adenovirus p53 gene therapy), the ability of antibody therapy to restore/sensitize apoptotic pathways makes this strategy an attractive adjuvant to chemotherapy and radiation therapy to augment their antitumor effects.

Low molecular weight drugs target intracellular enzymatic activity and protein-protein interactions.[460,461] The greatest number of these agents target signal transduction pathways

governing growth- and survival-promoting kinases. Ras, a proto-oncogene mutated in 30% of all tumors, is dependent on farnesylation for activity.[462,463] Inhibitors of farnesyl protein transferase (the tricyclic SCH66336 and the methylquinolone R115777) are being investigated as potential anti-Ras therapeutic agents in a wide variety of solid tumors. Imatinib mesylate, a drug that interferes with the abnormal Bcr-Abl tyrosine kinase fusion protein, has been approved to treat patients with chronic myelogenous leukemia in blast crisis.[464] Synthetic inhibitors, such as ZD1839, erlotinib (OSI-774, Tarceva), tyrostin, lavenditin, and quinazoline, are being investigated to block tyrosine kinase overactivity of oncogenes.[465-467] In addition to some of the low molecular weight drugs targeting the major tumor cell phenotypes addressed in the following section, other drugs in clinical development address such diverse events as tumor metabolism, histone deacylation, demethylation, and DNA repair.[468-470]

Virtually every molecular change is being explored as a potential diagnostic and therapeutic target: large and small chromosomal changes, gene expression alterations, as well as gene products.[3] Oncoproteins and growth suppressor proteins, including extracellular ligands, cell surface receptors, secondary messengers, and transcription factors, serve as a means to combat malignant tissue while sparing nor-

Targeted Therapy Based on Tumor Behavior

Cancer is a multistep process due to the accumulation of multiple genetic alterations. These molecular alterations govern cellular characteristics evolved during tumorigenesis in a Darwinian selection process. Therefore, a cancer "cure" will necessitate multiple biologic targets that affect many of the behavioral hallmarks of the cancer cell: uncontrolled proliferation, evasion of growth arrest/apoptosis, neovascularization, and metastasis.[471,472]

Uncontrolled proliferation exhibited by cancer cells is a primary target for biologically based cancer therapeutics. The majority of oncogenes and tumor suppressor genes are components of signal transduction pathways that govern cell division.[9] Cancer-associated ligands, ligand receptors, secondary messengers, and transcription factors have all been explored as therapeutic targets.[449,450] For example, EGFR pathways are commonly altered in a wide variety of cancers and have been aggressively investigated.[473,474] Overexpressed and mutated (and constituently activated) receptors are being targeted using monoclonal antibody-based strategies (trastuzumab, ertumaxomab) and by blocking transmission of the tyrosine kinase-mediated signal transduction pathway (erlotinib, gefitinib, afatinib).[473-475] The goal of EGFR-targeted therapeutics and similar strategies is to modulate uncontrolled upstream stimulation of the cell cycle.[468-470] Additional approaches are being explored to specifically control the cell cycle clock.

The inactivation of CDK inhibitors (such as p16INK4a and p27kip1), as well as tumor suppressors (such as p53 and pRb), results in the uncontrolled cell proliferation of cancer cells through the constitutive activation of CDK-cyclin complexes.[476,477] Limiting the cancer cell's ability to cycle would not only check tumor growth but might also lead to reduction of the mass through induction of apoptotic pathways.[478] A variety of gene expression inhibitors, low molecular weight agents, biologically active peptides, monoclonal antibodies, and gene therapy approaches have been employed to exploit this cancer behavior.[479,480] One promising approach is the development of CDK inhibitors (CDKi) as novel antitumor agents.[481,482] Many of these compounds target either the catalytic CDK subunit or regulatory pathways that govern CDK activity.[480,483] Flavopiridol, a protein kinase inhibitor, appears to be a potent CDKi by binding and directly inhibiting CDK-1, -2, -4 and -6.[482,484,485] In addition, flavopiridol induces apoptosis by activating the MAPK pathway and inhibiting anti-apoptotic molecules such as Bcl-2 and IAP. CDKi is also being investigated as an adjuvant to current chemotherapeutic protocols.[480] Resistance to current chemotherapeutic agents is due, in part, to the ability of the cancer cell to manipulate cell cycle position to allow repair and avoid apoptosis.[486] By proper timing of the appropriate CDKi, the chemotherapeutic agent can more effectively kill the cancer cell.[480,487] Newer generation CDKis, such as dinaciclib, appear to be even more potent and have a wider therapeutic window/more selective effects than flavopiridol.[484]

Following arrest of cancer cell cycling, other biologically based chemotherapeutic agents might lead to cancer cell killing (apoptosis) or growth arrest (differentiation, senescence). The suppression of apoptosis in cancer cells is not only a fundamental mechanism of tumor formation and progression, but a means of resistance to therapy.[488-490] Like uncontrolled proliferation, many of the oncogenes and tumor suppressor genes identified in human cancers are important regulators of apoptosis.[491] Also, like the targets of uncontrolled proliferation, many types of biologically based therapies are under investigation. Current chemotherapeutic agents depend not only on the cell cycle, but on intact apoptotic programs.[492] At present, chemotherapy induces apoptosis in a general manner, rather than targeting cancer cells only.[493] Therefore, novel apoptosis-based agents need not only to target cancer cells, but to protect normal cells against dose-limiting side effects of chemotherapy or radiation. An example of normal cell survival factors includes G-CSF, a growth factor that counteracts depletion of neutrophils by enhancing proliferation of hematopoietic stem cell proliferation and differentiation.[494,495] In addition to protecting normal tissues from damage, several molecularly based approaches are based on our knowledge of the defects in the apoptotic pathway. Apoptosis-inducing ligands and cell surface receptors, such as the TRAIL signaling pathway, have been targeted using soluble recombinant proteins and antagonistic antibodies.[496-498] Defects in the p53 pathway have been targeted using adenovirus gene therapy.[428,499-501] Low molecular weight agents act directly against p53, such as PRIMA-1, and p53 inhibitors, such as MDM2.[252,502-504]

Inhibitors of apoptosis, such as the Bcl-2 and IAP gene families, have been targeted using RNAi and small peptides, such as BH3 mimetics ABT-737 and ABT-263, that block protein-protein binding.[439,505] Like biologically based approaches to uncontrolled proliferation, targeting of cancer-specific genetic lesions that lead to evasion of apoptosis requires identifying which molecular events may selectively modulate the cancer cell without adverse effects on other cell types or organ systems.

An alternative approach to lead cancer cells to exit the cell cycle is to induce differentiation or senescence.[506,507] Although the bulk of cancer therapy is based on cancer cell killing or resection, a new concept for cancer therapy is termed "tumor dormancy therapy."[508] The goal of this approach is to prolong patient survival time while retaining quality of life. Several differentiation-inducing therapeutic agents are under investigation, including nerve growth factor, trans-retinoic acid, dimethyl sulfoxide, peroxisome proliferator–activated receptor-gamma, 12-0-tetradecanoylphorbol 13-acetate, hexamethylene-bis-acetamide, TGF-β, butyric acid, cAMP, and vesnarinone.[507] Senescence-based therapies can be divided into replicative senescence and premature senescence approaches.[509,510] Replicative senescence, the process leading to growth rate decline in normal metabolically active cells, is primarily subverted by telomerase activity, an event present in 85% to 90% of cancer cells.[510-512] Telomerase inhibition strategies include natural/chemical inhibitors (GRN163L, β-rubromycin, and oleic acid), small molecule inhibitors (such as Vx-001), antisense oligonucleotides (such as GRN 163L), immunotherapies (such as GRVAC1 and GV1001), and gene therapies.[513-516] G-quadruplex stabilizers, such as tankyrase, have also been investigated.[517] Premature senescence, also referred to as oncogene-induced senescence, is targeted using selective microRNA expression epigenetic modifications or stress conditions to influence cell growth arrest through pathway mediators such as p21(Waf1/Cip1/Sdi1).[510,518,519] Likewise, several telomerase inhibitors, such as MST-312, have been shown to induce senescence.[520] Pathways that govern cell differentiation and senescence are much less defined (and likely more variable) than those that govern proliferation and apoptosis. A chief concern in both approaches is a transient or incomplete therapy-induced response.[261] Biologically based therapeutics targeting proliferation, apoptosis, differentiation, and senescence all target cancer cell biology. Therapeutic strategies targeting other cancer cell behaviors, such as neovascularization and metastasis, often target non-neoplastic cells as well to control cancer growth.

Tumor neovascularization is a primary target of biologically based cancer therapy.[275,521] Angiogenesis-targeted therapy has been used in cytotoxic and cytostatic ("tumor dormancy therapy") strategies.[522] Both the cancer cell and stromal cells can be targeted. Therapies focusing on the cancer cell offer the advantage of attacking tumor-specific molecular alterations; however, the genomically unstable cancer cell is also prone to evolving a therapy-resistant phenotype.[522] Stromal cells (principally endothelial cells) are genomically stable and therefore less likely to develop resistance. However, caution must be taken not to target gene activity that is necessary to maintain normal physiologic activity in healthy organ systems that require angiogenesis. Inhibition of tumor neovascularization has been achieved primarily using agents that affect endothelial cells directly. This strategy arrests endothelial cell proliferation (and vessel growth) and promotes tumor-associated endothelial cell death.[523,524] In addition, endothelial cell progenitor recruitment is blocked. Targeting the endothelial cells reduces the overall bulk of the tumor-associated vascular work, normalizing the chaotic pattern and abnormal architecture.[21] The overall therapeutic effect reduces the delivery of nutrients to the metabolically active cancer cells and improves the delivery of conventional chemotherapeutic agents. However, endothelial cell-related mechanisms can be overcome by tumor-secreted VEGF and survival factors. The endothelial cells can also be protected by other stromal cells or rendered irrelevant by vascular mimicry or cooptation.

In addition to endothelial cells, stromal cells targeted in anti-angiogenic therapy include mural cells, fibroblasts, and hematopoietic cells.[522] Inhibition of PDGF pathways reduces differentiation of progenitor cell pools into endothelial cells, as well as destabilizing smooth muscle cells that might cover and protect endothelial cells.[140] Furthermore, fibroblast recruitment of progenitor cells is inhibited. Last, chemokine antagonist inhibition of signaling from inflammatory infiltrate (specifically, IL-8) reduces the recruitment, differentiation, and cytokine production of mature leukocytes. This strategy also has important treatment implications for metastasis.[525] However, there is much redundancy in chemokine signaling, and inhibition of specific signals often results in overexpression of others.

Cancer cell–related anti-angiogenic therapy consists of both conventional (chemotherapy, radiation) and biologically based treatments.[526] Even some anti-angiogenic therapy is cytotoxic to cancer cells by interfering with survival pathways and enhancing sensitivity to treatments.[275] The result of a decreased tumor mass is a reduction of pro-angiogenic factors and decompression of the existing vasculature (thereby improving drug delivery).[21] However, cancer cells frequently will upregulate other pro-angiogenesis factors or, because of their genomic instability, select clones that adapt to the more unfavorable microenvironment.[522] The primary classes of anti-angiogenic therapeutic agents are monoclonal antibodies and small molecule tyrosine kinase inhibitors. Leading examples of monoclonal antibody therapeutic agents include bevacizumab (anti-VEGFR-1/2), cetuximab (anti-EBFR), and panitumumab (anti-EGFR).[527-529] Small molecule tyrosine kinase inhibitors include erlotinib (EGFR), sorafenib (VEGFR-1/2/3, PDGFR-β?and Raf-1), and sunitinib (VEGFR-1/2/3, PDGFR-β?and RET).[530] Other anti-angiogenic strategies are emerging.[531] Rapamycin and other mTOR inhibitors block the PI2/AKT pathway.[532] Bortezomib, a proteasome inhibitor, attacks the cancer cell directly.[533] Thalidomide and zoledronate possess

immunomodulatory, anti-inflammatory, and anti-angiogenic properties.[534,535] Endostatin and combretastatin A4 induce apoptosis in endothelial cells. Interferon-α inhibits bFGF and VEGF.[536]

In short, anti-angiogenesis therapy can be used alone to inhibit tumor growth (and thereby manage it as a chronic disease) or in combination with other conventional cancer therapies to enhance their efficacy.[537] Success of anti-angiogenesis therapy will depend on targeting multiple molecules/cell types and exploring strategies to delay, minimize, or even avoid resistance.[341,538] Last, novel agents will need to be identified that only affect cancer-associated neovascularization without affecting quiescent vessels in healthy organs.[539]

Like tumor neovascularization, metastasis progresses because of a synergy between cancer cells and stromal cells. However, the underlying biology of metastasis remains poorly understood.[9] Many current biologically based therapies targeting metastasis use strategies that address other malignant phenotypes, including neovascularization. For example, therapy targeting cancer cell phenotypes such as uncontrolled proliferation also affects key molecular events governing metastasis. Monoclonal antibodies targeting the EGFR 2 (HER2 or HER2/neu) are effective as an adjuvant and as treatment for metastatic breast cancer.[540] Furthermore, low molecular weight tyrosine kinase inhibitors have also proven to be effective anti-metastatic agents, especially for central nervous system metastases that are refractory to available chemotherapeutic agents.[541] Emerging targets of cancer invasion/metastasis include the HGF-c-MET signaling axis and the integrins. Aberrant expression of c-MET is widely associated with cancer invasion and metastasis.[542,543] Therapeutics designed to block HGF-MET binding include competitive HGF analogues (NK4); truncated, soluble forms of MET that serve as decoys; and monoclonal antibodies (rilotumumab, onartuzumab).[544,545] Small synthetic MET kinase inhibitors targeting the ATP binding site or an inactivating loop binding site have also entered clinical trials.[546,547] Last, attenuation of the MET signal via plant-derived polyphenols is under exploration.[548]

Therapeutic targets of metastasis affect not only cancer cells, but stromal cells as well. Integrins, a family of cell adhesion molecules that help transmit signals from the extracellular matrix into the cell, are important mediators of cell proliferation, and angiogenesis, as well as invasion and metastasis.[549] E-cadherin (discussed earlier in this chapter) is an important integrin involved in suppression of cancer metastasis. Integrins are believed to be involved in several steps of the metastatic cascade, including invasion through the basement membrane into the stromal connective tissue, dissemination of the cancer cell from the primary tumor, intravasation, lymphatic/blood stream transport, extravasation, and proliferation of the cancer cell at the secondary site.[147] Like antibodies, integrin antagonists have easy access to the cell surface.[550,551] Integrin antagonists act as competitive inhibitors, as allosteric inhibitors (changing the integrins' conformation into a less active form), or via antibody-mediated functional blocking (likely through both competitive and allosteric inhibition).[552,553] Other integrin-mediated anti-metastatic strategies include downregulating integrin gene expression using low molecular weight drugs or constructing integrins with compounds toxic to the cancer cell in a manner similar to immunoconjugates discussed earlier.[554,555] Biologically-based therapeutic agents based on metastasis-specific molecular alterations will require more experimentation to reveal their efficacy and limitations. Like angiogenesis-based therapies, agents targeting metastasis are being successfully employed as adjuvants to existing chemotherapy protocols. Although these combinations may not cure cancer, they may prolong patient survival and convert cancer to a chronic, manageable disease.[556-559]

As the molecular alterations leading to cancer are being defined, each change identified can serve as a means to better diagnose and treat the disease.[3] Panels of biomarkers can now be used to determine a molecular signature of cancer activity. In addition, cancer-associated molecular alterations can be used to develop designer drugs that can better address the biology of the disease in an individualized manner. Currently, these novel therapeutic strategies, alone or as adjuvants to current chemotherapeutic protocols, can improve patient survival and allow cancer to be treated as a chronic disease. Development and evaluation of novel cancer cures.

Summary and Future Directions

Advances in molecular biology are already having an impact on clinical oncology. Alterations of DNA structure, gene expression, and protein function ultimately disrupt key regulatory pathways and pathway networks. As these molecular alterations are accumulated, the cancer cell acquires important traits that confer a selective advantage over its normal neighbors. These cancer-associated behaviors include deregulated cell proliferation, evasion of apoptosis, neovascularization, and metastasis. Identification of the molecular alterations underlying these cancer cellular characteristics not only provides insights into the biology of the disease but highlights critical targets that may improve the diagnosis and treatment of the oncology patient. Though there are many achievements in the more than 30-year history of molecular oncology, several challenges remain for the future. New molecular alterations continue to be identified. Challenges remain to prioritize their biologic importance and determine the feasibility of translating this knowledge from the bench to the bedside. In the future, high-throughput analysis of cancer-related alterations may allow cancers to be categorized by their molecular makeup rather than clinical parameters such as tissue of origin or size. Identification of the biomarkers indicative of the malignant phenotype

will allow us to predict clinical behavior long before conventional microscopic or imaging techniques. However, challenges remain in standardization of specimen collection, interpretation of results, and identification of a rapid, inexpensive, robust, and technically feasible protocol for a clinical setting. In the future, DNA-mRNA-protein marker panels may determine risk/prevention, diagnosis, treatment choice, and monitoring of the cancer patient. Last, cancer-associated molecular changes are also providing important therapeutic targets. However, challenges remain regarding dose/timing, delivery, and treatment duration. In the future, molecularly based designer drugs may augment or replace conventional therapeutic strategies, reducing cancer to a manageable, chronic disease.

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27

Sarcomas of the Jaws

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Introduction

mal origin include bone, cartilage, fibrous tissue, muscle, vascular tissue, neural tissue, and adipose tissue. Among the various tissue types, approximately 80% of all sarcomas originate from soft tissue components, whereas the remaining 20% comprise neoplasms originating from [1]

States.[2,3] When considering the specific anatomic subsite of the head and neck, sarcomas represent only 1% of all primary head and neck malignancies.[4,5] Furthermore, primary sarcomas of the head and neck represent only 2% to 15% of all adult sarcoma diagnoses.[5,6] However, in pediatric populations, up to 35% of all sarcomas will arise within the head and neck region.[7]

Classification

origin, the histologic grade of the neoplasm, and the anatomic subsite within the head and neck from which the tumor arises. Each of these features provides valuable information regarding prognosis and can also be useful for developing treatment plans, as well as determining the need for adjuvant or neoadjuvant therapy. For most sarcoma subtypes, there is little to no controversy as to which tissue type the sarcoma derives from. However, for some sarcomas, it remains unclear as to which tissue type serves as the progenitor for the neoplasm. Immunohistochemistry and the advent of new molecular oncology markers have aided in the ability to definitively classify sarcomas; however, as many as 20% of sarcomas will their respective tissue of origin are listed in Table 27-1.

The histologic grade of head and neck sarcomas is a reliable predictor of prognosis and consequently is a designated component of the American Joint Committee on Cancer (AJCC) staging system. By definition osteosarcomas, malignant fibrous histiocytomas (MFHs), rhabdomyosarcomas, angiosarcomas, synovial sarcomas, and Ewing sarcomas are all considered to be high-grade neoplasms,[1,9,10] whereas dermatofibrosarcoma protuberans, desmoid tumors, and atypical lipomatous tumors are all considered low grade.[4,11] Additionally, there are a number of sarcomas that require their own individualized histologic grading systems, including chondrosarcomas, fibrosarcomas, leiomyosarcomas, liposarcomas, neurogenic sarcomas, and hemangiopericytomas.[12] The prognostic importance of histologic grade for sarcomas is reflected in the near-100% 5-year survival rates for patients with grade 1 sarcomas reported in one series, whereas patients with grade 2 and 3 sarcomas experienced 5-year survival rates of only 64%.[13] Furthermore, high histologic tumor grade has also been shown to be associated with increased rates of local recurrence and increased rates of distant failure, as well as decreased rates of disease-specific survival.[14]

Classifying sarcomas based on the anatomic subsite within the head and neck has also proven to be useful in terms of prognosticating outcomes and guiding treatment decisions. Tumor location and proximity to other anatomic structures in the head and neck can influence the aggressiveness of surgical interventions, especially when considering the anticipated morbidity and functional deficits that are incurred postoperatively. Although negative margin status remains a critically important aspect of operative intervention for head and neck sarcomas,[1,4,6,9,15] unacceptable morbidity following surgical resection can often serve as a basis for consideration of non-operative treatment modalities, particularly in cases of pediatric head and neck sarcomas. The use of microvascular free tissue transfer in reconstruction of

TABLE 27-1 Histologic Subtypes of Head and Neck Sarcomas According to Tissues of Origin

- Bone
  - Osteosarcoma
- Cartilaginous
  - Chondrosarcoma
- Fibrous
  - Malignant fibrous histiocytoma
  - Fibrosarcoma
  - Dermatofibrosarcoma protuberans
- Muscular
  - Rhabdomyosarcoma
  - Leiomyosarcoma
- Vascular
  - Angiosarcoma
  - Hemangiopericytoma
- Neural
  - Neurogenic sarcoma
- Adipose
  - Liposarcoma
- Histogenesis Unclear
  - Synovial sarcoma
  - Ewing sarcoma
  - Alveolar soft part sarcoma

oncologic defects has enabled much more complex surgical resections to be planned and executed for head and neck sarcomas; however, high-grade tumors in unresectable locations can still preclude the use of surgery for primary disease control. Ultimately, when considering all anatomic sites, the presence of a sarcoma within the head and neck is a poor prognostic factor in and of itself. When compared to other anatomic sites, sarcomas arising within the head and neck are associated with the highest rates of local recurrence and the poorest disease-specific survival.[14,15]

Etiology of Sarcomas

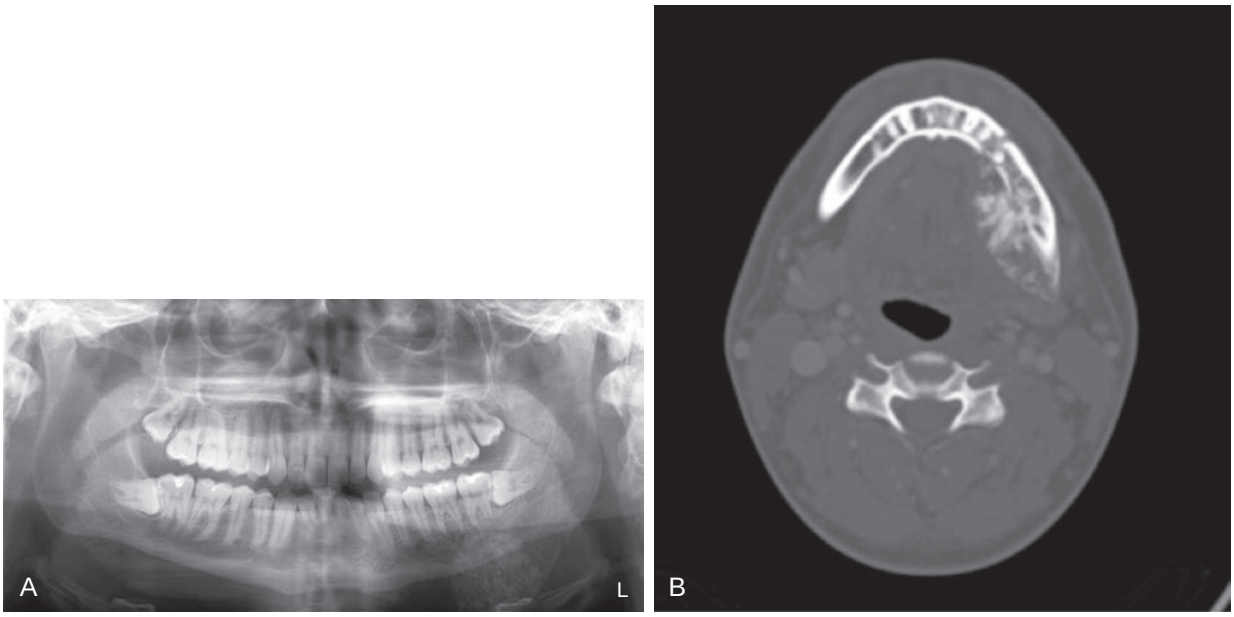
Although sarcomas can certainly occur de novo in patients without any known risk factors, there are a multitude of known genetic and environmental risk factors predisposing to the development of sarcomas. Li-Fraumeni syndrome, neurofibromatosis type I, Gardner syndrome, nevoid basal cell carcinoma syndrome, Carney triad, heredity hemochromatosis, and Werner syndrome have all been linked to the presence of sarcomas.[16-18] Li-Fraumeni syndrome is an autosomal dominant disorder involving mutation of the p53 tumor suppressor gene. Affected individuals suffer from breast cancer, soft tissue sarcomas, central nervous system malignancies, leukemia, and adrenocortical carcinomas.[16,18] Neurofibromatosis type I is an autosomal dominant disorder involving mutation of a gene on chromosome 17 responsible for controlling cell division.[17] Patients affected by this disorder are predisposed to increased rates of childhood rhabdomyosarcomas, liposarcomas, and fibrosarcomas in addition to neurogenic sarcomas, which tend to develop in adulthood.[18] Gardner syndrome represents an autosomal dominant disorder involving mutation in the adenomatous polyposis coli (APC) gene. These patients experience a multitude of benign and malignant neoplastic processes including osteomas, epidermal cysts, fibromas, lipomas, desmoid tumors, and hundreds of adenomatous colorectal polyps which inevitably progress to colorectal cancer, as well as an array of extracolonic malignancies involving the duodenum, thyroid, pancreas, stomach, central nervous system, liver, and adrenal glands. Nevoid basal cell carcinoma syndrome, an autosomal dominant disorder involving mutation in the PTCH1 gene on chromosome 9, has been linked with development of rhabdomyosarcomas and fibrosarcomas.[19] Carney triad, a specific subtype of multiple endocrine neoplasia (MEN) syndrome, is characterized by the presence of three classically associated tumors: gastric epithelioid leiomyosarcoma, pulmonary chondroma, and extra-adrenal paraganglioma.[20] Hereditary hemochromatosis is an autosomal recessive disorder involving mutation in the HFE gene leading to increased intestinal absorption of iron and has been associated with sarcomas of the liver.[21,22] Werner syndrome is a rare autosomal recessive disorder involving a mutation in the WRN gene, which is responsible for encoding a DNA helicase and a DNA exonuclease.[23] The syndrome is characterized by the appearance of premature aging, and it is associated with a significantly increased susceptibility to the development of soft tissue sarcomas.[23]

Numerous environmental factors have also been suggested as causative agents in the development of sarcomas. External beam radiation therapy,[24] exposure to various radioisotopes,[18] high-intensity electromagnetic fields,[25] phenoxyacetic acid–based herbicides,[26] Agent Orange,[26] dioxin,[26] polyvinyl chlorides,[18] thorium oxide (Thorotrast),[18] and inorganic arsenic[18] have all been implicated in the formation of sarcomas. Prenatal exposure to cocaine and marijuana has been shown to be associated with an up to fivefold increased risk of developing pediatric rhabdomyosarcoma.[27] The use of smokeless tobacco products has also been shown to correlate with increased risk of developing sarcomas of the upper aerodigestive tract, and this risk is further intensified by concomitant cigarette use.[28]

Although multiple genetic and environmental factors have been found to be associated with the development of head and neck sarcomas, the vast majority will not be attributable to any specific exposure or underlying genetic syndrome. The relative rarity of these tumors as a whole also makes it exceedingly difficult to accurately determine relative risk values across populations for different exposure types. Ultimately, for most patients afflicted with sarcomas of the head and neck, the true etiologic cause is likely the end result of a complex interplay occurring between environmental factors and some level of an underlying baseline genetic predisposition.

Diagnosis

The clinical presentation of head and neck sarcomas can be highly variable depending on the specific area of involvement and the proximity to surrounding anatomic structures. Tumors involving the nasal cavity or paranasal sinuses may present with nasal obstruction, orbital proptosis, diplopia, or recurrent epistaxis. Sarcomas involving the ear and lateral

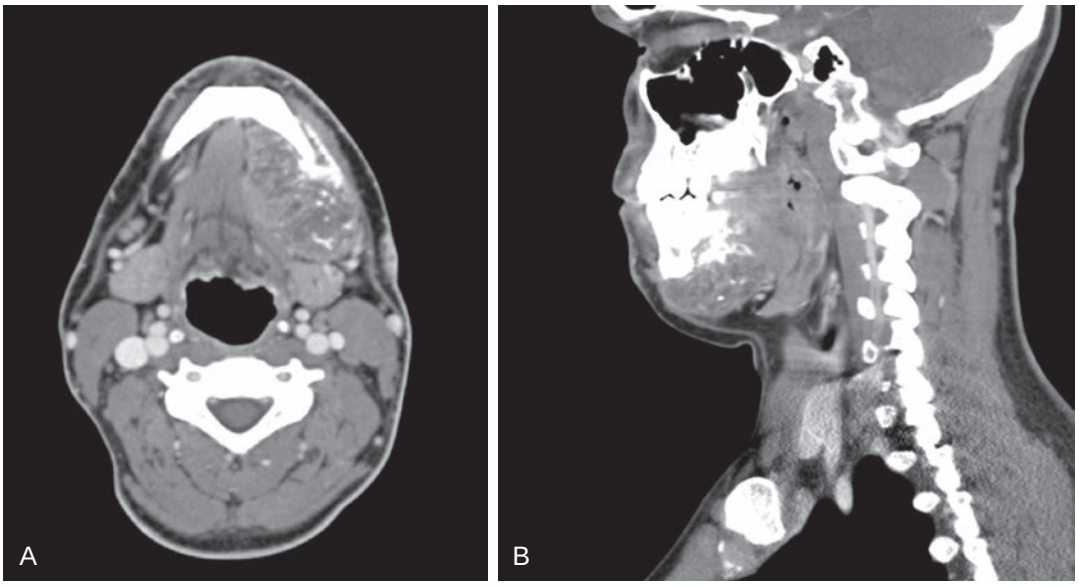


• **Figure 27-1** High-grade chondroblastic osteosarcoma of the right mandible in a 21-year-old male. Panoramic x-ray **(A)** and axial computed tomography scan **(B)** demonstrate periosteal reaction and radial spicules with "sunburst" appearance.

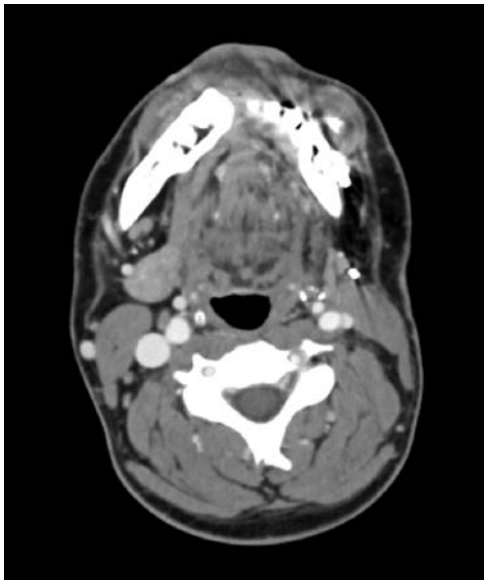
skull base can present with possible facial paralysis, hearing deficits, otalgia, or equilibrium disturbances. Tumors that involve the oral cavity can present with odontalgia, tooth mobility, paresthesias, and facial asymmetry. Involvement of the neck can result in impingement of neurovascular structures leading to dysphagia, hoarseness, and in rare instances even dyspnea. However, despite the widely variable presentations of head and neck sarcomas a common, but not necessarily specific, unifying symptom seen in up to 80% of sarcoma patients is the presence of a painless expansile mass.[4]

Thorough physical examination, although always a requisite, can occasionally be somewhat limited in terms of fruitfulness depending on tumor location. Accordingly, advanced imaging studies are vital adjuncts to the physical examination when evaluating for the presence of head and neck sarcomas. Advanced imaging modalities are able to much more accurately determine the exact size and location of a lesion and can also provide valuable information regarding bony invasion, intracranial extension, and regional nodal involvement. In virtually all instances, obtaining a high-resolution computed tomography (CT) scan or magnetic resonance imaging (MRI) will be indicated before consideration of definitive treatment planning. Specific advantages of CT scanning over MRI include reduced time required for image capture, diminished problems with motion artifact, increased sensitivity for osseous lesions, and an overall reduced higher soft tissue resolution (enabling better interrogation of perineural invasion, dural involvement, bone marrow extension, orbital invasion, etc.), lack of radiation exposure, and identification classic of T1- versus T2-weighted image changes associated with specific sarcoma types and can aid in pre-pathologic tumor characterization.

It is important to note that certain histologic subtypes of sarcomas tend to demonstrate classic radiographic findings on either CT or MRI, which if present, can be extremely useful from both a treatment planning and a diagnostic standpoint. For example, osteosarcomas are well known to demonstrate a hallmark periosteal "sunburst" reaction that can be visualized on plain radiographs as well as on CT imaging (Figure 27-1). Osteosarcomas can also present with findings of significant osseous destruction, peripheral soft tissue calcifications, and evidence of new or abnormal bone formation (Figures 27-2 and 27-3). Extraskeletal Ewing sarcomas will typically appear as hypodense lesions with evidence of irregular enhancement when visualized with CT imaging. Ewing sarcomas will also typically show evidence of significant muscle and subcutaneous tissue infiltration. On MRI imaging, Ewing sarcomas will typically present as a hypointense lesion on T1-weighted imaging, which will then appear hyperintense on T2-weighted projections. MRI evaluation of liposarcomas reveals a hyperintense T1-weighted signal and only modest signals on T2-weighted imaging. Alveolar soft-part sarcomas tend to show a hyperintense signaling on both T1- and T2-weighted images. Comparatively, malignant fibrous histiocytomas typically exhibit an isointense T1-weighted signal and a hyperintense T2-weighted signal. CT imaging of malignant fibrous histiocytomas also typically reveals evidence of significant bone destruction, local expansion, and extensive bone remodeling. Leiomyosarcomas can appear as non-enhancing masses with areas of cystic necrosis when visualized on CT. However, these lesions should be distinguished from



• **Figure 27-2** Axial **(A)** and sagittal computed tomography **(B)** scan demonstrating a large, heterogemass effect on the adjacent musculature.



• **Figure 27-3** Metastatic, recurrent high-grade osteosarcoma preleft mandible.

hemangiopericytomas, which can also demonstrate areas of cystic necrosis, but will also typically present with speckled calcification and an intense hypervascular enhancement.[26]

Although all of the aforementioned imaging findings are useful for assisting with diagnosis, none of the findings alone are sufficient for diagnosis. Furthermore, the "classic" imaging hallmarks of specific sarcoma subtypes are not always evident, and heterogeneity of sarcomas on advanced imaging is not an unexpected finding.[29] Accordingly, tissue biopsy will always be required before a definitive diagnosis can be rendered. Generally imaging should always be performed before procurement of a biopsy specimen in order to reduce any postsurgical inflammatory changes that may obscure image quality or alter the innate imaging characteristics of the lesion itself. Options for diagnostic biopsy of a presumed head and neck sarcoma include fine-needle aspiration (FNA), core needle biopsy, or an open incisional biopsy. FNAs are often chosen for suspected sarcomas of the parotid, neck, or parapharyngeal spaces. Conversely, transmucosal incisional biopsies are often appropriate for most tumors involving the oral or nasal cavities; however, the surgeon must be conscious not to inadvertently "seed" the tumor into uninvolved areas when performing the biopsy itself. Regardless of whatever option is chosen, the surgeon must also be cognizant of the potential advantages and disadvantages of each technique and the eventual implications for accurate diagnosis. For example, a complete surgical resection of a tumor involving the parotid, neck, or parapharyngeal space is preferable to an attempt at open biopsy if the initial FNA was equivocal in order to prevent contamination of uninvolved areas. Furthermore, the surgeon must also be mindful of the specific expertise and preferences of the pathologists working at his or her institution, as not all pathologists will be as skilled or adept at rendering an appropriate diagnoses from a biopsy modality with which they are less familiar. Ideally, if suspicion for head and neck sarcoma is high, the specimen should be sent to a pathologist who is experienced in interpretation of sarcoma histology, as an inaccurate diagnosis could have catastrophic implications for both the patient and provider. One should not overlook the importance of second opinions from outside facilities if there remains any doubt or question over the histologic diagnosis. However, given the relative rarity of head and neck sarcomas, identification of centers with such specific expertise can sometimes prove to be difficult.

Finally, once a histologic diagnosis of a head and neck sarcoma has been rendered, it is exceedingly important to further investigate for the presence of distant metastases. The most commonly involved site of distant metastasis for all head and neck sarcomas is the lungs.[26] Accordingly, chest imaging should be obtained and can be limited to plain films for low-grade lesions; however, high-grade tumors will necessitate more advanced CT imaging.[30] Positron emission tomography (PET) is also useful in identifying the presence of distant metastases both at the time of initial diagnosis and during interval surveillance following primary tumor management.[31]

Osteosarcoma

Osteosarcomas, also commonly termed osteogenic sarcomas, represent the most common nonhematopoietic primary malignant neoplasm of bone, and they are known to occur anywhere in the body.[32-34] The majority of osteosarcomas will present in the long bones of adolescent patients with a particular predilection for the long bones around the knee.[26,35] Appendicular osteosarcomas typically demonstrate a bimodal age distribution, with most occurring between the ages of 10 and 20 years, and a smaller subset occurring in adults more than 50 years of age. Specific involvement of head and neck subsites is an uncommon occurrence, with less than 10% of all primary osteosarcomas arising within the head and neck region.[26,35-37] However, osteosarcomas do represent one of the most common histologic subtypes of sarcoma presenting within the head and neck, and they account for approximately 10% to 15% of all sarcoma diagnoses within this anatomic area.[38] The average age of diagnosis for patients with primary head and neck osteosarcoma is typically within the third and fourth decades of life, which exceeds the age of patients diagnosed with long bone osteosarcoma by approximately 10 to 15 years.[26] Although osteosarcomas can occur de novo, they are also well known to arise secondarily from multiple known risk factors. Previous history of head and neck radiation or chemotherapy for another tumor,[39-41] syndromic conditions (Rothmund-Thompson syndrome, Li-Fraumeni syndrome),[8,42-44] bone dysplasias (Paget disease, fibrous dysplasia, enchondromatosis),[8] chronic osteomyelitis,[45] trauma,[45] and transformation from a preexisting benign tumor[46] have all been described to be associated with the development of osteosarcomas.

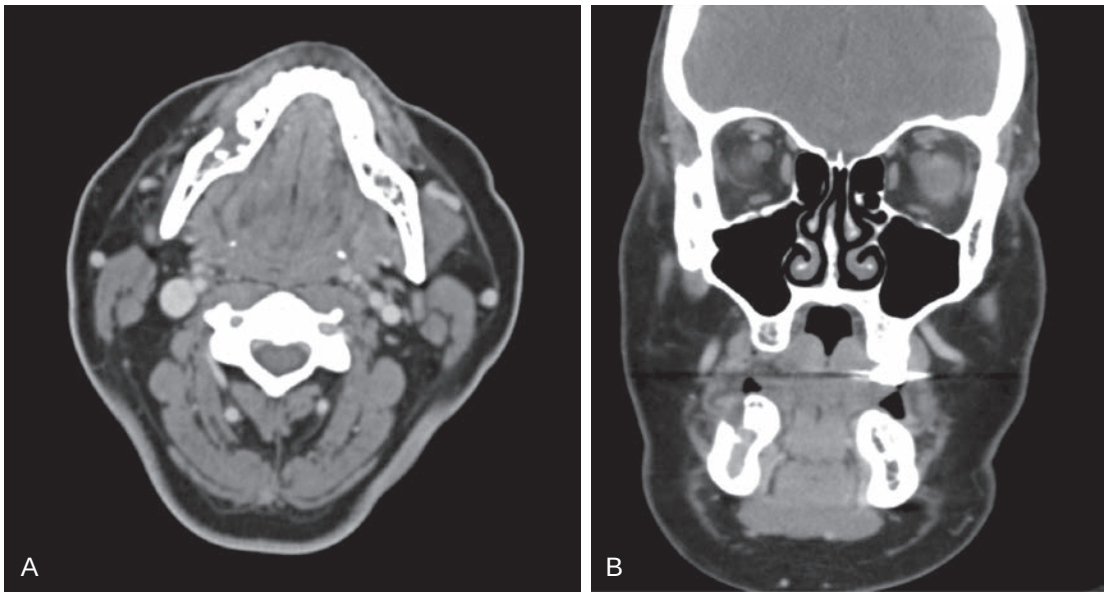
The majority of patients with osteosarcoma will present with a rapidly growing, painless mass; however, some patients can experience symptoms for a protracted period of time, suggesting that some osteosarcomas can be slow growing (Figure 27-4). Average duration of symptoms before initial diagnosis typically ranges between 2 and 6 months.[35,47,48] Osteosarcomas frequently involve the maxilla and the mandible, and approximately 50% of osteosarcomas will originate from either of these two structures (Figure 27-5).[26] The most frequently reported site of mandibular involvement is the posterior body and horizontal portion of the mandibular ramus, whereas maxillary lesions typically present in the inferior portions of the maxilla, including the alveolar ridge, sinus floor, and palatine processes.[8] Accordingly, loosening of teeth, pain, paresthesias, and nasal obstruction are not uncommon findings.



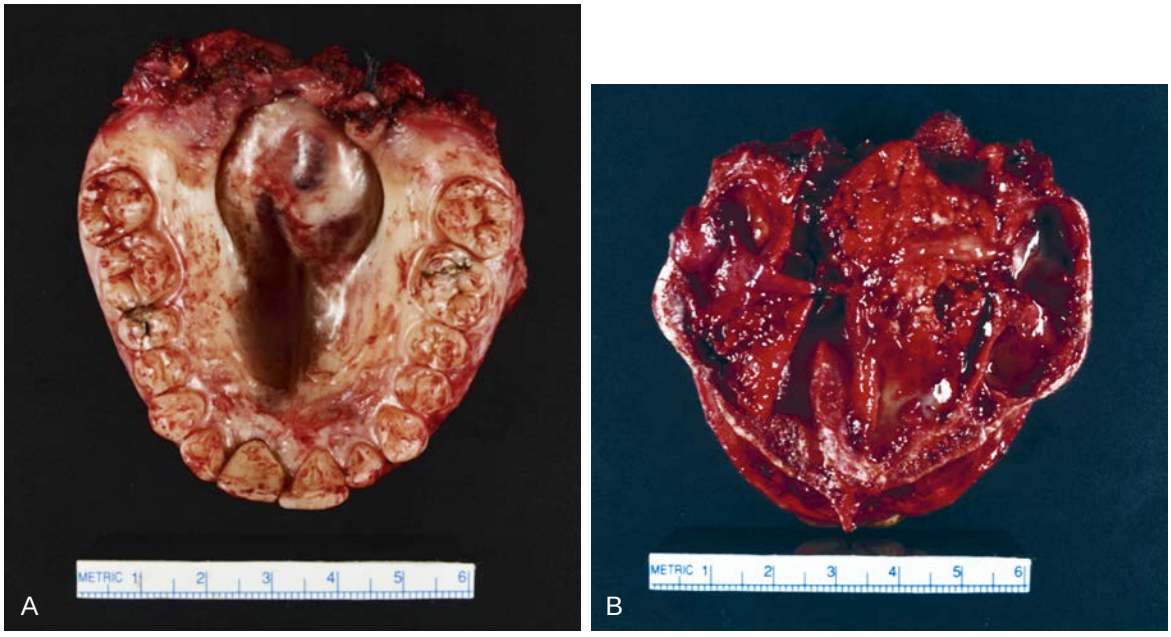
• **Figure 27-4** 34-year-old man with a 6-week history of rapidly enlarging palatal mass.

Histologically, osteosarcomas of the head and neck are indistinguishable from osteosarcomas involving the appendicular skeleton.[49] The primary characteristic of all osteosarcomas is the production of an osteoid matrix, which will appear as an eosinophilic hyalinized material on hematoxylin and eosin staining. The osteoid is also typically surrounded by a rim of osteoblasts and is interspersed with spindle-shaped stromal cells that will display varying degrees of anaplasia and mitotic activity.[32,50] There are a total of seven histologic subtypes of osteosarcomas: osteoblastic, chondroblastic, fibroblastic, small cell, giant cell, telangiectatic, and parosteal. The osteoblastic, chondroblastic, and fibroblastic variants represent the three most common subtypes.[8] Because chondroblastic osteosarcomas can closely resemble the histologic patterns seen in chondrosarcomas, the identification of bone formation within the tumor is essential to distinguishing the former from the latter. For specific variants of osteosarcoma, the clinical behavior of the lesion can occasionally be correlated with the specific histologic subtype. For example, telangiectatic osteosarcomas are known to be highly aggressive tumors, whereas parosteal osteosarcomas are considered to be low-grade neoplasms and are associated with a more favorable prognosis.[51,52] Additionally, the chondroblastic subtype has been proposed to be associated with poorer survival outcomes, whereas the fibroblastic variant is reported to have the most favorable prognosis.[48] However, histologic subtype has failed to demonstrate a statistically significant impact on survival in the largest reported series of head and neck osteosarcomas.[48,53]

Although the optimal treatment protocol for head and neck osteosarcomas remains controversial, complete surgical resection of the tumor with negative margins remains the singular unifying theme in all purported regimens (Figure 27-6). Surgical resection achieving negative margins remains the single most important aspect in the treatment of osteosarcoma, and numerous studies have demonstrated



• **Figure 27-5** 47-year-old woman with low-grade osteosarcoma of the right mandible body. Axial **(A)** and coronal **(B)** computed tomography scans demonstrate a well-marginated, cortical defect.



• **Figure 27-6** Bilateral infrastructure partial maxillectomy for treatment of palate chondroblastic osteosarcoma after neo-adjuvant chemotherapy. **A,** Maxillectomy specimen palatal view. **B,** Maxillectomy specimen superior view. Tumor invades through palatal bone.

significant reduction in local disease control and survival rates when nonsurgical treatment modalities are selected.[45,47,54] Elective neck dissection for the treatment of osteosarcoma is unnecessary, as regional spread of osteosarcomas to cervical lymph nodes is exceedingly uncommon.[26] However, selective neck dissection should be performed if there is frank clinical or radiographic evidence of nodal involvement or if there is direct extension of the primary tumor into the soft tissues of the neck.

Chemotherapy and radiotherapy have also both been used as neoadjuvant and adjuvant treatment modalities in combination with surgical resection.[38,45,49,54,55] The use of neoadjuvant chemotherapy carries the advantage of preemptively evaluating the response to various chemotherapeutic agents and can aid in the eventual selection of optimal adjuvant regimens. The chemotherapeutic drugs presently in use to treat osteosarcoma include high-dose methotrexate with leucovorin rescue, adriamycin, cisplatin, ifosfamide, and

cyclophosphamide.[8] The rationale for use of chemotherapy regimens is predominantly directed toward destruction of pulmonary micrometastases, which are present in as many as 80% of appendicular osteosarcomas at the time of diagnosis.[56] However, only 7% to 17% of patients with head and neck osteosarcomas will go on to develop distant metastases (most commonly to the lung and brain),[49,54] and therefore the use of chemotherapy in this patient population may potentially hold less utility. Nevertheless, systemic neoadjuvant chemotherapy has been shown to correlate with initial improvements in disease-free survival as well as overall survival rates for head and neck osteosarcomas.[49,54,57]

The use of radiation therapy as an adjuvant modality in the treatment of head and neck osteosarcoma has become increasingly frequent, particularly in cases of high-grade tumors or large lesions, and in patients with close or positive surgical margins.[45,47,54] Surgical margin status seems to be the predominant factor in the decision to use radiation therapy, as obtaining clear margins for head and neck osteosarcomas can often prove to be more difficult when compared to lesions involving the appendicular skeleton.[47] A consensus regarding the benefit of radiation therapy for head and neck osteosarcoma has not definitively been reached, as some report no survival benefit from either external beam radiation or brachytherapy,[49] whereas others report improved local control, disease-specific survival, and overall survival in patients with positive or close margins following surgery.[58] Nevertheless, the use of radiation therapy must also be weighed against the known risks of developing a post-irradiation osteosarcoma, which is associated with significant morbidity and unfavorable outcomes.[26]

Despite the ongoing controversy regarding the optimal treatment regimen for head and neck osteosarcomas, the overall survival rates remain exceedingly poor. Overall 2-year survival rates are reported to be 53% to 66%,[49,54] and 5-year survival rates are 42% to 55%.[47,49,54] Disease-free survival at 5-year follow-up is achieved for only 25% to 30% of all patients.[47,54] A number of prognostic factors for head and neck osteosarcomas have been repeatedly identified within the literature. Surgical margin status is widely known to correlate significantly with both local disease control and overall survival rates. The presence of a positive margin has been shown to dramatically reduce the 5-year survival rates from 75% in patients with negative margins, to a mere 35% where negative margins are not achieved.[47,49] Recurrent osteosarcomas as well as post-irradiation osteosarcomas are also known to have a significantly worse prognosis.[49] Conversely, osteosarcomas of the maxilla and mandible portend higher survival rates given a greater likelihood for complete resection when compared to other extragnathic head and neck locations.[55]

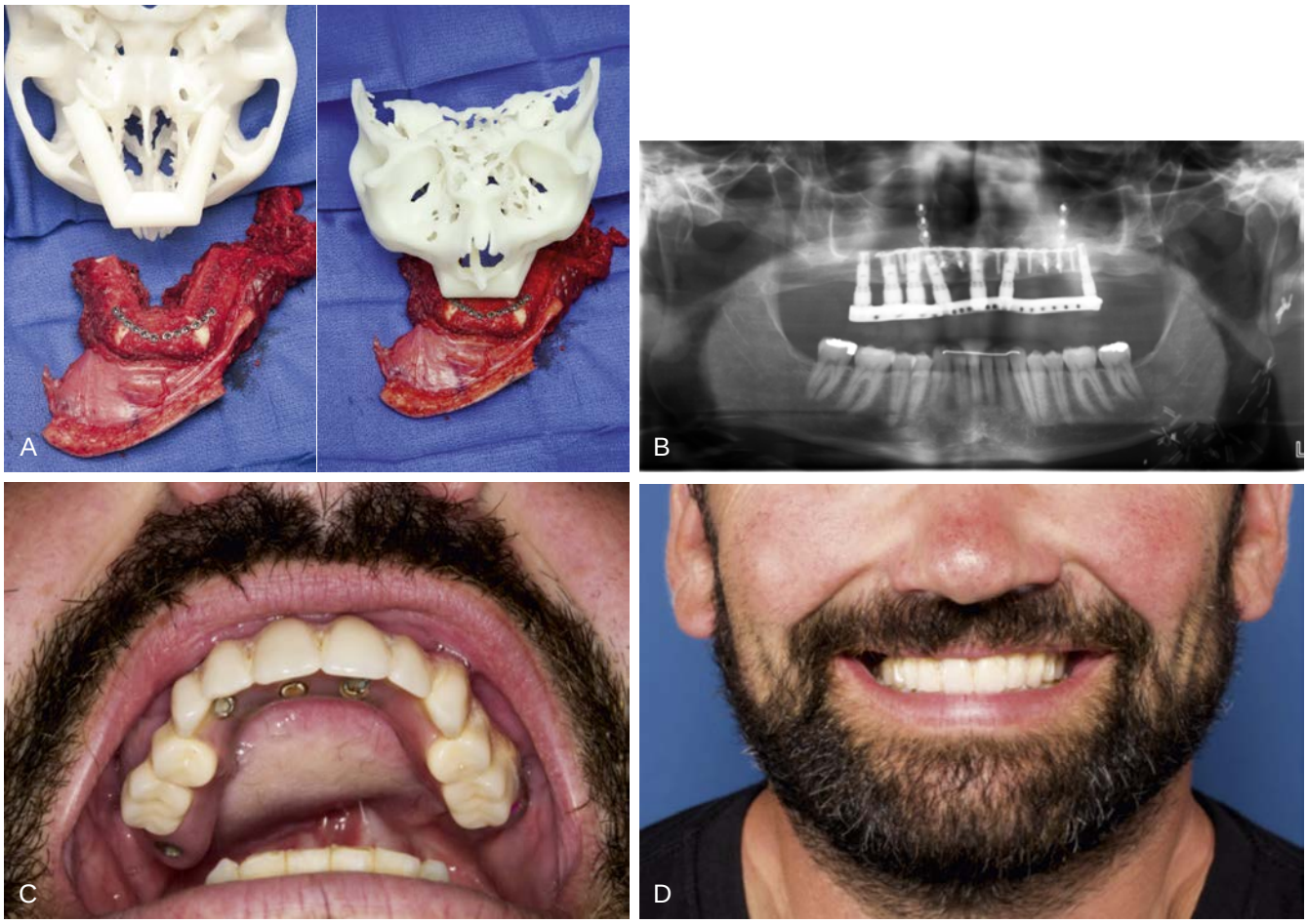
In conclusion, osteosarcomas of the head and neck represent extremely rare neoplasms, although they are one of the most common subtypes of sarcomas presenting within the head and neck. They represent extremely aggressive tumors and by definition are considered high-grade malignancies. Although optimal treatment regimens have not definitively been established, complete surgical resection with negative margins (Figure 27-7) remains a cornerstone of multimodal treatment strategies that can dramatically affect local disease control and overall survival rates.

Chondrosarcoma

Chondrosarcomas are rare neoplasms, which, not unlike osteosarcomas, are more commonly found affecting appendicular skeleton and have specific predilection for the extremities, pelvis, and long bones.[59] Presentation within the head and neck is uncommon, with only 5% to 10% of all chondrosarcomas occurring within this region of the body.[60] Additionally, chondrosarcomas constitute less than 10% of all head and neck sarcoma diagnoses overall.[60] These neoplasms are exceedingly uncommon in pediatric populations, and there are only a handful of case reports and case series available in the literature.[61] Owing to the relative rarity of chondrosarcomas, the typical age of presentation reported is widely variable, with some suggesting onset within the third and fourth decades of life,[62] whereas others report peak presentation within the fifth to seventh decades.[61] No male or female predominance has been demonstrated within the available literature of reported cases.[26]

The most commonly affected subsite within the head and neck is the sinonasal tract, with approximately 50% of head and neck chondrosarcomas occurring within this region.[60,62,63] Other commonly affected head and neck sites are the mandible and the larynx, which combine for the majority of the remaining chondrosarcomas diagnosed within the head and neck region.[62-64] The typical presenting symptoms of chondrosarcomas are largely dependent on the specific subsite affected; however, the most common presentation is that of a painless mass or swelling. Relative to osteosarcomas, pain is a less frequently reported complaint with chondrosarcomas. Large chondrosarcomas involving the sinonasal tract or maxilla can cause nasal obstruction, sinusitis, epistaxis, and loosening of teeth. Proptosis, photophobia, or even visual loss can also occur if there is extensive orbital invasion.[61]

Histologically, chondrosarcomas are composed of a chondroid matrix with lacunar formation and varying degrees of chondrocyte maturation and cellularity. Four distinct histologic variants of chondrosarcomas have been identified: clear cell, dedifferentiated, myxoid, and mesenchymal.[65] The mesenchymal and myxoid variants constitute the majority of head and neck cases.[8] As previously mentioned, chondroblastic osteosarcomas can be easily confused with the histologic presentation of chondrosarcomas, and the presence of bone formation is a requisite for distinguishing the former from the latter. Immunohistochemical markers are also useful in confirming the diagnosis of chondrosarcoma, as these neoplasms generally express positivity for vimentin, CD99, S-100, and Sox-9.[60] Histologic grading of chondrosarcomas is unique from the standard WHO four-grade system for all cancers excluding lymphomas and leukemias (Grade 1: Well Differentiated; Grade 2:



• **Figure 27-7** Bilateral infrastructure maxillectomy and immediate reconstruction with a free fibula flap **(A)** and secondary endosseous implant reconstruction of the neomaxilla **(B).** The interim maxillary prosthesis serves as a tissue conformer **(C)** and provides good function and aesthetics **(D).**

Moderately Differentiated; Grade 3: Poorly Differentiated;[66]

mitotic activity, and degree of cellularity. Histologic grading is an important prognostic indicator for chondrosarcomas, as increasing histologic grade portends a more aggressive clinical behavior of the neoplasm, an increased risk of distant metastasis, and an overall poorer prognosis.[65,67] Grade 1 chondrosarcomas are moderately cellular with abundant hyaline cartilage matrix. Chondrocytes are small with either round nuclei or binucleate in morphology, and mitotic figures are absent from all microscopic fields.[67,68] Grade 2 chondrosarcomas are typified by increased cellularity and a reduced proportion of chondroid matrix. Chondrocytes demonstrate enlarged nuclei, which can appear vesicular or hyperchromatic. Mitotic figures will be present; however, they will be widely scattered throughout the specimen.[67,68] Grade 3 chondrosarcomas are typically highly cellular and show absent or sparse chondroid matrix. Chondrocytes will exhibit obvious nuclear pleomorphism, and mitoses are easily detectable. The vast majority of chondrosarcomas arising within the head and neck are histologic grades 1 or 2, with grade 3 tumors being much more uncommon.[17]

Treatment of head and neck chondrosarcoma involves complete surgical excision including all involved structures in an attempt to attain negative margins. Regional nodal metastases are exceedingly uncommon, and elective neck dissection is generally not required unless there is direct invasion of the tumor into the neck structures or there is frank clinical or radiographic evidence of regional nodal involvement.[26] However, local recurrence is common and direct invasion into vital structures of the head and neck represents the leading cause of disease-related deaths.[69] Approximately 10% to 30% of patients will go on to develop distant metastases, most commonly to the lungs; however, this is typically in association with recurrent or uncontrolled local disease.[59,60,64] Radiation and chemotherapy have both been used as adjuvant therapies in the treatment of chondrosarcoma,[8,61] but the benefits of these modalities have yet to be demonstrated by any non-randomized or randomized prospective studies.[8] Traditionally radiation and chemotherapy were reserved for the treatment of locally advanced disease or unresectable tumors, in spite of the widely held

belief that chondrosarcomas are in fact radiotherapy- and chemotherapy-resistant neoplasms.[8,61] Nevertheless, some authors report a radioresponsiveness for chondrosarcomas,[70-72] although higher radiation doses (>65 Gy) are typically required for effect.[8] More recently, proton beam therapy has also been suggested as an adjunctive modality in the treatment of head and neck chondrosarcoma in order to reduce the morbidity associated with external beam radiation therapy.[73-75] However, the reports of proton beam therapy for the treatment of chondrosarcoma are limited to a few case studies, and evidence is presently insufficient to recommend its widespread use.

The overall 5-year survival rate for head and neck chondrosarcomas is reported to be 77.6%, and 5-year disease-specific survival is reported to be 87.2%.[65] The observed 10-year survival and 10-year disease-specific survival is reported as 64.3% and 70.6%, respectively.[65] Factors that have been identified to correlate with a poorer prognosis include tumors with high histologic grade and the presence of regional or distant disease at the time of diagnosis.[65] Additionally, 5-year disease-specific survival rates were also found to be poorer in mesenchymal and myxoid histologic variants of chondrosarcoma when compared with conventional chondrosarcomas.[65]

In conclusion, chondrosarcomas represent exceedingly rare neoplasms within the head and neck. The clinical behavior of the tumor and overall prognosis are closely tied to the histologic grade of the lesion, with higher histologic grades being associated with increased risk of distant metastasis as well as poorer prognosis. Treatment of chondrosarcomas is surgical, with complete excision and negative margins being the ultimate goal. The use of radiation, chemotherapy, and more recently proton beam therapy have all been reported in the treatment of chondrosarcoma; however, insufficient evidence currently exists to recommend use of these modalities as a standard of care.

Malignant Fibrous Histiocytoma

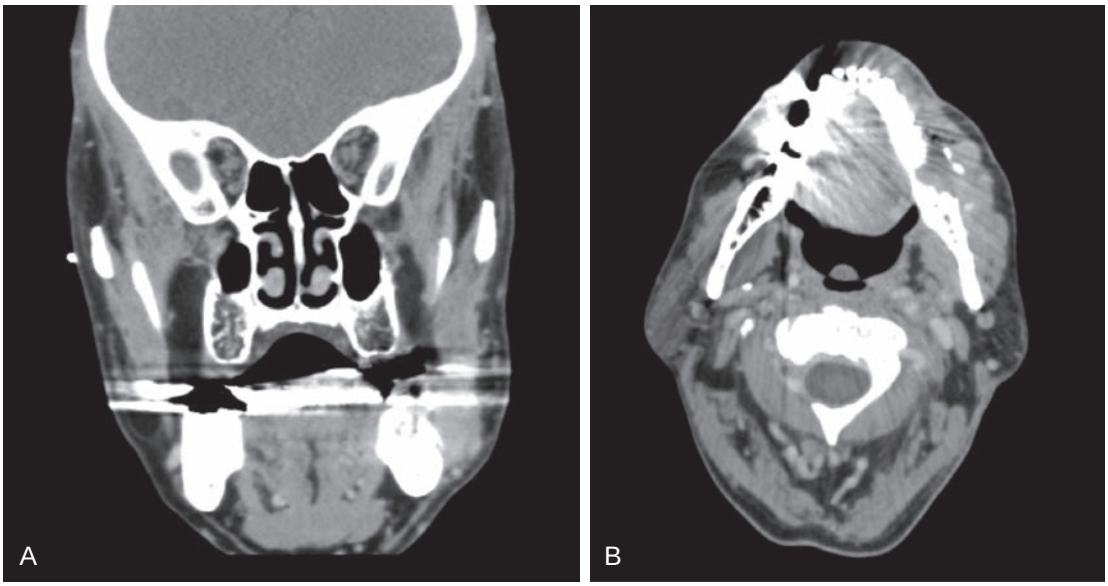
Malignant fibrous histiocytomas (MFHs) are soft tissue sarcomas deriving from fibrous tissue, and they represent the most commonly diagnosed sarcoma within the head and neck region.[8,26] MFHs also represent one of the most common varieties of soft tissue sarcomas when all anatomic subsites are considered; however, head and neck MFHs comprise only 3% to 10% of all diagnosed cases.[8,26] MFHs most commonly present in the fifth and six decades of life. They have a 2:1 male-to-female predominance, with a tendency for earlier age of presentation in women than in men.[8] Previous history of exposure to ionizing radiation is strongly associated with the development of MFHs, and many cases involving the head and neck occur in the wake of previous radiation therapy for squamous cell carcinomas or lymphomas.[76,77]

Similar to many other head and neck sarcomas, the most common presentation of MFH is that of a painless swelling;[78] additional symptoms will be dependent on the specific area and anatomic structures involved. The most commonly involved subsites within the head and neck include the sinonasal tract, the upper aerodigestive system, and the parotid gland, with relatively equal distribution among these three areas.[79,80] Typically, MFHs will present in either a submucosal or subcutaneous location; however, the tumors can also arise centrally in bone as well.[26] Multifocal presentations have been reported, but this is extremely uncommon.[26,78] Approximately one third of cases will go on to develop distant metastases, most commonly involving the lungs, liver, and bone.[8]

Histologically MFHs are composed of spindle-shaped fibroblastic cells admixed with mononuclear histiocytic cells in a storiform pattern with interspersed multinucleated giant cells. A total of five different histologic variants have been identified: inflammatory, giant cell, myxoid, storiform-pleomorphic, and angiomatous.[8] The storiform-pleomorphic variant is the most common.[8] Histologic features of MFHs can closely resemble those of a multitude of other neoplastic processes, including anaplastic lymphomas, pleomorphic leiomyosarcomas, pleomorphic liposarcomas, malignant melanomas, anaplastic carcinomas, malignant peripheral nerve sheath tumors, malignant gliomas, and gliosarcomas.[8,81] Accordingly, thorough histologic review by pathologists experienced in the diagnosis of head and neck sarcomas is of paramount importance. Positivity for a number of immunohistochemical markers including vimentin, α1-antichyemotrypsin, and Ki-67 can also be useful if diagnosis is in question. Tumor immunonegativity for S-100 and cytokeratins can also facilitate distinction of MFHs from other types of neoplastic processes.[8] Historically, histiocytic markers such as CD68, α1-chymotrypsin, and factor XIII were previously used to identify MFHs; however, these markers have fallen out of favor, given the nonspecific nature of their immunoreactivity.[82]

Surgical resection with generous margins is the primary treatment modality for MFHs. Given the relative infrequency of regional metastasis, elective lymphadenectomy is generally not indicated.[8,26,83] Postoperative radiation is typically recommended for unresectable tumors and tumors with close or positive margins.[78,83] However, adjuvant radiation therapy has been shown in some series to impart superior local disease control regardless of margin status for MFHs of the head and neck, as well as other anatomic subsites.[84,85] Adjuvant chemotherapy in the treatment of MFH has typically been implemented in the setting of metastatic disease. Adjuvant chemotherapy trials for MFH have demonstrated significant improvement in local recurrence-free survival, distant recurrence-free survival, and overall recurrence-free interval; however, these trials have also failed to show a significant overall survival advantage.[86]

Overall 5-year survival rates for head and neck MFHs are reported to be approximately 40% in larger series; the reported 5-year survival rates range from 19% to 75%.[1,26,78] Local recurrence occurs in approximately 20% of patients, and most disease-related deaths are secondary to distant metastases, most commonly involving the lungs.[78] Positive



• **Figure 27-8** Fibrosarcoma left perimandibular region in the setting of previous radiation therapy for treatment of nasopharyngeal carcinoma. Coronal **(A)** and axial **(B)** computed tomography scans demonstrate a mass in the left perimandibular region with calcification and mandibular cortical destruction.

margin status, tumor size greater than 5 cm, tumors originating in bone, high histologic grade, and specific involvement of the head and neck are all prognostic factors adversely affecting outcome and survival.[78,87,88]

In summary, MFHs represent the most common variety of soft tissue sarcoma and are the most common sarcoma diagnosed within the head and neck region. They typically affect older adults and are strongly associated with prior exposure to head and neck radiation. Histologically, these tumors can resemble a number of other malignancies, and review by an experienced pathologist is critical. Immunohistochemistry can be a used as a diagnostic adjunct if the histologic diagnosis is in question. Treatment is surgical, with adjuvant radiation indicated for close or positive margin status. Elective neck dissection is typically unnecessary given the low propensity for regional metastasis.

Fibrosarcoma

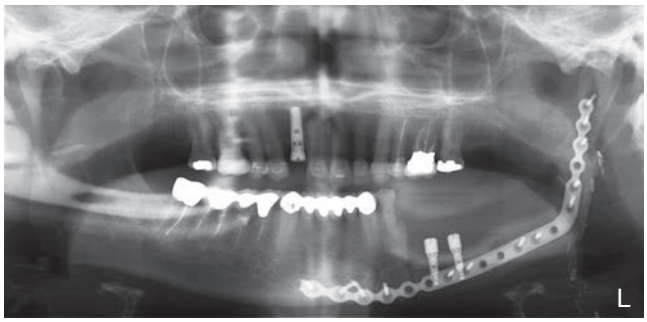
Fibrosarcomas represent a very common variant of soft tissue sarcoma; however, only 5% of fibrosarcomas occur within the head and neck region.[89] The majority of fibrosarcomas will occur in the fourth or fifth decade of life,[90,91] yet the tumors are also known to occur in young adults and children. Prior head and neck radiation exposure is a well-known risk factor for the development of fibrosarcomas, and approximately 10% of patients with fibrosarcomas of the head and neck will have this history (Figure 27-8).[81,90,91] Most reported series on head and neck fibrosarcoma also suggest a slight male predominance.[81,90,91]

The most common presenting symptom of fibrosarcomas is the presence of a painless expanding mass, as fibrosarcomas typically need to reach a relatively large size before inducing symptoms of pain. Fibrosarcomas most commonly occur on the face, scalp, or neck; however, cases have also been documented involving the nose and paranasal sinuses.[26,81,90,91] On CT imaging, fibrosarcomas typically appear as isodense tumors and are only mildly enhancing following contrast administration.[92] MRI imaging demonstrates low to intermediate signal intensity on all sequences and only mild to moderate enhancement with gadolinium contrast.[92]

Histologically, fibrosarcomas demonstrate fascicles of spindle-shaped cells that are classically arranged in a herringbone pattern.[92] The spindle cells typically exhibit scant cytoplasm and relatively homogenous size and shape, as well as prominent hyperchromatic nucleoli.[92] Mitotic figures are typically seen; however, they can be variable in number across specimens. Poorly differentiated tumors typically show less organized cellular architecture, and the fibroblastic cells can have a more round or ovoid appearance. Less differentiated tumors will also demonstrate less collagen production than well-differentiated tumors.

Treatment of fibrosarcomas involves wide surgical excision for tumors that demonstrate low-grade histology (Figure 27-9). Negative surgical margins are critical, as local recurrence is the primary mode of treatment failure and eventual death.[90] High-grade tumors, large tumors, or tumors with positive surgical margins are indicated for adjuvant chemotherapy or radiation therapy.[8,81,90] Neck dissection is indicated only in patients with clinically positive cervical lymph nodes, and elective treatment of the neck is not required on a routine basis.[91]

Prognosis for fibrosarcoma is relatively favorable when compared to other types of head sarcomas. Overall 5-year survival rates are reported to range from 62% to 82%



• **Figure 27-9** Composite resection and immediate reconstruction of left mandible for treatment of low-grade fibrosarcoma.

with 5-year disease-free survival rates ranging from 32% to 57%.[1,4,9,81,90,91] However, there is a high propensity for local recurrence, as this occurs in approximately 31% to 62% of patients.[26] Distant metastases are reported to occur in 12% to 21% of patients and most commonly involve the lungs.[81,90,91] Distant metastases have been reported to occur even after multiple decades,[89] highlighting the importance of long-term follow-up. Prognostic factors associated with improved outcomes include lesions with low-grade histology, tumors less than 5 cm in diameter, and negative surgical margin status.[9,81,89-91] High-grade tumors portend a poor prognosis irrespective of margin status, and multimodal therapy is typically recommended despite a lack of evidence for improved survival with multimodal strategies.[26,81]

In summary, fibrosarcomas are a relatively common subtype of soft tissue sarcoma that most frequently involves the extremities and are a very rare entity within the head and neck region. A history of head and neck radiation exposure is a well-documented risk factor for the development of fibrosarcomas. Treatment of low-grade, small fibrosarcomas is effectively carried out with wide surgical excision alone. Strong consideration for multimodal therapy involving surgery and postoperative adjuvant therapies should be given for high-grade lesions and large tumors. Generally, the prognosis for fibrosarcomas is favorable when compared to other types of head and neck sarcomas, yet local recurrence remains a significant problem.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans represents a rare low-grade cutaneous sarcoma that most commonly arises on the skin of the trunk and extremities.[93] Dermatofibrosarcoma protuberans constitutes less than 5% of all soft tissue sarcoma diagnoses and only 4% to 10% of all head and neck sarcomas.[1,4,15,90,91] The typical age of occurrence is in the early to mid-adult life, with a mean age of presentation of 31 years.[26,94] The tumors are known to occur in children, and congenital cases have also been described, yet these are exceedingly rare occurrences.[95,96] Men are more commonly affected; the male-to-female ratio is reported to be 7:3.[94,97]

Clinically, the tumors present as painless, raised, sclerotic plaques or nodules on the skin and typically possess a blanchable reddish-blue color.[26] The most commonly affected subsite within the head and neck is the scalp, with the face and neck combining as the next most common locations of tumor origination.[98-100] Dermatofibrosarcoma protuberans typically begin as a single plaque that will demonstrate a slow, locally infiltrative growth over a period of several years.[94,95] In more advanced stages, multiple satellite nodules can coalesce to form a larger protuberant mass, hence the name dermatofibrosarcoma *protuberans*.[11] Because of the slow-growing and indolent nature of the lesions, dermatofibrosarcoma protuberans can easily be misdiagnosed as keloids, basal cell carcinomas, or even scleroderma.[11] Dermatofibrosarcoma protuberans is known to occur most commonly in areas of healthy skin, but also has been reported to arise in areas of repeated trauma including vaccination sites, irradiated skin, and scars.[95] Ultrasonography of these lesions typically demonstrates hypoechoic or mixed echoic tumor with Doppler flow patterns involving either the entire tumor or just in the periphery of the lesion.[92] On CT, the tumors appear isodense to hypodense and can show moderate peripheral enhancement if concomitant central necrosis is present.[92] On MRI, the lesions will appear hypointense to isointense relative to adjacent muscle on T1-weighted imaging, whereas T2-weighted imaging generally demonstrates an isointense to hyperintense signal relative to muscle.[92]

Histologically, dermatofibrosarcoma protuberans typically occurs within the subcutaneous soft tissues, in a plane superficial to the superficial fascia of the skin. Origination deep to the superficial fascia is also reported, albeit much less commonly.[92] On hematoxylin and eosin staining, dermatofibrosarcoma protuberans appears as a conglomeration of monomorphic spindle cells arranged in a storiform pattern embedded in variable amounts of fibrous stroma. The spindle cells are typically monotonous, with bland tapered nuclei and sparse mitotic figures.[92] Immunopositivity for the otherwise nonspecific CD34 marker represents the most valuable diagnostic immunohistochemical finding; however, additional immunostaining for factor XIIIa may also be required to distinguish dermatofibrosarcoma protuberans from dermatofibromas.[101]

Treatment of dermatofibrosarcoma protuberans is ideally carried out with wide surgical resection with histologically negative margins, as these tumors have extremely high recurrence rates, but very low metastatic potential.[26,95] The adequacy of surgical resection remains the most important factor in patient outcome, as local recurrence rates are reported to be as high as 20% to 55%.[5,11,97-100] Obtaining negative margins at the time of surgery is often complicated by the multiple projections into the surrounding tissues that are characteristically present with dermatofibrosarcoma protuberans.[11,95,99] It has been reported that even obtaining 5-cm margins around the macroscopic tumor at the time of surgery can still leave residual disease in 5% of patients.[102] Accordingly, Mohs micrographic surgery is often recommended in order to ensure adequacy of resection margins while not simultaneously compromising functional or

esthetic outcomes with overzealous excision.[95,97,103] The use of adjuvant radiation therapy has been described and is typically reserved for recurrent lesions, positive margin status, or in cases where wider excision is not possible due to anatomic limitations.[104,105]

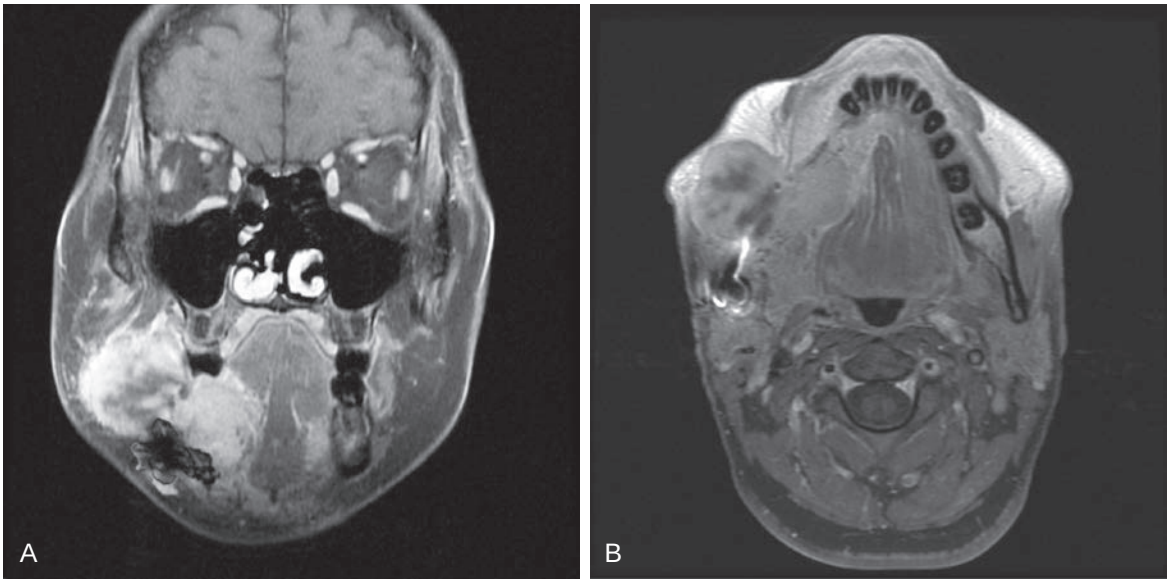
Prognosis for patients with dermatofibrosarcoma protuberans is quite good, particularly if truly negative margin status is achieved with the initial resection. Overall 5-year survival rates are reported to approach 100% with truly negative margins.[1,4,99] However, the head and neck represents a relatively common site for tumor recurrence relative to other sites within the body,[95] which possibly reflects a tendency of surgeons to obtain narrower margins given the anatomic constraints inherent to this area.

In summary, dermatofibrosarcoma protuberans represent rare low-grade malignancies that are uncommon within the head and neck region. Clinically, the tumors can resemble a number of other pathologic conditions, given their propensity for indolent but locally invasive growth. Treatment is via complete surgical excision with negative margins whenever possible, and the use of Mohs micrographic surgery holds specific utility for tumors involving the head and neck region. Complete surgical resection with truly negative margins portends an extremely favorable prognosis; however, these tumors have a very high potential for local recurrence with inadequate resection.

Rhabdomyosarcoma

Rhabdomyosarcomas (RMSs) are soft tissue sarcomas that most commonly affect children and adolescents, with only rare presentation in adult populations.[8] RMSs comprise approximately 4% to 8% of all pediatric cancer diagnoses, and they represent the most common type of sarcoma affecting children.[106-108] Collectively, rhabdomyosarcomas constitute up to one fourth of all head and neck sarcoma diagnoses,[1,4,9,84,106] and of these 90% will occur in children.[106,109] When considering all anatomic subsites within the body, approximately 40% of rhabdomyosarcomas occur within the head and neck (Figure 27-10).[106,109] Males and females appear to be equally affected, with some studies suggesting only very slight male predominance.[107-109] A limited number of epidemiologic studies suggest a higher incidence of pediatric RMS in patients exposed to radiation in utero,[110] in children from low socioeconomic status,[111] and in children of mothers using cocaine and marijuana during pregnancy.[27]

Accurate diagnosis of RMS necessitates both a thorough clinical and radiographic examination by the astute clinician; however, specific interrogation of the neck is also of paramount importance, as head and neck RMSs are well known to metastasize to the regional cervical lymph nodes.[107,112] Additional investigation for distant metastases is also indicated given the reported 9% to 23% of patients harboring distant disease at the time of diagnosis.[26,108,112] Of the relatively few cases diagnosed in adult patients, the most common anatomic subsite involved is the sinonasal tract.[107,108] In pediatric patients the orbit is most commonly involved, followed by the nasopharynx, paranasal sinuses, ear, oral cavity, neck, parotid gland, and facial soft tissues.[113] The constellation of presenting symptoms for head and neck RMS are variable and dependent on the anatomic subsite involved. However, the most commonly reported symptoms in children include nasal obstruction, rhinorrhea, recurrent otitis media, and orbital proptosis.[114]



• **Figure 27-10** Coronal **(A)** and axial T1-weighted magnetic resonance imaging **(B)** showing a large spindle cell rhabdomyosarcoma involving the right masticator space, buccal space, maxilla, mandible, and floor of the mouth.

Histologically, RMSs are categorized according to the ity, spindle cell morphology, stroma characteristics, growth patterns, and correlative immunohistochemical studies. The five currently recognized histologic subtypes of RMSs include embryonal, botryoid, spindle cell, alveolar, and undifferentiated. [115] The botryoid and spindle cell RMSs both represent less common variants of the embryonal subtype. Appropriate histologic classification of RMSs is of critical importance, as the various histologic subtypes are each associated with widely differing prognoses (Table 27-2). In pediatric patients younger than 10 years, embryonal subtype is the most commonly diagnosed RMS, whereas in patients older than 10 years, alveolar RMSs become the most common diagnosis.[8] However, embryonal RMSs represents the most common type of RMS presenting within the head and neck region overall.[26,107]

In children, head and neck RMSs are also classified based their site of origin: orbital, parameningeal, or non-parameningeal.[116] Parameningeal sites include the middle ear, nasal cavity, paranasal sinuses, nasopharynx, and infratemporal fossa. Non-parameningeal sites are defined as the scalp, parotid gland, oral cavity, oropharynx, hypopharynx, larynx, thyroid/parathyroid, and neck.[116] Because the anatomic site of origin correlates with prognosis, the three head and neck origin sites are also incorporated into a pretreatment tumor-node-metastasis (TNM) staging for RMSs (Table 27-3).[116,117] The IRSG also uses surgicopathologic criteria in pediatric patients (local extension, regional metastasis, distant metastases, amount of residual tumor tailor therapy options based on the severity of a patient's specific disease burden as well as their relative prognosis following the initial surgical resection. The work of the IRSG ter assessment of long-term comparisons between treatment various regimens.[8,26] Accordingly, dramatic advancements have been made in the treatment of pediatric RMSs, which have subsequently led to improvement in survival rates from roughly 25% in the early 1970s to 71% in 2001.[8,113]

Treatment of all RMSs is based on the principle of "risk-adapted therapy," which takes into account the various staging and prognostic classification schemes delineated by the IRSG in order to appropriately target therapy to the specific disease severity. Complete surgical resection remains the cornerstone of therapy for most patients; however, complete resection of head and neck RMSs can be precluded by unacceptable functional or cosmetic outcomes and involvement of vital anatomic structures.[26] Accordingly, a multimodal approach involving radiation therapy

TABLE 27-2 Prognosis of Rhabdomyosarcomas Based on Histologic Subtype

Superior Prognosis

Botryoid rhabdomyosarcoma
Spindle cell rhabdomyosarcoma

Intermediate Prognosis

Embryonal rhabdomyosarcoma

Poor Prognosis

Alveolar rhabdomyosarcoma
Undifferentiated sarcoma

TABLE 27-3 Tumor-Node-Metastasis (TNM) Staging for Rhabdomyosarcomas

Stage	Site	Tumor Size	Nodal Involvement	Presence of Metastases
I	Orbit Head and Neck Genitourinary (non-bladder, non-prostate)	<5 cm or >5 cm	N0, N1, NX	M0
II	Bladder/prostate Extremity, trunk Parameningeal Other	<5 cm	N0, NX	M0
III	Bladder/prostate Extremity, trunk Parameningeal Other	>5 cm	N1, N0, NX	M0
IV	All sites	<5 cm or >5 cm	Any N	M1

N0, no regional nodal metastases; N1, regional nodal metastases; NX, unknown nodal status; M0, no distant metastases; M1, distant metastases

TABLE 27-4

Localized disease, completely removed
a. Confined to muscle or organ of origin
b. Infiltration outside of organ or muscle of origin; regional nodes not involved

Total gross resection with evidence of regional spread
a. Grossly resected tumor with microscopic residual disease
b. Regional disease with involved nodes, completely resected with no microscopic residual disease
c. Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual and/or histologic involvement of the most distal regional node in the dissection

Incomplete resection, or biopsy with presence of gross disease

Distant metastasis

and multi-agent chemotherapy is often implemented for RMSs involving head and neck subsites (Figure 27-11). A multitude of chemotherapeutics are currently used to treat RMSs, including vincristine, dactinomycin, doxorubicin, ifosfamide, etoposide, cyclophosphamide, actinomycin-D, topotecan, irinotecan, cixutumumab, and temozolomide.[8] The specific type of multimodal management differs based on site of origin for head and neck RMSs. Orbital RMSs are unique in that surgical resection does not confer any survival benefit over radiation and chemotherapy.[118] Accordingly, combined chemo-radiation therapy is the preferred modality given the significant morbidity caused by loss of an eye, and orbital exenteration is generally reserved for cases of recurrent disease.[117] Parameningeal RMSs are also generally less amenable to surgical resection given a greater likelihood of incomplete resection, significant risk to major cranial nerves, and greater disfigurement of the facial skeleton.[119] Consequently, limited surgical resection coupled with combined radiation and chemotherapy confers the least amount of morbidity while still maintaining adequate survival rates.[119] Treatment of non-parameningeal RMSs involves surgical resection and chemotherapy (typically vincristine and dactinomycin, with or without cyclophosphamide), with or without radiation therapy.[120] With this regimen more than 80% of patients with parameningeal RMSs are expected to be cured of their disease, and elective cervical lymph node dissection is generally unnecessary.[120] Surgery is often also useful as a "second-look" procedure wherein patients deemed to be

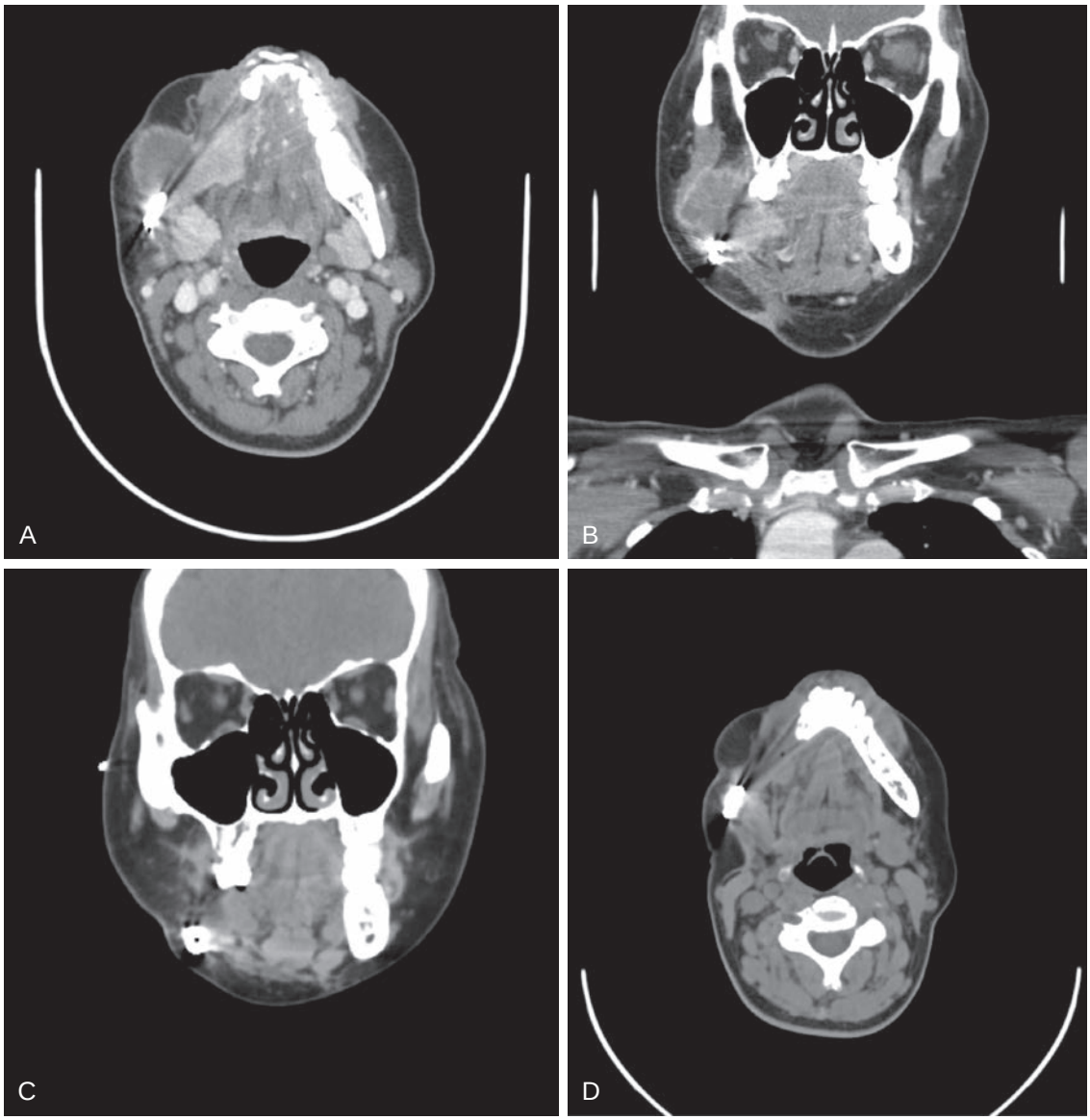
the past 5 decades. The 5-year survival rates for parameningeal head and neck RMSs are reported to be 50% to 70%, whereas 5-year survival rates for non-parameningeal sites are reported to be 70% to 80%.[121] This is to be taken in distinction to the pre-1970s 5-year survival rates for head and neck RMS of 25%.[121] The 5-year overall survival rates for pediatric RMSs at all sites are currently 89%, 86%, 69%, and 30% for stage I, II, III, and IV tumors respectively.[7,26] Because of the rarity of RMSs in adults, survival data for non-pediatric RMS are limited. However, outcomes for adult RMSs are reported to be much poorer, with 5-year survival rates reaching only 30%.[8,26] A number of prognostic factors have been identified to correlate with a worse prognosis for head and neck RMSs, including older age at diagnosis, local invasiveness, presence of metastases at diagnosis, regional nodal involvement, unresectability, tumor size, tumor grade, and alveolar histologic subtype.[106,108,109,122,123]

In summary, RMSs represent the most common type of sarcoma presenting in pediatric populations and constitute approximately 25% of all head and neck sarcoma diagnoses. Five distinct histologic subtypes are currently recognized, and each subtype is associated with a different prognosis. Staging and tailoring treatment regimens. Multimodal therapy involving combinations of surgery, radiation, and chemotherapy has produced significant survival improvements for pediatric RMSs over the past 50 years due to intense research and clinical protocols designed to optimize treatment strategies. Nevertheless, adult patients and some subsets of pediatric patients still suffer from exceedingly abysmal prognoses in spite of the recent advancements.

Leiomyosarcoma

Leiomyosarcomas are rare soft tissue sarcomas that are believed to originate from either smooth muscle cells or pluripotent undifferentiated mesenchymal stem cells.[124] Leiomyosarcomas most commonly arise in the uterus, digestive tract, and retroperitoneal fossa. Leiomyosarcomas of the head and neck are exceedingly rare, with around 100 cases reported within the literature.[125] Leiomyosarcomas also represent the least common type of soft tissue sarcoma originating in the head and neck region, as they accounting for only 5% of all head and neck sarcoma diagnoses.[1,4,9,84] Patients with head and neck leiomyosarcoma most commonly present within the fifth to sixth decade of life, and no gender predilection has been reported.[9]

Diagnosis of head and neck leiomyosarcoma does not differ significantly from the diagnosis of other types of head and neck sarcomas, as appropriate clinical and radiographic examinations are requisite before obtaining a definitive tissue diagnosis. However, additional imaging investigations



• **Figure 27-11** Axial **(A)** and coronal **(B)** computed tomography (CT) scans demonstrating the presence of a spindle cell rhabdomyosarcoma with associated increased surgical morbidity in order to obtain negative surgical margins. Good treatment response to multimodal treatment consisting of radiation therapy and four cycles of ifosfamide and doxorubicin as demonstrated in coronal **(C)** and axial **(D)** CT scans.

including chest films or CT, abdominal ultrasound, abdominal CT, or radioisotope bone scans may also be warranted given the possibility of a secondary head and neck leiomyosarcoma arising from a metastatic gastrointestinal or genitourinary primary.[126] The most common site of presentation for primary head and neck leiomyosarcomas is the neck, which constitutes approximately 30% to 50% of all tumors presenting within this region.[4,84] Other commonly reported head and neck subsites include the oral cavity, scalp, and jaws.[127] Involvement of the sinonasal tract parapharyngeal spaces is much less common, although a limited number of cases have been reported.[127-129]

Histologic examination of leiomyosarcomas reveals fascicles of spindle-shaped cells with abundant eosinophilic fibrillary cytoplasm. Nuclei are often oval to elongated (cigar-shaped) and can appear hyperchromatic with varying degrees of atypia and pleomorphism.[126] Mitotic figures will typically be scattered throughout multiple fields and can vary in number from infrequent to abundant.[126] Immunohistochemical analysis typically shows positivity for one or more of the following markers: desmin, muscle-specific actin, smooth muscle myosin, vimentin, and smooth muscle actin.[126,129]

Treatment of leiomyosarcomas is best accomplished with complete surgical excision with negative margins when possible. The success of the initial surgical management is of paramount importance, as this has been found to be a notable prognostic factor in terms of outcome and likelihood of

local recurrence.[124,126,130] Adjuvant radiation and chemotherapy are employed in the treatment of leiomyosarcomas; however, they are generally reserved for cases of residual disease following surgery, for inoperable tumors, or for palliative treatment.[128] Elective neck dissection is unnecessary given the extremely low propensity for regional nodal metastases. Local recurrence is known to occur in approximately 45% of cases and likely represents an underlying inadequacy of the initial surgical treatment.[124,130] Distant metastases are also common and are reported to occur in approximately 17% to 35% of patients.[26]

Prognosis for head and neck leiomyosarcomas is variable, owing to the relative rarity of this sarcoma subtype within the head and neck region. Overall survival rates for tumors involving the oral cavity and sinonasal tract are reported to range from 32% to 43%,[124,130] whereas larger scale series report survival rates as high as 70%.[9,84] Prognostic factors that are likely to correlate with worse outcomes include high histologic grade,[9] local tumor extension,[128] residual disease following surgical resection,[26] and posterior anatomic locations (infratemporal fossa, pterygoid plates, mandibular condyle).[126]

In summary, leiomyosarcomas are exceedingly uncommon tumors within the head and neck and account for only 5% of all head and neck sarcoma diagnoses overall. Diagnostic evaluation of head and neck leiomyosarcomas should also include evaluation of the gastrointestinal and genitourinary systems, given the possibility for metastatic disease presenting within the head and neck. Treatment of leiomyosarcomas is optimally carried out via complete surgical excision, as residual disease predisposes to recurrence and is correlated with poorer overall survival.

Angiosarcoma

Angiosarcomas are extremely rare malignant endothelial cell tumors of lymphatic or vascular origin.[8] Collectively angiosarcomas represent less than 1% of all soft tissue sarcoma diagnoses; however, they make up approximately 15% of sarcoma diagnoses within the head and neck region.[1,4,131] Approximately 50% of all angiosarcomas will occur within the head and neck when all anatomic locations are considered.[132-135] The typical age of onset is after the fifth decade of life, and individuals younger than 50 years of age are rarely affected.[132,133,136,137] Caucasians are much more commonly affected than African Americans, and there is a 2:1 male to female predominance.[8,133,134] Several environmental and genetic risk factors have been implicated in the development of head and neck angiosarcomas, including previous history of head and neck radiation, chronic lymphedema, Milroy syndrome, vinyl chloride, arsenic, anabolic steroids, BRCA1 mutation, BRCA2 mutation, neurofibromatosis type I, Maffucci syndrome, and Klippel-Trénaunay syndrome.[138]

Clinically, most angiosarcomas will present as violaceous bruise-like macules and plaques, and correct diagnosis is often delayed because of their mimicry of other dermatologic conditions. Typically, the tumor will be present for a number of months before more ominous symptoms of bleeding, ulceration, and pain occur.[132,133] Additionally, some angiosarcomas lack the characteristic vascular appearance and assume a more nodular form that lead to misdiagnosis as folliculitis, benign vascular formations, malignant melanoma, Merkel cell carcinoma, or basal cell carcinoma.[26] The most common locations for head and neck angiosarcomas are the face and scalp,[8,26] and coupled with its predilection for Caucasian individuals, this has led some to suggest a potential etiologic correlation with sun exposure—although this has never been clearly demonstrated within the literature. At the time of diagnosis, approximately one third of patients will present with multifocal head and neck lesions; however, only 10% of patients will exhibit regional cervical metastases.[26] The presence of distant metastases at the time of diagnosis occurs in approximately 20% to 45% of patients, and the most commonly involved site is the lungs.[8,132,133,135,137] Tissue diagnosis is most appropriately obtained through the use of incisional biopsy, given the most typical location of the lesion on the skin of the face and scalp. Excisional biopsies are generally not preferred, as an inadequate initial excision could lead to disruption of the macroscopic tumor margins and would eventually complicate a future and more definitive surgical resection.[6,30]

Histologically, angiosarcomas are composed of an infil-

demonstrate varying levels of atypia. Neoplastic cellular proliferation into the lumina of the vascular spaces is also characteristic.[26] Immunopositivity for CD31, CD34, factor VIII, and von Willebrand factor is noted in up to 60% to 80% of cases and can help to facilitate appropriate histologic diagnosis.[132,139]

The optimal treatment of head and neck angiosarcomas has not yet been clearly delineated owing to the relative rarity of the neoplasm and its universally dismal prognosis.[26] Because of the propensity for these neoplasms to exhibit rapid subcutaneous spread over large areas, the ability to achieve negative margin status is dramatically impaired and local recurrence is an almost universal clinical hallmark of the disease.[134,137] Even with the use of fresh frozen–section analysis at the time of the initial surgery, obtaining truly negative margins remains unlikely. This is exemplified by the finding that negative margin status was not correlated with overall patient survival in several studies.[140,141] Accordingly, adjuvant wide-field radiation therapy has been used with increasing frequency, and it has been shown to improve both survival rates and local disease control when administered in combination with chemotherapy.[8,132,133,137] Some investigators have also suggested that definitive radiation therapy without surgical resection plus or minus chemotherapy may even offer adequate primary local disease control.[133,142-144]

Prognosis for patients affected by angiosarcomas of the head and neck remains exceedingly poor, as 5-year survival

rates range from only 12% to 33% overall.[133,134,137] Complete resection of all macroscopic disease before initiation of adjuvant radiation therapy has been associated with improved rates of local disease control,[144] and lesions less than 10 cm in diameter have also been associated with a more favorable prognosis.[133,134] Interestingly, the histologic grade of angiosarcomas has never been shown to correlate with survival, which is an atypical characteristic relative to virtually all other types of head and neck sarcomas.[26] Overall, angiosarcomas behave like aggressive high-grade malignancies and typically cause death via distant metastases.[26,132-134,144]

In conclusion, angiosarcomas are extremely rare sarcomas that are uncommon overall, but have a high propensity for presenting within the head and neck when they do occur. Angiosarcomas most commonly affect older Caucasian males and are associated with a number of genetic and environmental risk factors. Appropriate clinical diagnosis can be delayed by relatively innocuous clinical appearance of the lesions, and they can be easily confused with a number of other dermatologic conditions. Optimal treatment regimens for angiosarcomas have yet to be established; however, most recent evidence suggests utility in combination multimodal therapy involving surgery, radiation, and chemotherapy. Unfortunately, even attaining negative margin status at the time of surgery does not affect survival, and patients have an almost universally dismal prognosis overall.

Hemangiopericytoma

Hemangiopericytomas represent rare vascular sarcomas that originate from the pericytes of Zimmermann, which are cells that encircle capillary endothelium and function as baroreceptors within the capillary walls.[145] Literature on this rare neoplasm is scant and is predominantly made up of case reports and small case series.[146] The majority of hemangiopericytomas originate in the pelvis, retroperitoneum, and lower extremities; however, approximately 25% present within the head and neck.[145] Hemangiopericytomas can present over a wide age range, and the peak incidence occurs between the third and fifth decades of life.[145] No gender predilection has been observed based on reported cases, and no etiologic risk factors have been identified.[26,146]

The most common clinical presentation of hemangiopericytomas is that of a soft, slow-growing, painless mass.[147,148] Accordingly, these tumors can easily be mistaken for lipomas or other benign neoplasms, leading to a delay in proper diagnosis.[147,148] However, despite being described as an indolent tumor, local invasion with destruction of adjacent anatomic structures and metastatic spread are also common features of this sarcoma.[149] The most frequently involved head and neck subsite is the sinonasal tract,[145-147] and tumors in this region can produce various symptoms including nasal obstruction, epistaxis, pain, headache, and visual disturbance.[145,146] CT imaging of hemangiopericytomas typically reveals a noncalcified soft tissue mass displacing adjacent structures and occasionally eroding bone. Contrast-enhanced CT imaging will typically highlight the vascular nature of these lesions,[145] and angiography can be used for large tumors in order to delineate the anatomy of the vascular supply.[146] Preoperative arterial embolization can also be used to help minimize blood loss prior to the primary surgical resection.[146]

Histologically, hemangiopericytomas are typically well-acteristic "staghorn" or "antler-like" appearance.

Treatment of hemangiopericytoma is ideally carried out through complete surgical resection with negative margins. Local recurrence as well as distant metastasis is reported to occur frequently after surgical resection; however, head and neck hemangiopericytomas have less propensity for distant spread than do tumors originating in other anatomic regions.[147] Long-term follow-up of patients is required, as the mean time to recurrence is 46 months following initial treatment, and recurrence has been reported to occur up to 17 years following primary management.[146] Elective cervical lymphadenectomy is unnecessary, as regional lymph node involvement has not been observed.[145] The use of adjuvant radiation and chemotherapy remains largely untested.[26] However, patients undergoing adjuvant radiation therapy following incomplete surgical resection have demonstrated a non-statistically significant increase in disease-free survival and a statistically significant decrease in rate of recurrence in a limited number series.[146] The use of radiotherapy alone as the primary treatment modality has been shown to correlate with higher rates of recurrence as well as tumor-related death.[146]

Accurately establishing prognosis for head and neck hemangiopericytomas is hindered by the limited number of cases available within the literature, as well as by a relative lack of adequate observational follow-up—although 10-year survival rates have been reported to reach as high as 70%.[145,146] When all anatomic subsites are considered, the overall survival rates for hemangiopericytomas range from 40% to 76%.[84,145-147,149] However, local recurrence rates for head and neck hemangiopericytomas are reported to reach as high as 40%, and metastatic disease develops in 15% of cases—typically involving the lungs, liver, and bone.[145] A number of negative prognostic factors affecting survival have been identified, including presence of tumor necrosis, high histologic grade, more than four mitotic figures per high-power field, and tumor size greater than 6.5 cm.[146]

In summary, hemangiopericytomas represent extremely rare vascular sarcomas that most commonly involve the sinonasal tract within the head and neck. They are locally aggressive and typically have a high rate of local recurrence, particularly in cases of incomplete surgical resection. Treatment is predominantly surgical, although there is some early

evidence that adjuvant radiation therapy can delay time to recurrence in cases of residual disease after resection. Accurate assessment of prognosis for head and neck hemangiopericytomas is severely limited by the neoplasm's propensity for delayed recurrence and inadequate durations of follow-up for many of the reported cases within the literature.

Neurogenic Sarcoma

Neurogenic sarcomas are rare soft tissue sarcomas that are known by a multitude of different names including neurofibrosarcomas, malignant neurofibromas, malignant peripheral nerve sheath tumors, malignant neurilemmomas, and malignant schwannomas.[150-152] Neurogenic sarcomas make up roughly 5% to 10% of all soft tissue sarcoma diagnoses;[153] however, up to 20% of these tumors will present within the head and neck.[154] Considering only head and neck subsites, neurogenic sarcomas represent 5% to 15% of all sarcomas diagnosed within this region.[4,6,9,15,84,131] Neurogenic sarcomas predominantly affect adults and occur over a wide age range (fourth to sixth decades of life) with a roughly equal sex predilection.[150,151,154,155] They are known to occur de novo, from a preexisting neurofibroma, or more rarely, they can also arise from a preexisting schwannoma.[155] Neurogenic sarcomas also possess an extremely strong association with neurofibromatosis type I (NF1), as well as a weaker association with neurofibromatosis type II (NF2).[152,154] Patients affected by NF1 have an approximately 4600 times greater risk of developing neurogenic sarcomas relative to individuals of the general population, and approximately 50% of all neurogenic sarcomas occur in patients with NF1.[154] Furthermore, approximately 10% of neurogenic sarcomas are also associated with previous history of radiation exposure, either therapeutic or environmental.[155]

The most common clinical presentation of neurogenic sarcomas is that of a painless enlarging neck mass, although a neuropathy within the distribution of the nerve of origin is also a common presenting symptom.[150] Neurogenic sarcomas are highly aggressive and are known to grow rapidly along nerves with infiltration of surrounding tissues.[153] MRI is most commonly used to delineate the extensiveness of these tumors, and concomitant CT imaging is also useful to assess for any evidence of osseous invasion.[153,156] Imaging findings commonly reported for neurogenic sarcomas include heterogeneous contrast enhancement, contour irregularity, and evidence of tumor necrosis.[152,153,156] Unfortunately, the aforementioned imaging findings are not specific enough to allow neurogenic sarcomas to be distinguished from other types of benign or malignant nerve sheath tumors; ultimate diagnosis requires analysis of a tissue specimen.[153,156]

Histologically, the specific "cell of origin" for neurogenic sarcomas has yet to be definitively established, although it is postulated that these tumors may arise from neural crest cells.[155] The accurate diagnosis of neurogenic sarcomas is also significantly impeded by the absence of specific morphologic, immunohistochemical, and molecular criteria for these lesions.[155] Typical histologic features include fascicles of atypical spindle-shaped cells in a palisading arrangement, nuclear atypia, bizarre giant cells, mitotic figures, and necrosis.[156] However, the histologic patterns seen within neurogenic sarcomas can also closely resemble findings seen within other spindle cell neoplasms such as malignant fibrous histiocytoma, fibrosarcoma, leiomyosarcoma, angiosarcoma, and even malignant melanoma.[150,155,156] Immunohistochemically, there are no diagnostic markers specific to neurogenic sarcomas, as S-100, CD34, TLE1, nestin, Sox10, and HMGA2 all exhibit variable expression by these tumors.[155] Accordingly, accurate diagnosis requires good correlation with clinical history, presence of NF1/NF2 diagnoses, and exclusion of similar neoplasms by a combination of immunohistochemistry and molecular genetic analysis.[155] Histologic identification of a nerve trunk or evidence of a preexisting neurofibroma or schwannoma from which the tumor originates can also facilitate the diagnosis.[150]

Treatment of neurogenic sarcomas involves wide local excision; however, the resectability of the tumor can be limited by the neuroanatomic extension of the lesion.[91,150,151] Every attempt should be made to obtain negative margins at both the proximal and distal extension of the originating nerve, as positive margin status correlates with poor outcomes.[151,154] Resection of adjacent anatomic structures may also be required, given the lack of true capsules surrounding these tumors and their propensity for local tissue invasion.[157] Elective neck dissection is unnecessary, given the rarity of regional nodal involvement seen with neurogenic sarcomas.[150,151,154,157] The role of adjuvant therapies has been widely reported within the literature because of the neurogenic sarcoma's propensity for local recurrence;[150,151] however, the utility of adjuvant therapies remains unclear given the tumor's limited sensitivity to both radiation and chemotherapy.[155]

The prognosis for neurogenic sarcomas is relatively poor, with overall 5-year survival rates reported to range from 47% to 61% and 10-year survival rates ranging from 35% to 24%.[9,131,157] Approximately 40% of patients will develop local recurrence, and one third of patients will go on to develop distant metastases, most commonly to the lungs and bone.[150,151,155] Factors associated with poor prognosis include tumors larger than 5 cm, positive surgical margins at the time of resection, higher histologic grade, mitotic index greater than 6/10 per high-power field, and tumors associated with NF1.[9,154,155,157]

In summary, neurogenic sarcomas represent rare soft tissue sarcomas within the head and neck region. They possess a strong association with the presence of NF1 and are also weakly associated with both NF2 and a previous history of ionizing radiation exposure. They are highly aggressive neoplasms with a propensity for both local recurrence and distant metastases. Accurate diagnosis is challenging due to the histologic features shared by a number of other neoplastic processes and a relative lack of distinguishing immunohistochemical markers. Treatment is predominantly via surgical resection with full attempt at obtaining negative

margins. The role of adjuvant therapies remains controversial, although they are recommended by numerous authors. Prognosis remains relatively poor overall owing to the propensity for local recurrence and metastatic spread.

Liposarcoma

Liposarcomas represent a relatively common type of soft tissue sarcoma and account for approximately 35% to 45% of all soft tissue sarcoma diagnoses.[158] Most liposarcomas originate in the lower extremities or retroperitoneum.[15,159] Liposarcomas of the head and neck are exceedingly rare, with only 2% of liposarcomas presenting in this region.[8] Liposarcomas most commonly present in adults in the fifth to sixth decades of life with a median age at diagnosis of 51 years.[158,160] Males are more commonly affected, with a 5:3 male-to-female ratio.[160] Known etiologic risk factors for liposarcoma include neurofibromatosis type I (NF1), history of soft tissue trauma, and previous history of radiation exposure.[8]

Diagnosis of head and neck liposarcoma does not differ significantly from diagnosis of other types of sarcomas originating within the head and neck region. The upper aerodigestive tract (oral cavity, oropharynx, hypopharynx, and larynx) is the most commonly involved head and neck subsite, representing approximately 50% of liposarcoma cases.[160-164] The upper aerodigestive tract is followed closely by the neck, which is responsible for approximately one third of the remaining head and neck liposarcoma cases.[160-164] Presenting symptoms will depend on the specific anatomic area involved but can include dysphagia, dyspnea, airway obstruction, and hoarseness, given the common involvement of the upper aerodigestive tract. As is the case for numerous other types of head and neck sarcomas, the most commonly reported presenting symptom is that of a painless expansile mass.[158]

Histologically, liposarcomas are characterized by vacuolated lipoblasts with pleomorphic nuclei and varying levels of hyperchromatic stroma. Four distinct histologic variants have been described: well-differentiated, myxoid, pleomorphic, and round cell.[165] Liposarcomas are also categorized into low-grade and high-grade tumors depending on the specific histologic variant seen. Well-differentiated and myxoid variants are classically low-grade lesions, whereas pleomorphic and round cell variants represent high-grade tumors.[165] Appropriate histologic classification is important in the management of liposarcomas, as the histologic grade of the lesion predicts tumor behavior and also affects the overall prognosis.[8,158,160,161]

Treatment of liposarcomas involves complete surgical resection of the tumor whenever possible, as local recurrence represents the main pattern of treatment failure.[26] Regional metastases are exceedingly rare, and therefore elective management of the neck is typically not indicated.[163] Adjuvant radiation therapy has been shown to reduce rates of local recurrence; however, it does not seem to affect overall survival.[8] Nevertheless, adjuvant radiation therapy is often recommended for close or positive margins or in patients with unfavorable histologic variants (pleomorphic or round cell subtypes).[163]

Prognosis for head and neck liposarcomas remains variable depending on histologic grade. The overall 5-year survival rate for patients with well-differentiated liposarcomas is reported to be 100%, whereas survival rates for the myxoid variant are reported to range from 60% to 73%.[158,160,166] Patients with the pleomorphic variant can expect 5-year survival rates of 42%, whereas the round cell variant possess the most dismal prognosis with expected 5-year survival rates of 0%.[160] Histologic grade also portends the likelihood of experiencing distant metastases, as well-differentiated variants virtually never metastasize and the myxoid variant is known to occasionally spread to nonpulmonary sites.[26] Pleomorphic and round cell variants also demonstrate a propensity for distant metastases; however, these variants most commonly involve the lungs.[160,161] It has been reported that tumors involving the oral cavity, pharynx, and neck appear to have a worse prognosis than lesions involving the scalp and face;[160] however, more recent series have reported contradictory findings.[158] Interestingly, tumor size does not appear to affect survival for head and neck liposarcomas.[160,161]

In summary, liposarcomas represent one of the most common forms of soft tissue sarcoma; however, it is exceedingly uncommon for them to present within the head and neck region. They most commonly affect older males, and the most common site of involvement within the head and neck is the upper aerodigestive tract. Appropriate histologic diagnosis and accurate assessment of histologic grade are of paramount importance, as this not only predicts prognosis, but also can aid in identifying patients who require more aggressive forms of treatment. Complete surgical resection remains the gold standard treatment for all histologic variants of liposarcomas, and adjuvant radiation therapy is typically indicated in cases of high-grade neoplasms or when clear surgical margins are not obtained. Long-term follow-up with appropriate serial imaging studies is indicated based on the histologic variant of the resected tumor and the respective propensity for distant metastases.

Synovial Sarcoma

Synovial sarcoma is a relatively common soft tissue sarcoma that represents approximately 10% of all soft tissue sarcoma diagnoses.[167] However, head and neck synovial sarcoma is extremely rare, with less than 6% of all reported cases occurring within the head and neck region.[168,169] Furthermore, synovial sarcomas make up only 3% to 5% of all head and neck sarcoma diagnoses.[170] The majority of synovial sarcomas occur in the lower extremities, which account for approximately 70% of all cases.[170] Although para-articular locations for synovial sarcomas are common, these tumors rarely involve or originate from a true synovial structure.[170,171] Rather, their true cellular origin is believed to be from pluripotent mesenchymal cells, and their name is

actually derived from the tumor's histologic resemblance to normal synovial membrane.[170-172] Head and neck synovial sarcomas have a median age at diagnosis of approximately 32 years; however, they have been reported to occur over an exceedingly wide range of ages (4 to 76 years).[169] There is a slight male predominance based on the roughly 100 cases of head and neck synovial sarcoma reported within the literature.[169,173]

Diagnosis of synovial sarcoma can be challenging, as the tumors can occasionally be slow growing, have variable size presentation, and can also appear benign on imaging studies.[169] Accordingly, synovial sarcomas have been reported to be one of the most commonly misdiagnosed soft tissue malignancies.[169] Over 90% of synovial sarcomas contain a specific balanced translocation between the X chromosome and chromosome 18, t(x;18)(p11.2;q11.2), and identification of this translocation can greatly facilitate the appropriate diagnosis.[171] The most commonly involved head and neck subsites for synovial sarcomas include the hypopharynx and parapharyngeal spaces; however, they have also been reported to occur in the tonsils, tongue, and orofacial soft tissues.[167] The most commonly reported presenting symptom is that of a painless slow-growing expansile mass;[171,173] however, additional symptoms, including pain, dysphagia, dyspnea, paresthesias, limited mandibular opening, and migraine headaches, have also been reported.[169,170]

Histologically, synovial sarcomas are composed of two morphologically distinct, but histogenetically related cell types: epithelioid cells and spindle cells.[169,172] A biphasic form is noted when both cell types are present histologically; however, monophasic forms composed of only one of the two cell types can also occur.[169,172] Depending on the predominance of the two cell types and the degree of differentiation, synovial sarcomas form a continuous spectrum of histologic variants including biphasic, monophasic fibrous, monophasic epithelial, and poorly differentiated (round cell).[169] The biphasic form is most readily diagnosed; however, the monophasic forms represent a greater diagnostic challenge, and immunohistochemical analysis is often required to distinguish monophasic synovial sarcomas from other types of spindle-cell neoplasms.[167] Immunopositivity for vimentin, cytokeratin, and EMA is rarely identified in other neoplasms, and with combined positivity for CD99 and Bc12, a definitive diagnosis of monophasic synovial sarcoma can be rendered.[167] Nevertheless, it is also recommended to corroborate diagnosis with negative immunostaining for S-100 and SMA to rule out neurogenic or smooth-muscle derived sarcomas.[167]

Treatment of synovial sarcomas is primarily based on wide surgical resection in an attempt to achieve negative margins.[167,172,173] Given the rarity of regional nodal metastasis, elective management of the neck is not indicated on a routine basis.[167] Numerous reports also suggest the utility of postoperative radiation and chemotherapy; however, given the relative rarity of head and neck synovial sarcoma, optimal management protocols have yet to be established.[169,171-173] Some evidence exists that postoperative adjuvant radiation therapy may have a positive impact on both local control and overall survival rates; however, future longitudinal prospective investigations will be required in order to fully validate these results.[169]

Prognosis for synovial sarcomas is not well delineated owing to the relative rarity of this tumor within the head and neck region. Reported 5-year survival rates vary widely depending on the study and range from 36% to 81%.[169,172,173] Head and neck synovial sarcomas are well known to exhibit very high rates of distant metastatic spread, most commonly involving the lungs, and this represents the leading cause of death for this sarcoma.[172,173] Prognostic factors that have been reported to correlate with unfavorable outcomes include tumor size larger than 5 cm, positive margins, non-calcifying tumors, and monophasic variants.[169,173-175]

In summary, synovial sarcomas are common soft tissue sarcomas that rarely present within the head and neck region. Their histogenetic origin remains unclear, although it is proposed that they derive from pluripotent mesenchymal cells. They commonly arise from para-articular regions within the extremities; however, they do not originate from true synovium and can be found in complete isolation from synovial structures. Histologic diagnosis is greatly aided by the use of immunohistochemistry, particularly in the case of monophasic tumors. Optimal treatment strategies have yet to be developed; however, wide surgical resection followed by adjuvant radiation therapy has been suggested to improve local recurrence rates and possibly survival.

Ewing Sarcoma

Ewing sarcomas represent the second most common primary malignant bone cancer in children and adults (following osteosarcoma), and these sarcomas account for roughly 10% of all malignant osseous tumors.[176,177] Ewing sarcomas most commonly arise in the pelvis or long bones of the lower extremities, and involvement of the head and neck is exceedingly rare.[176,178,179] In fact, Ewing sarcomas of the head and neck represent only 1% to 4% of all reported cases.[176,179] Ewing sarcomas most commonly affect children and young adults, with the peak incidence occurring during the teenage years.[176-180] No gender predilection has been observed based on reported cases.[177,178,180]

The most common presenting symptom for patients with head and neck Ewing sarcoma is that of a rapidly growing expansile mass.[177,179-181] Associated symptomatology depends on the anatomic area of involvement; however, pain, paresthesias, and visual disturbances have all been reported as common complaints.[176,181] The most commonly involved head and neck subsites are the maxilla and mandible, followed closely by the skull.[177,179,181] A number of other areas, including the orbit, scalp, sinonasal tract, paravertebral areas, and neck have all been reported as less common sites of origination.[177,178,180]

Histologically, Ewing sarcomas are composed of small, round hyperchromatic cells with scant cytoplasm, well-delineated uniform nuclei, and indistinct cellular borders.[181] The tumor cells are often arranged in broad sheets with fibrovascular septa separating the tumor into lobular domains. Analogous to synovial sarcomas, the exact histogenesis of Ewing sarcomas remains unclear, yet there is increasing evidence to support a neuroectodermal origin.[176,179-181] Over 90% of Ewing sarcomas share a chromosomal translocation commonly found in primitive neuroectodermal tumors, (t:12;22)(q;24:12), and identification of this translocation greatly facilitates diagnosis in cases with equivocal histology.[181] Immunohistochemical analysis revealing positivity for FLI1 and CD99 can also be used to confirm the diagnosis of Ewing sarcoma.[181]

Treatment of head and neck Ewing sarcomas is greatly aided by the well-known chemo- and radiosensitivity of these tumors.[179] However, reports describing outcomes for head and neck Ewing sarcomas are limited given the relative rarity of tumors within this region, and many management decisions are extrapolated from investigations evaluating Ewing sarcomas of the appendicular [179]

tion neoadjuvant chemotherapy regimens coupled with surgical resection have greatly improved survival rates in patients with localized disease.[177] Accordingly, wide surgical resection in conjunction with chemotherapy remains a cornerstone of treatment for head and neck Ewing sarcomas.[181] The use of radiation therapy for head and neck Ewing sarcoma remains somewhat controversial; however, its use is widely recommended for cases of large unresectable tumors where operative morbidity would be significant or in cases of residual disease following initial surgical resection.[176,178,179,181] Opponents of radiation therapy as primary treatment for head and neck Ewing sarcoma cite the well-documented risk of inducing secondary post-radiation malignancy, as well as the inevitable radiation-induced disturbance of facial growth centers in children and adolescents.[179,181]

Prognosis for Ewing sarcomas at all anatomic sites has been dramatically improved over the past 20 years with the use of multimodal therapy, and 5-year survival rates, once 10%, are currently 50% to 70% overall.[179,181] Prognosis for head and neck Ewing sarcomas remains less well defined owing to the rarity of this lesion within this region; however, some evidence suggests that patients may actually fare better with head and neck tumors when compared to other anatomic sites.[178] Head and neck Ewing sarcomas are noted to be less likely to present with distant metastases at the time of diagnosis; however, it remains unclear whether this is the result of tumor biology or higher likelihood of earlier diagnosis when compared to other anatomic areas.[179] Ultimately, local tumor control remains a mainstay of improving survival and reducing rates of distant metastases, as patients with residual disease following surgical resection suffer from a significantly worse prognosis.[178]

In conclusion, Ewing sarcomas are the second most common primary malignant bone cancer in children and adults; however, they are extremely uncommon within the head and neck region. They most commonly affect children and young adults, and they most typically arise from the gnathic structures within the head and neck. Their histogenetic origins have not been fully delineated, yet the most currently favored hypothesis is that of a neuroectodermal lineage. Treatment primarily involves multidrug neoadjuvant chemotherapy followed by surgical resection; however, radiation therapy continues to be investigated in both definitive and adjuvant applications. Overall prognosis for head and neck Ewing sarcomas is likely more favorable than for tumors arising in other locations; however, the rarity of these sarcomas precludes accurate assessments of true prognosis.

Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma (ASPS) is a soft tissue sarcoma of uncertain histogenetic origin that makes up less than 1% of all soft tissue sarcoma diagnoses.[182] ASPSs most commonly occur in the tissues in the upper and lower extremities of adolescents and young adults, with a nota-

and neck subsites is exceedingly uncommon owing to the overall rarity of this neoplasm; however, approximately 25% of all ASPSs will occur within the head and neck region.[185-187]

Clinically, ASPSs are usually slow-growing neoplasms with minimal features that would suggest a malignant process.[183] ASPSs also are noted for exhibiting very indolent clinical courses even in patients with underlying metastatic disease at the time of diagnosis.[182] The most common clinical presentation of ASPS is that of a painless, slow growing mass, and the most commonly involved head and neck subsites are the orbit and the tongue.[184-186,188] MRI of ASPS does reveal a characteristic high-intensity signaling on both T1- and T2-weighted images that can help to distinguish this neoplasm from other types of soft tissue sarcomas, which are typically isointense and hyperintense on T1- and T2-weighted images, respectively.[189]

Histologically, ASPS has a pseudovascular appearance with clusters of large polygonal tumor cells containing eosin- [185]

has been lent to the myogenic theory given the results of more recent immunohistochemical characterization. ASPS typically demonstrates immunopositivity for both vimentin

and desmin, while conversely showing immunonegativity for EMA, cytokeratins, chromogranin A, synaptophysin, S-100, HMB45, and Melan-A.[183,185] Another defining feature of ASPS is the presence of cytoplasmic crystals containing PAS-positive and diastase-resistant material that are either rhomboid or rod-like in appearance. This finding is present in over 80% of reported cases.[185,188]

Given the relative rarity of ASPS, optimal treatment recommendations have largely been extrapolated from therapies established for other soft tissue sarcomas.[26,185] There is general agreement that the primary treatment modality is wide surgical resection with no need for elective neck dissection given the very low rates of regional metastasis.[185,186,188,190] The role of radiation therapy remains controversial, as earlier studies demonstrated no significant benefit with adjuvant radiation therapy; however, more recent studies have demonstrated significant improvements in rates of local control following primary surgical resection.[185] Given the extremely high propensity for distant metastatic spread seen with ASPS, recommendations for adjuvant chemotherapy have been previously proposed, yet multiple studies have demonstrated extremely poor responsiveness to multiple cytotoxic agents.[185] Nevertheless, given the highly vascular composition of ASPS, newer antiangiogenic agents, such as bevacizumab, sunitinib malate, and cediranib have shown some early promise in clinical trials for both primary and metastatic ASPS.[185]

Long-term prognosis for ASPS remains exceedingly poor, owing in large part to high rates of distant metastases, which are present in up to 65% of patients at the time of diagnosis.[191] The most common sites of metastatic spread are the lungs, followed by the bones, brain, and lymph nodes.[186] Overall 5-year survival rates with adequate primary surgical resection are reported to be as high as 65%; however, these rates drop to 38% at 10 years and 15% at 20 years, which highlights the inevitable impact of local recurrence and metastatic spread.[186] Prognostic factors affecting survival are difficult to establish given the rarity of ASPS in the head and neck region; however, large tumor size and more advanced AJCC stage have been suggested to correlate with reduced rates of survival.[185]

In summary, ASPS is an extremely rare soft tissue sarcoma that makes up less than 1% of all sarcoma diagnoses overall. Its overall rarity makes head and neck presentations uncommon; however, up to 25% of ASPS occur in head and neck subsites—particularly in pediatric and adolescent populations. Accurate diagnosis is critical, as these tumors often do not exhibit clinical features of malignancy, and the presence of metastatic dissemination at the time of diagnosis is common. Optimal treatment strategies have yet to be developed, although wide surgical resection remains a cornerstone of management. More recent studies suggest the utility of adjuvant radiation therapy in improving local disease control, and newer antiangiogenic agents are currently in trials for both primary and metastatic ASPS. Overall, the prognosis for ASPS remains poor given the high rates of distant metastasis.

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28

Squamous Cell Carcinoma of the Oral and Maxillofacial Region

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Introduction

Oral cavity and oropharyngeal cancer account for more than 7000 deaths annually, with an annual incidence of more than 30,000 new cases within the United States.[1] Worldwide it is the sixth most common malignancy, with incidence varying greatly among different geographic locations. Its prevalence can range from countries with rates similar to those in the United States, to countries such as India, where death from oral cavity cancer is one of the top three forms of cancer death. Even within the U.S. population, a fivefold difference in mortality is seen among states, likely a result of differences in ethnic and socioeconomic factors as well as the use of tobacco products.[2] Despite improvements in treatment, long-term survival rates are relatively unchanged over the past 30 years. For the oral and maxillofacial surgeon, an understanding of this disease and its impact on society, as well as the surgeon's role in identification and treatment, is imperative.

Anatomy

The oral cavity extends from the vermilion border of the lips to an imaginary coronal plane at the junction of the hard and soft palates and the circumvallate papilla. There are seven anatomic subsites included within the oral cavity: lips, buccal mucosa, lower and upper alveolar ridges, hard palate, floor of mouth, tongue (anterior two thirds), and the retromolar trigone. Subsite variation in cancer incidence, lymph node drainage, and overall prognosis exists.

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digastric muscles bilaterally.

- Level II—includes the upper jugular lymph nodes extending from the base of the skull to the level of the carotid artery bifurcation. The anterior border is the lateral aspect of the sternohyoid muscle, with the posterior border of the sternocleidomastoid (SCM) muscle serving as the posterior border of the level. Level II is also subdivided into levels IIA (inferior medial) and IIB (superior lateral) by the spinal accessory nerve.
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anterior and posterior boundaries as levels II and III.

- Level V—includes nodes anterior to the anterior border of the trapezius and posterior to the posterior border of the SCM. The inferior border of this level is the clavicle.

Buccal Mucosa

The buccal mucosa includes all mucous membranes lateral to the alveolar sulcus from the lips anteriorly to the retromolar trigone and pterygomandibular raphe posteriorly. Lymphatic drainage from these sites is primarily to levels I and II in the neck. It should be noted that cancer of the buccal mucosa can perforate beyond the buccinator muscle to the buccal fat and subcutaneous tissues, which may drain to the periparotid lymph nodes.

Alveolar Ridge

The alveolar ridges include the maxillary and mandibular alveolar processes and the overlying mucosa. On the maxilla, this extends from the buccal sulcus to the hard palate. In the mandible, the alveolar ridge extends from the buccal sulcus to the free mucosa of the floor of the mouth. Lymphatic drainage from the upper and lower buccal aspects is to the submandibular and submental (level I) nodes. The lingual aspects of the upper and lower alveolar ridges are to the submandibular (level I), superior deep jugular (level II), and retropharyngeal nodes.

Floor of the Mouth

The floor of the mouth extends from the lower alveolar ridge to the ventral surface of the tongue. Its posterior limit is the anterior tonsillar pillar. The floor of the mouth has both superficial and deep drainage systems that drain to the submandibular nodes (level I) and to levels I, II, and III, respectively. Crossover drainage to the contralateral side has been demonstrated in anterior portions of both the deep and superficial systems.

Retromolar Trigone

The retromolar trigone (RMT) is the triangular region overlying the ascending ramus of the mandible. The base is formed by the last tooth in the arch with the apex at the maxillary tuberosity. Medial and lateral borders are formed by the anterior tonsillar pillar and the buccal mucosa. The mucosa in this region is tightly adherent, leading to early bony invasion. Lymphatic drainage is primarily to the superior deep jugular (level II) nodes, with some drainage from this region to the periparotid and retropharyngeal nodes.

Hard Palate

The hard palate extends from the superior alveolar ridge to the palatine bones posteriorly. Tumors in this region may access additional sites through the incisive and greater palatine foramina. Drainage from the palate is primarily to levels I and II.

Tongue

The anterior two thirds of the tongue (mobile tongue) anterior to the circumvallate papillae is included in the oral cavity, whereas the base is a part of the oropharynx. Six paired muscles form the mobile tongue. Lymphatic drainage is oid nodes. The posterior compartments drain primarily to upper jugulodigastric nodes. As with the floor of the mouth, communication across the midline exists.

Epidemiology

Risk Factors

Tobacco

Large, well-designed, population-based studies affirm the correlation between tobacco use and the risk of oral cavity cancer.[3,4] Tobacco smoking is an independent risk factor; compared to nonsmokers, smokers are six to eight times more likely to develop oral cavity cancer.[5] This is especially true for women, who are twice as likely as men to develop oral cancer given the same amount of tobacco consumption.[6] More than 300 chemicals in tobacco smoke have been identified as contributing to carcinogenesis.[7] It is thought that exposure to these carcinogens leads to malignant transformation of cells. Smoking cessation is effective in reducing risk, though not in its complete elimination. Individuals who refrained from smoking 1 to 9 years showed a 30% reduction of risk, with a 50% reduction for individuals abstaining from smoking more than 9 years.[3]

Outside of cigarettes, both pipe and cigar smoking increase the risk for the development of oral cancer. The role of smokeless tobaccos within the United States has long been accepted to increase cancer risk, especially gingival and buccal cancers. A North Carolina–based study from 1986 showed a fourfold increase in risk in women users of smokeless tobacco.[8] Recently some have disputed the results of this study, claiming a lack of causation. Bouquot and Meckstroth reviewed statistics from West Virginia (the state with the highest per capita consumption of smokeless tobacco) in regard to incidence and mortality of oral and pharyngeal cancer, concluding that rates were less than the national average.[9] Accortt and colleagues categorized 6779 subjects 45 to 75 years of age. In their study, exclusive use of smokeless tobacco was not shown to increase incidence of oral cancer in males or females. No synergistic effects were observed between smoking tobacco and smokeless tobacco.[10] The use of smokeless tobacco, however, has been correlated with other cancer risk factors, with a recommendation for educating these patients regarding their overall cancer risk.[11] It is likely that the debate over causation for smokeless tobacco and oral cancer will continue, and patients should be aware at present that risks may exist.

Other forms of chewed tobacco have been shown as independent risk factors for oral cancer. Likely the most prominent is use of tobacco and betel nut in parts of India and Southeast Asia. In one study the incidence of oral cavity cancer was 123-fold higher for individuals who smoke and chew betel nut.[12] These data imply that 40% to 50% of all cases of oral cavity cancer in this geographic region occur in individuals with this habit.

Alcohol

The relationship between alcohol and cancer is clear for hard Swedish-based study of more than 1300 individuals showed moderate alcohol intake alone (<10 g/day) did not increase risk significantly, but high intake (>50 g) was an independent risk factor with a relative risk of 5.5. In addition, alcohol in conjunction with smoking was synergistic, with a relative risk of 22.1 compared to a relative risk of 6.5 from smoking alone.[14] In another study looking at extreme alcohol consumers, the risk for cancer from alcohol has been found to be greater than that from smoking alone.[15] Alcohol may predispose to cancer in any location in the oral cavity and is thought to possibly contribute more highly to dependent sites such as the floor of the mouth and lower buccal vestibule.

Viruses

A number of human viruses have been suggested as etiologic agents for oral cavity cancer through their transformation of human DNA. Herpes simplex virus type 1 (HSV-1) and human papillomaviruses (HPVs) have been reported by various authors. An association between HSV-1 and smoking with oral cancer development was suggested using immunologic parameters.[16] Animal model studies using HSV-1 in rats have been suggestive as well.[17]

Although the role of HPV in oropharyngeal cancer has been established, the role of HPV in oral cavity cancer at present is controversial. HPV-6 and HPV-16 have been most commonly implicated using polymerase chain reaction (PCR) assays of human tissue. In one study, HPV-16 was found to be present in tumor at a rate five times that of normal mucosa.[18] Additionally, in one study, oral squamous cell carcinoma cases were reported to have the presence of HPV.[19] Studies reporting on 5-year survival have revealed an improved prognosis for patients with and without nodal disease who have HPV-16-positive tumors compared to those who lack HPV.[20] Despite these positive studies, a number of institutions have reported minimal or no association between HPV and the oral cavity. Furthermore, a causative role has not been clearly established, and questions have been raised regarding possible contamination of specimens and faulty analysis.[21,22] At present, HPV's role in cancer development of the oral cavity remains unclear.

Other Factors

Although causation has not been established, a number of other factors are found in higher degrees among patients with oral cavity cancer. Nutritional deficiency including iron and vitamins A, C, and E has been documented. A number of well-designed studies have suggested the protective benefits of diets high in total vegetable and fruit intake as well as fiber found in green vegetables.[23,24] In a U.S.-based case-control study of second primary cancers, the risk of developing a second primary was 40% to 60% lower among those individuals with the highest levels of intake for total vegetables, demonstrating the protective nature of this diet.[25]

Patients with oral cancer are found to have higher degrees of oral disease including periodontal disease and caries.[26] Although association is present, no direct causation can be attributed.

Genetic Abnormalities and Clinical Implications

Chromosomal Abnormalities and Genetic Instability

Chromosomal abnormalities resulting from severe DNA damage have been extensively documented in head and neck squamous cell carcinoma (HNSCC).[27,28] Abnormalities include both losses and gains in genetic material on chromosomes 3, 4, 7, 8, 9, 11, 13, 17, 18, and 19. Evidence suggests that some chromosomal alterations may be linked to malignant progression. For example, changes at 3p and/or 9p with any other chromosomal abnormality were associated with a 33-fold increase in risk of cancer.[29]

Genetic instability includes microsatellite alterations and loss of heterozygosity. Microsatellites are highly polymorphic tandem repeat sequences of DNA that can be examined following amplification by polymerase chain reaction. Loss of heterozygosity (LOH) results from loss of one parent's contribution to part of the cell's genome. Both microsatellites and LOH are common findings in cancer. Microsatellites have been successfully used as tumor markers in a large number of malignancies including oral cancer.[30] Using 52 known tumor-associated alterations in tumors compared to normal tissue in the same patient demonstrated 29% of patients to have at least one microsatellite marker present in tumor.[31] Sidransky and colleagues examined microsatellite markers or loss of heterozygosity in 21 patients and showed that 18 (86%) demonstrated LOH and 5 had both LOH and microsatellite alteration. Malignant progression has also been documented through microsatellite changes.[32] From a clinical perspective, tetranucleotide microsatellite instability has been tested at surgical margins for recurrence prediction.[33]

p53 (TP53 *Gene*)

TP53 is located on the short arm of chromosome 17 at 17p13.1. It functions primarily to produce arrest of the cell cycle for DNA repair. Ultimately, if repair is unsuccessful, p53 is one of the leading signals causing cells to engage in programmed cell death, or apoptosis, via a number of complex cellular signaling pathways.[34,35] Mutations to *TP53* are one of the most frequent abnormalities in HNSCC cell lines and tissue specimens, variably reported in 30% to 75% of tumors.[36,37] Prognostic significance of p53 mutation has been reported. For example, node-negative oral squamous cell carcinoma patients with p53 overexpression were found to have poorer survival.[38]

Epidermal Growth Factor Receptor

Epidermal growth factor receptor (EGFR) has been frequently found to be overexpressed in HNSCC. EGFR is a receptor tyrosine kinase that can be bound by ligands including EGF (epidermal growth factor) and transforming growth factor-alpha (TGF-α). Activation of EGFR leads to changes in a number of pathways including *RAS* and *STAT* for regulation of cell growth. EGFR mRNA is overexpressed in 92% of HNSCC, with evidence of increased expression in advanced-stage and poorly differentiated tumors.[39] A number of studies have additionally documented the association of EGFR upregulation as an independent predictor for decreased disease-free survival.[40,41] In addition, higher levels of EGFR have been noted in the oral cavity and pharynx compared to other HNSCC sites.[42] Overexpression is the result of both decreased receptor downregulation and increased mRNA synthesis. Association between EGFR activation and matrix metalloproteinase (MMP) has been suggested, lending evidence to EGFR's role in invasion and metastasis.[43]

A number of therapeutic strategies are in various stages of development to specifically target this receptor. Gefitinib (Iressa), a small-molecule EGFR-selective inhibitor of tyrosine kinase activity that blocks EGF autophosphorylation and activation, has shown limited success primarily because of its side effects and a lack of increase in patient survival. Preclinical models under current investigation include anti-EGFR variable regions VHH (nanobodies), immunoliposomes created with Fab′ fragments, and antisense or small interference RNA to EGFR.

In March 2006 the Food and Drug Administration approved Erbitux (cetuximab) for head and neck cancer as the first treatment in 45 years to increase survival when combined with radiotherapy for unresectable disease. Its approval followed trials that confirmed a survival advantage to patients with locoregionally advanced disease who underwent radiation therapy with cetuximab versus radiation alone.[44]

Nuclear Factor-Kappa B

Nuclear factor-kappa B (NF-κB) is a transcription factor for inflammatory and immune response that serves as a cytokine modulator.[45] In the normal cellular environment it remains in the cytoplasm tightly associated with protein inhibitors (I-κBs). With activation, I-κBs are phosphorylated and ubiquitinated with subsequent proteosomal degradation, freeing NF-κB as a heterodimer of p65 and p50 subunits for nuclear translocation and gene activation. NF-κB is activated by a number of carcinogens and tumor promoters as well as the tumor necrosis factor (TNF) superfamily.[46] Immunohistochemistry of biopsy specimens demonstrates that oral cancer expresses higher levels of NF-κB in comparison to normal and dysplastic tissue.[47] Downregulation of NF-κB has been attempted using nonsteroidal anti-inflammatory drugs, which have been shown effective in vitro.[48] To date no conclusive evidence to support this treatment exists in HNSCC.

Cyclin D1

Cyclin D1 is a regulatory protein that drives cells through the cell cycle. In HNSCC, cyclin D1 gene amplification has been recognized in 26% to 68% of cases.[49,50] The presence of cyclin D1 overexpression has been correlated with increased nodal involvement and decreased overall and tumor-free survival.[51,52]

Screening for Cancer

Five-year survival of oral cavity cancer is inversely related to tumor size, the presence of nodal involvement, and distant metastasis. Detection in early stages has been shown to dramatically affect survival rates and is the most important variable leading to disease-free survival.[53,54] Survival by stage for the oral cavity, reported by the American Joint Committee on Cancer, based on 1985 to 1991 data, is as follows: stage I, 65% to 70%; stage II, 50% to 55%; stage III, 38% to 44%; stage IV, 24% to 28%. Although these numbers are somewhat lower than the currently reported statistics, their trend stands true. Given this reality, the desire for early diagnosis in order to increase survival has continued as a favorable objective. Overall, the success of the oral screening exam has been variably reported, with sensitivities ranging from 57% to 61% and with a specificity of 98%.[55-59] In 1965 Sandler reported success with visual inspection alone, in which 70 of 287 carcinomas and 20 of 28 carcinomas in situ were thought to be benign on clinical exam. Campaigns to enhance public and professional awareness are ongoing as a result of a number of studies that demonstrate both to be lacking.[56,57] In addition, the desire for an early detection screening tool has led to the creation of adjuncts to the physical exam. At present, no accepted screening test is available, and current guidelines from the American Cancer Society recommend only routine clinical examination of the oral cavity in association with the health maintenance exam. A number of limitations exist in the early detection paradigm that are worthy of limited exploration, given the confines of this chapter.

Holmes and Dierks et al[58] shed light on early detection in the United States, reporting their patient referral patterns for oral and oropharyngeal cancer. Fifty-one patients were reviewed with the conclusion that symptomatic and symptom-free detection was most likely to be accomplished by a professional who was a regional specialist (routinely working in the oral cavity).[58] Half of all patients who initially visited a non-regional specialist did not receive a biopsy or referral at their first visit, regardless of the fact that they presented with later clinical and pathologically staged disease, compared to those examined by a regional specialist. Because the majority of the regional specialists in the report were primary care dentists, it is important to consider the access of these professionals to the general public for the purposes of screening.

The 2003 *National Health Care Disparities Report*[59] suggests that fewer than 50% of all individuals more than 45 years of age see a dentist on an annual basis. By age 65 the

from Holmes and colleagues,[58] it is clear that barriers exist in access to the individuals most capable of early detection. If organized screening is to be effective, it is likely that both provider and public awareness will need to be increased and access to care barriers addressed.

Until recently, no prospective data existed to validate mass screening for early detection of oral cavity cancer. In 2005 results from Kerala, India, offered the first support through

[62]

which was statistically significant. Overall 5-year survival

raise concerns, as well as the fact that neither cost analysis nor harm from false-positive or false-negative exams are addressed.[63]

Diagnostic Adjuncts

Because no true screening test other than oral exam exists at present, a number of adjuncts have been developed in an attempt to increase the sensitivity and specificity of the oral screening exam. These tests range from those with established records of utility to those recently introduced to the market for use.

Toluidine Blue

Toluidine blue is a metachromatic vital dye that binds nuclei with a high DNA or RNA content, such as may occur in precancerous (dysplastic) or cancerous lesions (Figures 28-1 and 28-2). Its use as an adjunct to the physical exam for cancer screening has been documented over the past three decades with numerous reports in the literature. The sensitivity for toluidine blue screening has been reported to be 100% for lesions histologically consistent with invasive squamous cell carcinoma. In one study of 87 total lesions, sensitivity for invasive cancer was 100% (18/18); dysplasia revealed a less predictive result at 80% (29/39). The authors noted an advantage for toluidine blue as a screening tool because of the fact that a number of lesions not clinically visible before its application were discovered. Toluidine blue is limited by its specificity, which in this study was reported as 54%.[60] Mashberg reported the ability to increase overall specificity with a two-wash technique in which positive results were followed by removal of irritants and repeat evaluation in 2 weeks. Using this technique, he and his colleagues were able to raise specificities into the 90s.[61,64] Onofre and colleagues[64a] reported on their experience with 50 lesions in which sensitivity was 100% for carcinoma and carcinoma in situ. Dysplasia overall had a sensitivity of 50% with 3/6 mild dysplasias positive but 0/2 moderate dysplasias with uptake. Overall the specificity again was low at 67%. In the hands of the knowledgeable user, toluidine blue may offer an advantage over clinical examination alone. As a mass screening device, the lack of specificity results in a large number of false positives. In these cases clinical judgment would be required to decide whether or not biopsy or other diagnostic tests would be indicated.

OralCDx (Brush Biopsy)

The brush biopsy was first reported via a multi-institutional randomized prospective trial in 1999.[65] Unlike cytology, which has been shown ineffective for diagnosis of oral cavity cancer, this technique uses a brush, which has the capacity to procure a transepithelial specimen for microscopic evaluation of individual cells. The procedure is relatively painless and can be easily accomplished in a clinical setting. The results of the test are reported as positive, negative, and atypical. In the original report using 945 enrolled patients, a sensitivity of 100% was reported for 131 atypical and positive results, all of which revealed malignant or dysplastic lesions on histopathology. Specificity for positive results was reported as 100% and 92.9% for atypical results, with 14 of 196 total benign lesions testing atypical on brush biopsy. In addition, 4.5% of innocuous lesions that would not have been biopsied before brush were subjected after positive or atypical brush results and found to be malignant or dysplastic. A number of limitations to this study have been subsequently explored, which raise concerns for this technique. Because of institutional review board (IRB) restrictions and patient loss, 618 patients were never subjected to biopsy, which could have significantly altered the results. In clinical practice, concerns have been raised over the possibility of false-negative results, although the examples used in the



• **Figure 28-1** Squamous cell carcinoma of lateral tongue.



• **Figure 28-2** Squamous cell carcinoma of lateral tongue stained with toluidine blue.

only publication to raise these issues are of questionable appropriateness for a brush biopsy technique.[66] Likely of greater clinical impact is the lower than expected positive predictive value of 38%, with 150 of 243 patients with positive or atypical results on brush being negative on scalpel biopsy. Two studies reported in *Oral Oncology* in September 2004 highlight the continued debate of this technique. Poate et al[68] reported on 112 patients with an overall sensitivity for dysplasia or cancer of 71.4% and a specificity of 32%. The positive predictive value of a positive or atypical result was 44% with a negative predictive value of 60%.[68] In the same publication, Scheifele et al reported on 103 patients studied with OralCDx in which brush biopsy positive for dysplasia and cancer showed a sensitivity of 92% and a specificity of 94%.[69] Although some have argued that these results are superior to accepted screening tools in other body sites, such comparisons are unwarranted given significant differences in disease epidemiology and alternative screening methodologies for each disease.

Because clinical oral examination alone suffers in sensitivity but not in specificity and screening tests suffer from the opposite, a combination of these techniques in trained individuals may offer an advantage. Clinical judgment is necessary not only for conducting an appropriate visual examination but also for making determinations of which lesions to immediately subject to biopsy and in which lesions an adjunct may be helpful, based on the pretest probability of the patient and the specific adjunct characteristics relating to sensitivity and specificity. It is highly likely that additional tests will continue to be developed and used (e.g., VisiLite plus, VELscope, Microlux/DL). It is imperative that practitioners become proficient in evaluating the utility of screening tools and diagnostic adjuncts, because these instruments may be of benefit to their patient population. Evaluating test characteristics using the concepts of pretest probability, sensitivity, and specificity is critical to the practice of oral and maxillofacial surgery, now and in the future, in which an increasing number of diagnostic adjuncts are likely to become available. Science, and not marketing, should guide clinical practice.

Diagnosis and Pretreatment Evaluation

Patients with cancer of the oral cavity should undergo an extensive evaluation before treatment, including a complete history and physical examination, dental evaluation, and location, and appearance of the primary lesion as well as clinical evidence of tumor spread to adjacent structures, such as trismus denoting muscle involvement and paresthesias denoting neurologic involvement. Specifically related to neural spread, otalgia may indicate involvement of the ninth and tenth cranial nerves, whereas hypoesthesia of the lingual, infraorbital, and inferior alveolar nerves may denote fifth cranial nerve involvement. Palpation is used to gain an understanding of potential depth of invasion, which should be confirmed histologically given its impact on treatment decisions. The neck must always be palpated in order to assess the potential for lymph node involvement for staging and treatment planning.

Global evaluation of the patient should include an assessment for determination of the patient's ability to tolerate treatment, which will most often involve surgical management. Outside of co-morbid medical conditions, it should be realized that weight loss caused by malnutrition and dehydration is a common finding in patients with later stages of disease.

A number of imaging techniques can be helpful in visualization of the complete extension of the primary tumor and of any nodal disease. Computed tomography (CT) imaging is most commonly employed for this purpose, allowing imaging of the primary tumor as well as an assessment of peritumoral invasion of structures, including bone of the mandible, maxilla, and palate. In addition, CT can simultaneously assess the potential involvement of lymph node basins. Alternatively, magnetic resonance imaging (MRI) may be employed and will provide greater detail of soft tissue for lesions, such as those confined to the tongue. MRI is also superior in cases in which a large number of dental restorations are likely to create CT artifact, which will obscure the view of the primary lesion.

Positron emission tomography (PET) continues to be studied in regard to its utility in the initial evaluation of confirmed oral cavity cancer, but to date, evidence for its superiority to the traditional techniques is limited. In addition, the higher cost of this technology is a limiting factor. Ultrasound has been used for screening of nodal disease, although it is not widely considered the diagnostic modality of choice. Imaging of the chest is indicated either through standard x-ray or by CT scan if warranted.

Staging

Clinical staging of oral cavity cancer uses the TNM staging system from the American Joint Committee on Cancer (AJCC) (Table 28-1). This system is based on the information gained from physical examination and imaging studies to categorize patients. Staging is important for effective communication among professionals, as well as for increased standardization in prognosis assessment. T stage refers to the size of the primary tumor, which may be measured intraorally and correlated with the radiographic evaluation for confirmation of final dimensions. N denotes nodal involvement of adjacent lymph node basins of the neck assessed by palpation and diagnostic imaging. M refers to evidence of distant metastasis. Staging then follows a logical progression in which higher stage patients have more aggressive disease and therefore decreased survival. It must be recognized that all factors known to affect survival are not taken into account by this system, including factors on histologic examination (such as perineural and perivascular

TABLE 28-1

Levels	Lymph Node	Boundaries	Comments	Primary Tumor Site
IA	Submental	Superior: symphysis of mandible Lateral: anterior bellies of digastric muscles Inferior: body of hyoid bone	Only submental lymph nodes belong to this level	Lower lip, anterior part of oral cavity, floor of mouth, anterior portion of alveolar part of mandible
IB	Submandibular	Superior: body of mandible Anterior: anterior belly of digastric muscle Posterior: stylohyoid muscle Inferior: posterior belly of digastric muscle	When metastases are present in this level, submandibular gland is also usually removed during neck dissection	Oral cavity, anterior portion of nasal cavity, soft tissues of face, submandibular gland
IIA	Upper jugular (subdivided into two sublevels)	Superior: skull base Anterior: stylohyoid muscle Posterior: accessory nerve Inferior: horizontal plane defined by inferior body of hyoid bone	Lymph nodes around region located anterior to accessory nerve belong to this level	Oropharynx (including retromolar region, soft palate, tonsils), thyroid gland, parotid gland
IIB		Superior: skull base Anterior: accessory nerve Posterior: lateral border of sternocleidomastoid muscle Inferior: horizontal plane defined by inferior body of hyoid bone	Lymph nodes around region located posterior to accessory nerve belong to this level	Oral cavity, nasal cavity, oropharynx (including retromolar region, soft palate, tonsils), nasopharynx, hypopharynx, parotid gland
III	Middle jugular	Superior: horizontal plane defined by inferior body of hyoid bone Anterior: medial border of sternocleidomastoid muscle Posterior: lateral border of sternocleidomastoid muscle, branches of cervical plexus Inferior: horizontal plane defined by inferior border of cricoid cartilage	These lymph nodes are jugular vein in this region	Oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, thyroid gland
IV	Lower jugular	Superior: horizontal plane defined by inferior border of cricoid cartilage Anterior: medial border of sternocleidomastoid muscle Posterior: lateral border of sternocleidomastoid muscle, branches of cervical plexus Inferior: clavicle	These lymph nodes are jugular vein in this region; Virchow's nodes, significant for gastric cancer, also belong to this level	Hypopharynx, thyroid gland, larynx, cervical esophagus, stomach
VA	Posterior triangle (subdivided into two sublevels; demarcation line is horizontal plane defined by inferior border of cricoid cartilage)	Superior: apex of convergence of sternocleidomastoid and trapezius muscles Anterior: lateral border of sternocleidomastoid muscle, branches of cervical plexus Posterior: trapezius muscle Inferior: horizontal plane defined by inferior border of cricoid cartilage	Lymph nodes along lower portion of accessory nerve	Nasopharynx, oropharynx, skin of posterior neck, skin of scalp
VB		Superior: horizontal plane defined by inferior border of cricoid cartilage Anterior: lateral border of sternocleidomastoid muscle, branches of cervical plexus Posterior: anterior border of trapezius muscle Inferior: clavicle	Lymph nodes along transverse artery and other supraclavicular nodes, except Virchow's nodes	Thyroid gland
VI	Anterior compartment	Superior: hyoid bone Lateral: common carotid arteries Inferior: suprasternal notch	paratracheal, prelaryngeal, precricoid, and perithyroidal lymph nodes and nodes along recurrent laryngeal nerves	Thyroid gland, glottic, subglottic larynx, apex of piriform sinus, cervical esophagus

From Subramanian S, Chiesa F, Lyubaev V et al: The evolution of surgery in the management of neck metastasis, *Acta Otorhinolaryngol Ital* 26:309-316, 2006.

invasion or nodal extracapsular spread), immune and nutritional status, and patient co-morbidities. As our knowledge continues to increase regarding factors affecting survival, it is likely that the staging system will continue to evolve.

Nonsurgical Management

Alternatives and adjuncts to the surgical management of squamous cell cancer and prevention of recurrence in the oral cavity exist. Outside of radiation and chemotherapy, these modalities are for the most part investigational. Still, it is hoped that the future treatment of oral cancer will evolve, and alternatives to surgery may include a combination of these current alternatives. The need for continued advances cannot be overstated in a disease for which the death rate has been basically unchanged for nearly half a century. In addition, treatment of advanced cases of head and neck cancer carries with it significant morbidity. Difficulties with swallowing and speech frequently may lead to need for permanent tracheotomy and percutaneous feeding tubes. In the face of this morbidity, classic radical therapy has been called into question as the importance of quality of life has taken precedence over quantity of life. Still, the ultimate goal of treatment in any patient is cure, if possible. An additional question arises when considering alternative therapies in regard to their applicability for earlier stage cancers where surgical management is not as deforming and morbidities from the alternatives may carry more morbidity than traditional surgical management.

Patients guided by their health care professional must understand the options in order to make appropriate decisions for treatment. As modalities other than surgery continue to evolve, the optimal choices for treatment may change; those involved in this process must keep up to date with ongoing advances in this area. At the present time, decisions regarding treatment options must take into consideration the location and size of the primary tumor, the status of regional lymph nodes, the status of distant metastatic disease, and the overall health status of the patient.

Chemoprevention

Research in the area of chemoprevention has been ongoing since the 1970s with the goal of identifying agents that are efficacious at preventing SCCHN with limited toxicity.[70] Currently, more than 2000 agents have been shown to have chemopreventive activity while being studied in a variety of in vitro and in vivo systems.[71] Of these agents, retinoids, in particular 13-*cis*-retinoic acid (13-cRA), have been the most extensively studied. The term retinoids refers to vitamin A and a number of its natural and synthetic derivatives. In vitro studies have demonstrated the ability of retinoids to inhibit malignant transformation of cells subjected to tumor promoters that would otherwise lead to tumorigenesis.

Clinical trials of these agents have revolved around two goals: preventing premalignant lesions from transforming into malignancy and prevention of secondary tumors in patients with treated disease. The effects of 13-cRA were studied in a randomized trial using 44 patients with oral leukoplakias.[67] Patients received 1 to 2 mg/kg/day doses or placebo for a total of 3 months with 6 months of follow-up. promising, two important limitations of the study were noted: (1) Toxic effects of the dosage given included skin dryness with peeling and facial erythema, conjunctivitis, and hypertriglyceridemia. Although these toxicities were tolerated for the 3-month period, it was noted that they would likely not be tolerable over extended periods of time. tolerated.

Subsequent studies to answer this dilemma have used treatment regimens with initial induction doses of 1 to 2 mg/kg/day with low-dose (0.05 mg/kg/day) maintenance. One-year follow-up results on these patients have been promising in regard to toxicity and efficacy.[72]

In the area of chemoprevention of second primary tumors and field cancerization, a number of studies have been completed. In one study patients with HNSCC received radiotherapy or surgical management followed by high-dose 13-cRA (100 mg/m^2/day) for 1 year after treatment.[73] This dose was decreased by half in 53% of patients, who could not tolerate the side effects of the medication. With a median follow-up of 55 months, the treated patients recurrence or survival rates.

Future research in this important area involves the identification of appropriate targets for chemoprevention with high efficacy and low toxicity. Ongoing studies are underway using the tools of molecular genetics in attempting to identify candidates for which available chemoprevention may be indicated.[74] At present the retinoids remain an area of greatest promise. Ongoing research enhancing our understanding of the mechanism of action of retinoids will further assist in the creation of targeted chemopreventive agents.

Photodynamic Therapy

Photodynamic therapy (PDT) has been actively investigated in clinical trials since the late 1980s, treating a large number of tumors including HNSCC. PDT uses a photosensitizing agent designed to selectively target the neoplastic cells with subsequent activation and killing of the target. Necrosis of the tumor is thought to involve vascular collapse associated with the generation of free oxygen radical production.[75] Advantages of this technique include selective targeting of neoplastic cells (by unknown mechanisms) and the ability to use this tool in conjunction with established regimens of

surgery, chemotherapy, and radiation therapy. A number of new photosensitizers are currently under study, with Photofrin being the most widely used agent at the present time. The treatment regimen consists of intravenous injection of Photofrin with laser photoactivation 48 hours later using 630-nm wavelength light. A major limitation of treatment with this wavelength is the penetration depth in tissue of only 0.5 to 1 cm. In addition, a side effect of treatment with Photofrin is photosensitivity, which may last up to 6 weeks. Newer agents under study attempt to minimize these limitations.

The results of treatment for early SCCHN in the oral cavity appear promising. In 2006 Biel[77] reported on 15 years of experience with the use of photodynamic therapy in which 183 oral cavity squamous carcinomas were treated. In addition, literature is reviewed from 505 reported cases of Cis, T1, and T2 lesions of the oral cavity, larynx, pharynx, and nasopharynx; 89.1% of these patients achieved complete clinical response.[77]

Fan et al reported the use of *meta*-(tetrahydroxyphenyl) chlorine (mTHPC), a second-generation photosensitizer, in 19 patients with histologically confirmed oral cancer.[78] The six single-lesion T1 and T2 patients were cleared with one treatment. Three of 6 T4 lesions were reported cleared as well. Lesions in patients with field cancerization changes were not as successful, with only 9 of 14 T1 and T2 lesions cleared, with 4 requiring additional treatments. The mean follow-up of patients in this study was 63 weeks. Copper and colleagues reported on 25 patients receiving mTHPC for T1 (63%), T2 (28%), and multiple primary tumors (8%).[79] The complete remission rate with 37 months follow-up was 95% for T1 lesions and 57% for T2 lesions. All cases with recurrent disease were salvaged with standard surgery and/or radiotherapy. Five of the patients at the time of salvage were positive for lymph node metastasis.

Photodynamic therapy presents significant advantages in the limitation of morbidity associated with treatment of HNSCC. At present, data exist in support of this modality for treatment of early-stage disease. Photodynamic therapy may be used in conjunction with other modalities. Continued documentation of long-term follow-up and also controlled clinical trials are needed to elucidate its ultimate role.

Immunotherapy

Active immunotherapy (administration of agents external to the patient) and passive immunotherapy (administration of agents originally obtained from the patient) continue to be studied extensively in regard to a variety of malignant tumors. Development of tumor vaccines that incorporate defined epitopes from the cancer cells as well as attempts to globally stimulate the immune system provide plausible avenues for ultimate treatment, or as an adjunct to treatment, of HNSCC. The requirements for this therapy to work include the following: (1) identification of tumor-specific antigens; (2) activation of antigen processing cells (APCs) to present antigens via major histocompatibility complex (MHC) to T cells; (3) directed T cells activated by APCs capable of recognizing tumor; and (4) lysis of tumor cells by activated T cells.

The tools of molecular biology have recently allowed the identification of many tumor-associated antigens.[80] These tumor antigens can be processed by APCs and presented to T cells, which do indeed infiltrate into tumor. Haeffner and colleagues demonstrated T cell recognition of antigen by the existence of activated tumor-infiltrating lymphocytes in squamous cell carcinoma after presentation of antigen.[76] Unfortunately, although evidence of activation was present, tumor lysis did not occur. One possible explanation for this is the finding that HNSCC often produces significant quantities of immunosuppressive cytokines, resulting in the inability to complete the T-cell mediated lysis.

One possible answer to this dilemma involves the boosting of the immune system through a variety of mechanisms. Studies using interferon-α, interleukin-2, tumor necrosis factor, and other immunomodulators have been conducted. Attempts have been made to administer these agents intralesionally, intralymphatically, and systemically. A study representative of many variations on this theme reported a phase II trial with neoadjuvant immunotherapy for oral squamous cell carcinoma. Interleukin-2 injection occurred in 19 patients, with 2 complete, 2 major (>50%), and 4 minor (>30% but <50%) responses. The overall response rate was 42%.[81]

With respect to SCCHN, immunotherapy at present remains investigational in nature and in need of additional controlled clinical trials to define its place in treatment modalities. SCCHN does possess the elements needed for treatment via modulation of the immune system, and immunotherapy in some fashion may likely play a role in the treatment of this disease as our understanding of the processes involved evolves.

Gene Therapy

Gene therapy is defined as the transfer of genetic material for treating human disease. This definition encompasses the transfer of new genetic material as well as the modulation of existing genes. The first report of a fully successful gene therapy treatment occurred in 2000 with the treatment of a child with severe combined immunodeficiency.[82] Gene therapy has the potential to treat HNSCC, which is known to involve multiple genetic "hits" in its transformation process from a normal cell to malignancy. At the present time, direct injection into tumor is a requirement for gene therapy in tumor treatment, making local HNSCC an acceptable target.

As reviewed by Xi and Grandis,[83] several general strategies are used in cancer treatment with gene therapy: addition of a tumor-suppressor gene (gene addition therapy), deletion of a defective tumor gene (gene excision therapy), downregulation of the expression of genes that stimulate tumor growth (antisense RNA), enhancement of immune surveillance (immunotherapy), activation of prodrugs that

have a chemotherapeutic effect ("suicide" gene therapy), introduction of viruses that destroy tumor cells as part of the replication cycle, delivery of drug resistance gene(s) to normal tissue for protection from chemotherapy, and introduction of genes to inhibit tumor angiogenesis.

Genetic material must be packaged and delivered in a vector to its target site. The ideal vector, not yet achieved, would specifically target the desired cells, deliver a precise amount of desired genetic material, and show no toxicity. Vectors currently in use are considered either viral or nonviral in nature. Viral vectors at the present time include adenovirus, adeno-associated virus, retroviruses, lentiviruses, herpesvirus, and hybrids of these. The nonviral vectors include the use of liposomes and naked DNA with chemical and physical transfection techniques. Of the present techniques available, one that appears particularly promising involves the creation of a recombinant adenovirus that selectively replicates and kills cells that are deficient in p53.

At the present time, gene therapy is a new investigational approach to the treatment of HNSCC. In the future, cancer-based gene therapy could be combined with known effective approaches to attempt to decrease tumor bulk and therefore the morbidity associated with treatment. As our understanding of the genetics of cancer and our ability to externally control those genes increases, HNSCC will be an attractive target for implementation of protocols for treatment. At the present time phase I, II, and III trials are underway in order to establish and delineate the role of gene therapy in the treatment of HNSCC.

Surgical Management

The Primary Tumor

The word *carcinoma* (*karkinos:* "crab") is attributed to the father of medicine, Hippocrates (460-370 BC), who noticed that blood vessels around non–ulcer-forming and ulcer-forming tumors looked like the claws of a crab. Hippocrates, and later Galen (129-199 AD), maintained that cancer was generated by a "humoral" etiology caused by an excess of "black bile." As a result of their theory, they did not believe in the surgical management of malignant tumors, but Galen performed several cancer resections, recommending excision through surrounding healthy tissue.[84] Galen also described how tumor growth developed again even after the scar healed. Intuitively, he presented the basic concepts of surgical resection with negative margins, and the potential for tumor recurrence. The skeptical approach toward surgery was maintained through many centuries, until 1845, when Lebert described cancer cells and recommended surgical excision for the treatment of breast cancer.[85]

Surgery is presently the most common treatment modality in the management of squamous cell carcinomas (SCCa) of the oral and maxillofacial region. Alternative therapeutic options should be considered based on such factors as the medical condition of the patient, tumor stage, and prognosis.

Basic principles of surgical oncology are applied: resection with curative intent of the primary tumor with *at least* 1 cm of negative surgical margins. In specific situations, patients who have unresectable tumors undergo surgery with palliative intent.

Several factors are significant in the incidence of local recurrence and overall survival rates: positive surgical margins, perineural invasion, bone invasion, pattern of invasion, lymphocytic response, vascular invasion, extracapsular extension, and tumor (T) size.[86-94]

Cancer of the Floor of the Mouth

Excision of T1 lesions of the floor of the mouth (FOM) can usually be performed through a transoral approach, and the area can be reconstructed with a split-thickness skin graft. Neck dissections may be required based on the depth of invasion of the cancer. Because of the variety of immediate surrounding tissues, this type of cancer may involve the salivary ducts of the submandibular and sublingual glands, the tongue, or the mandibular alveolar ridge (Figure 28-3).

A retrospective study of 63 specimens of FOM squamous cell carcinoma with inclusion of the sublingual salivary gland was conducted.[87] Seventeen cases (27%) had histopathologic sublingual gland invasion. Clinically, this was evident at the time of surgery in 15 patients (88%). Microscopic invasion into the sublingual gland without macroscopic evidence was present in only 4.2% of patients. The findings of the study support a wide local excision of early-stage superficial SCCa of the FOM without obtaining significant benefit by excising the sublingual gland unless there is macroscopic evidence of invasion, significant tumor depth, or an advanced T stage.

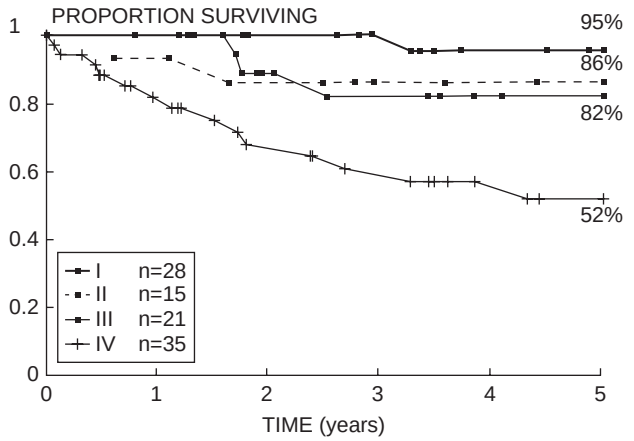
If the submandibular duct is in the area of the lesion and if a neck dissection is not planned, a sialodochoplasty would be indicated. A potential complication would be an obstructive sialoadenitis caused by scarring at the site of the repositioned duct. The use of sialodochoplasty in this clinical setting is supported by a study on outcomes of repositioning and



• **Figure 28-3** Squamous cell carcinoma of the floor of the mouth with extension into the ventral surface of the tongue.

cannulation of the submandibular duct after excision of floor of mouth cancer. The study identified an incidence of postoperative neck swelling in only 15% of patients within the first 25 postoperative months, concluding that sialodochoplasty is a sound procedure that does not compromise the cancer resection.[88] In T1N0M0 lesions, the reported incidence of occult metastasis has been 21% while it is 62% in T2N0M0 SCCa of the FOM.[9] Regardless of the T stage, Spiro and colleagues[89] suggested that tumor thickness (more than 2-mm depth of invasion having more incidence of cervical metastasis), rather than tumor staging, may be a better way to select oral cancer patients who are likely to benefit from elective neck dissections.

Disease-specific cumulative 5-year survival for patients with FOM cancer has been reported to be 76%, with 95% survival rate for stage I, 86% for stage II, 82% for stage III, and 52% for stage IV (Figure 28-4).[9]



(From Hicks WL, Loree TR, Carcia RI et al: Squamous cell carcinoma of the floor of mouth: a 20 year review. *Head and Neck* 19:400-405, 1997.)



• **Figure 28-5** Verrucous carcinoma of the buccal mucosa.

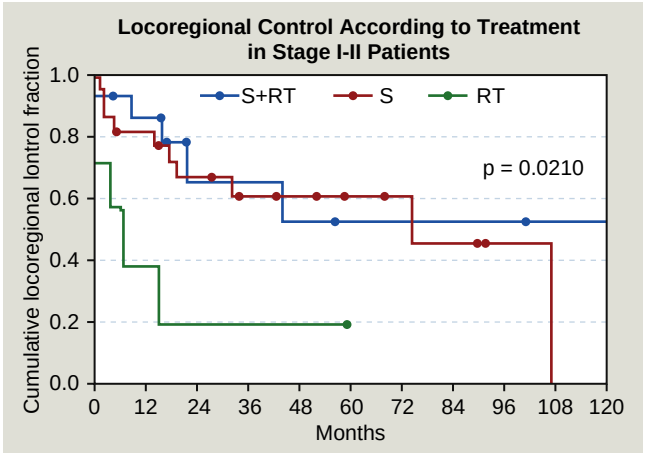
Cancer of the Buccal Mucosa

The incidence of squamous cell carcinomas of the buccal mucosa (Figures 28-5 and 28-6) in western countries is mostly related to the use of tobacco, with an overall low incidence of 10% of all oral cancers. In Southeast Asia (especially in India) the incidence of SCCa has been correlated with the chewing of a combination of tobacco, betel nut, and lime with an estimated prevalence of more than 40% of oral cancers in this geographical region.

In a retrospective review of 121 previously untreated patients with SCCa of the buccal mucosa, the locoregional recurrence was 57% for all patients, with 80% occurring in the primary site alone.[90] Even patients with T1 and T2 lesions who received surgery only had a recurrence rate of 41%. Patients with T3-T4 lesions had better long-term locoregional



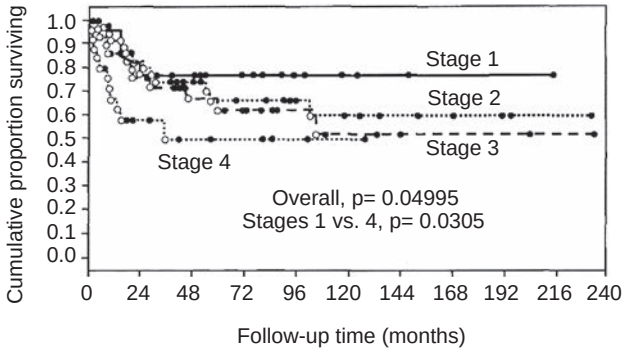
• **Figure 28-6** Invasive squamous cell carcinoma of the buccal mucosa and lower vestibule with gingival extension.



• **Figure 28-7** Locoregional control curve for patients with buccal mucosa cancer stage I-II disease. The 5-year locoregional control rates tively (p = 0.0210). *S*, Surgery alone; *RT*, radiotherapy; *S+RT*, surgery followed by postoperative radiotherapy. (From Lin CS, Jen YM, Cheng MF et al: Squamous cell carcinoma of the buccal mucosa: an aggressive cancer requiring multimodality treatment, *Head Neck* 28[2]:150-157, 2006.)

control and survival rates when treated by a combination of surgery and radiotherapy than when treated by either modality alone (Figure 28-7). Patients with buccal mucosa SCCa have a worse stage-for-stage survival rate than do patients with any other cancerous sites in the oral cavity. The presence of regional metastasis has a significant effect on survival rates. In a study conducted at the M.D. Anderson Cancer Center, the 5-year survival rate for patients with positive neck nodes was 43% versus 70% when the neck was negative[91] (Figure 28-8).

As a result of the reported high recurrence rate and potential poor prognosis of carcinomas of the buccal mucosa,[92] multimodality combinations of surgery and radiation with or without chemosensitizers are recommended for patients with this type of lesion. Nair and co-workers reported an 85% 3-year disease-free survival rate for stage I and 63% for stage II when the primary modality of treatment was radiotherapy with either interstitial radium needles or external beam.[93] Most publications provide better outcomes with a combination of surgery and postoperative radiation in more advanced stages.



• **Figure 28-8** Effect of disease stage on survival in buccal mucosa cancer. The impact of disease stage is shown here on a Kaplan-Meier plot. For patients with stage I, II, III, and IV disease, 5-year survival rates were 78%, 66%, 62%, and 50%, respectively. (From Diaz EM Jr, Holsinger FC, Zuniga ER et al: Squamous cell carcinoma of the buccal mucosa: one institution's experience with 119 previously untreated patients, *Head Neck* 25[4]:267-273, 2003.)

Cancer of the Tongue

Likely to be the most common oral cancer, SCCa of the tongue (Figure 28-9) accounts for about 20% of all oral and pharyngeal cancers, including lip cancer.[94]

Epidemiologic data show an increased incidence in younger adults ages 20 to 44[95] with some suggestive evidence of higher locoregional failure in the younger patients.[96] In a recent article, the overall survival rate has been correlated with tumor grade and tumor size, with no difference in survival rates between patients with tongue cancer and patients with cancer in other sites of the oral cavity[97] (Figure 28-10). Neck metastasis of early (T1-T2) squamous cell carcinoma of the tongue was correlated with tumor thickness, muscle invasion, poorly differentiated tumors, infiltrating-type invasion front, presence of perineural invasion, and presence of angiolymphatic invasion.[98]

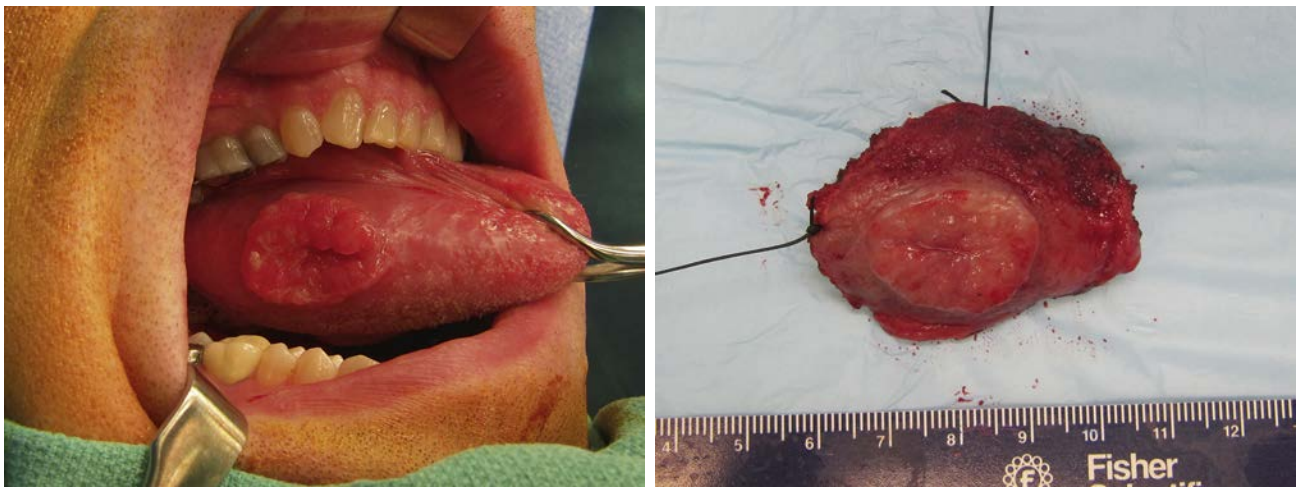
While positive cervical lymphatic metastasis has always been documented as having a very negative effect on survival, a retrospective analysis of 266 patients comparing clinical versus pathologic lymph node staging demonstrated statistically significant survival differences in pathologic lymph node stages as well.[99]

In the past decade, significant data has been added to the literature in the management of base-of-tongue cancer by Transoral Robotic Surgery (TORS).

A recent review of articles on the subject from 2000 to 2014 by Helman and associates concluded that TORS has a positive role in oropharyngeal cancer by decreased morbidity, length of stay and total intubation time.[99a] Prospective studies are being conducted comparing TORS to non-robotic approaches in oropharyngeal carcinomas.

Squamous Cell Carcinoma of the Retromolar Trigone, Alveolar Ridge, and Palate

The gingival tissues on the alveolar ridge or the retromolar trigone are in very close proximity to the underlying periosteum, and significant difficulties have been encountered

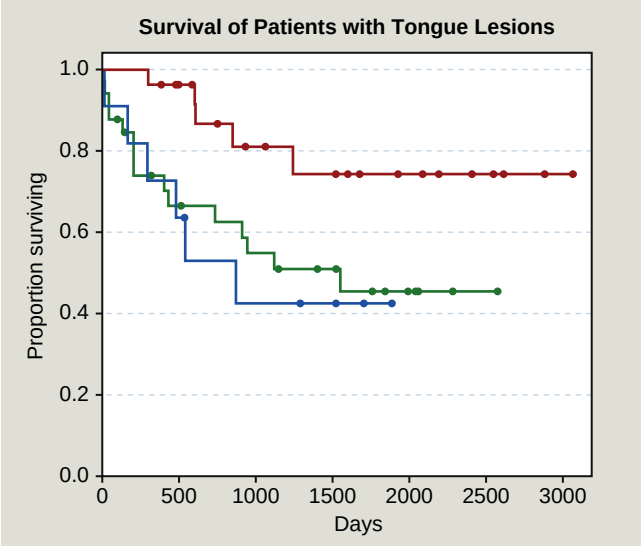


• **Figure 28-9** Squamous cell carcinoma of the tongue.

trying to identify bony invasion. Computed tomography has been useful in the diagnosis of bone involvement, but inaccurate. A study by Lane and colleagues[100] found an incidence of 50% mandibular invasion in retromolar SCCa that was not identified radiographically by CT in 27% of the patients. The effectiveness of skeletal scintigraphy is of relative value as well. Tsuchimochi and co-workers[101] described accumulation of technetium-99m methylene diphosphonate in areas of the mandible invaded by cancer. Bone scans have increased uptake in areas of osteoblastic activity; therefore the radioisotope concentrates in the immature bone surrounding the tumor as well as in the reactive periosteum in adjacent contact with the tumor, making this test highly sensitive but nonspecific with a potential false-positive result. Magnetic resonance imaging has a reported accuracy of 87% in establishing the involvement of the mandibular bone marrow, even in the absence of discontinuity of the cortical bone.[102]

A comparison between different imaging modalities and direct inspection after periosteal stripping was conducted by Brown and associates.[103] The results showed that orthopantomograms, CT, and periosteal stripping with direct inspection underpredicted the width and depth of bony invasion, whereas bone scans and MRI overestimated it.

Diagnosis of tumor extension into bone is critical to render proper treatment. Genden et al[104] recommended a panoramic radiograph and CT scan for all tumors of the retromolar trigone. In patients with trismus, extensive soft tissue involvement, or sensory disturbance, an additional MRI would be indicated.



• **Figure 28-10** Disease-free survival of tongue cancer with respect to tumor grade. Kaplan-Meier curve illustrating the disease-free probabilities with respect to tumor grade. Grade 1 is shown at the top as a *red* line, grade 2 at the bottom as a *green* line, and in the middle is grade 3 as a *blue* line. (From Friedlander PL, Schantz SP, Shaha AR et al: Squamous cell carcinoma of the tongue in young patients: a matched-pair analysis, *Head Neck* 20[5]:363-368, 1998.)

The treatment plan would include a bone resection in most cases. If the tumor approaches the periosteum, a marginal resection would be indicated to achieve tumor clearance and appropriate clean margins. When the cancer has early cortical mandibular invasion, conservation surgery preserving some mandibular continuity has been shown to be a valid option without evidence of disease 2 years after treatment in 78% of patients with T1, 73.1% of T2, 63.5% of T3, and 33.3% of T4.[105]

When the preoperative assessment is positive for involvement into the marrow space, a segmental resection is indicated. I. A. McGregor and colleagues[106] reported a readily available route of cancer spread through the porous alveolar ridge in edentulous patients. Of 46 nonirradiated mandibles (10 partially dentated and 36 edentulous), 41 were invaded through the alveolar ridge. They also found that perineural spread through the inferior alveolar nerve was a regular occurrence after bony invasion reached the mandibular canal.

A. D. McGregor and associates suggested that a more aggressive pattern of invasion through cortical bone was present in previously irradiated mandibles.[107] The pattern of invasion in 16 irradiated mandibles was more variable with multiple foci of tumor present in areas where the tumor was adjacent to the bone, implying the need for more radical resections in post-irradiated mandibles with tumor.

Boyle and Strong[108] recommended the following contraindications to marginal resections of the mandible:

1. Gross involvement of the cortical or cancellous bone of the mandible
2. Inability to preserve the inferior alveolar artery
3. Significant resorption of the mandible, suggesting very thin and weak residual bone
4. A previously irradiated mandible
5. Cancer abutting the mandible on more than two surfaces

Regarding contraindication 2, if the consideration to perform a radical resection because of the inability to preserve the inferior alveolar artery is based on evidence for direct invasion into the canal, then there is no doubt of the need to perform a segmental mandibulectomy and even evaluate the nerve margins for perineural spread.

On the other hand, the rationale is clouded if the justification for a segmental resection is based on the concern for vascular supply to the mandible as a result of the inability to preserve the inferior alveolar artery. If the canal was not infiltrated and there is no evidence of deep invasion, the mandible may remain viable through periosteal blood supply, even after sacrificing the inferior alveolar vessels.

Carcinomas of the hard palate and upper alveolus are uncommon. Alveolectomy, palatectomy, and infrastructure maxillectomy are the procedures of choice for this specific location.[109] Whereas squamous cell carcinomas still represent more than 50% of the malignant lesions of the hard palate, minor salivary gland tumors represent from one third to almost one half of the pathology in this location.[110,111]

The management of the neck in gingival and alveolar cancer has become a controversial issue that may require prospective data in order to establish a treatment strategy.

Soo and co-workers[112] reported an incidence of 14% neck metastasis at the time of diagnosis of maxillary gingival carcinoma. Overholt and colleagues[113] reported 13% neck metastasis at the time of diagnosis of palatal carcinoma.

More recent data from Simental and associates[114] have shown a much higher incidence of occult neck metastasis when patients with negative nodes at the time of presentation eventually developed neck metastasis despite control cervical failures at the site of first failure for a total of 34.6%. Similar data were published by Zwetyenga et al,[115] with a 28% incidence of positive lymph node(s) in advanced upper gingival and hard palate cancer. Additional data from Toronto, showed similar results with occult nodal metastases of 26% of patients clinically staged as N0.[115a] Montes and Schmidt demonstrated that the aggregate of all patients with different stages of oral maxillary squamous cell carcinoma, 42.9% of the patients manifested disease to the cervical lymph nodes.[115b]

The accumulated experience in the management of the negative neck in cancer of this location supports surgical intervention through a selective neck dissection.

Types of Neck Dissection

Several clinical and pathologic characteristics have been described as predictive factors for oral cancer metastasis to regional cervical nodes. The radical neck dissection, initially described by Jawdynski in 1888[116] and later published and systematized by Crile in 1906[117] and advocated by Martin in 1951,[118] is the main treatment modality in the management of tumor metastasis to the lymph nodes of the neck.

In 1963 Suarez[119] and later in 1967, Bocca[120] published bidity associated with the removal of these three structures.

In 1972 Lindberg[121] described the distribution of cervical metastasis in relation to the primary tumor after reviewing 2004 patients with SCCa of the head and neck. This finding, later validated in additional studies by Shah[122] and Byers and colleagues,[123] led to the implementation of selective neck dissections for patients with clinically negative necks or for very selected patients with positive necks. Outstanding and detailed reviews of the historic evolution of neck dissections have been published by Ferlito and colleagues[124] and Subramanian and associates.[125]

In 2001 the American Head and Neck Society proposed an update for the classification of neck dissections.[126] The different levels of the cervical lymph nodes and the new classification of neck dissections are represented in detail within Tables 28-1 and 28-2. The classification of 1991 differs only in the description of selective neck dissections (SNDs) (Figure 28-11), which are now described as SND with the use of parentheses to denote the levels or sublevels removed.

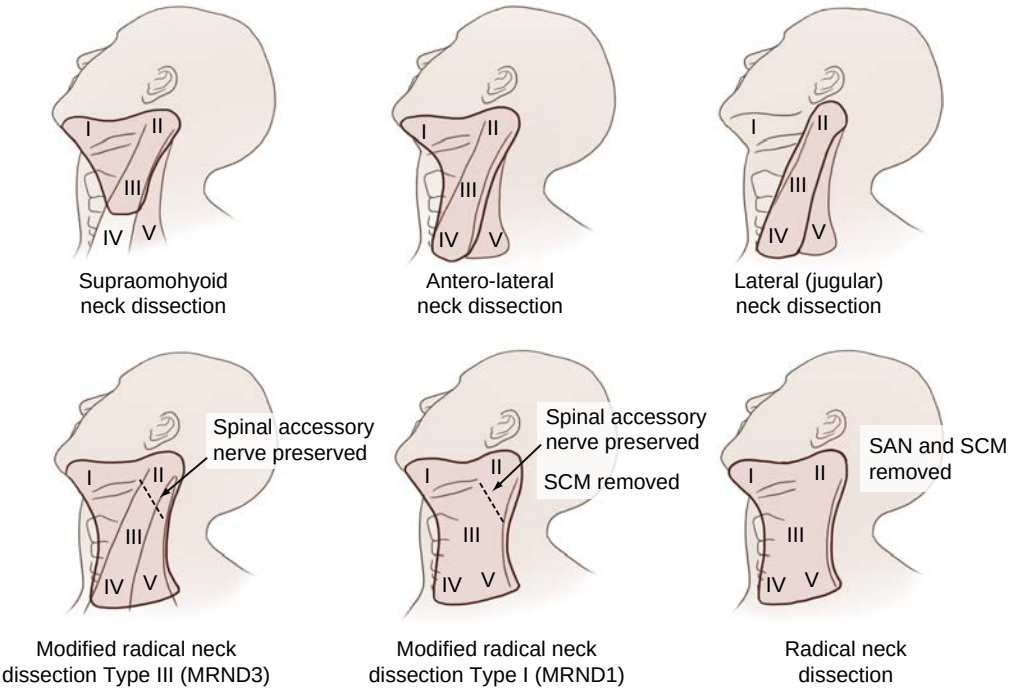
Despite performance of a neck dissection, the presence of extracapsular spread and soft tissue deposits of cancer diminishes the survival rates significantly. The presence of cervical lymph node metastasis reduced the 5-year survival rate by 50%, while extracapsular spread or soft tissue deposits of cancer roughly decreased the survival rate by an additional 50% (Figures 28-12 and 28-13).[127]

Since the early 1990s, sentinel lymph node biopsy has been used mostly for breast cancer and melanoma.[128,129] The technique involves the histologic sampling of the lymph node that drains a radioisotope after it is injected at the site of the primary tumor. A review by Devaney and colleagues concludes that a negative sentinel node biopsy does not necessarily exclude the presence of other positive cervical lymph nodes.[130] Therefore this technique should still be considered an investigational procedure until further data are available.

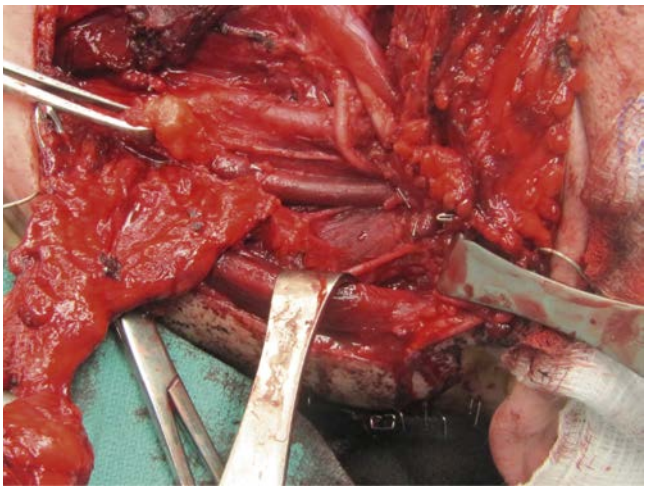
TABLE 28-2 Types of Neck Dissections

Surgery	Structures Removed
Radical neck dissection	
Extended neck dissection	least one lymphatic or nonlymphatic structure not sacrificed during radical neck dissection (parapharyngeal nodes, superior mediastinal nodes, perifacial nodes, carotid artery, hypoglossal nerve, vagus nerve, paraspinal muscles, etc.)
Modified radical neck dissection	Radical neck dissection minus at least one of the three major structures (namely, sternocleidomastoid named
Selective neck dissection	At least one of the six lymph node levels/sublevels preserved; none of the structures (namely, sterno- sublevels should be mentioned within parentheses: I-III, II-VI, VI, etc.)

From Subramanian S, Chiesa F, Lyubaev V et al: The evolution of surgery in the management of neck metastasis, *Acta Otorhinolaryngol Ital* 26:309-316, 2006.



A



B

• **Figure 28-11** **(A)** Types of neck dissections according to the classification of 1991. **(B)** The retractors are holding the sternocleidomastoid muscle and exposing the spinal accessory nerve which is the boundary between Level 2A and 2B. Above the Army-Navy retractors one can identify the carotid artery. (Courtesy Shah J: Patterns of cervical lymph node metastasis from squamous cell carcinomas of the upper aerodigestive tract, *Am J Surg* 160:405-409, 1990.)

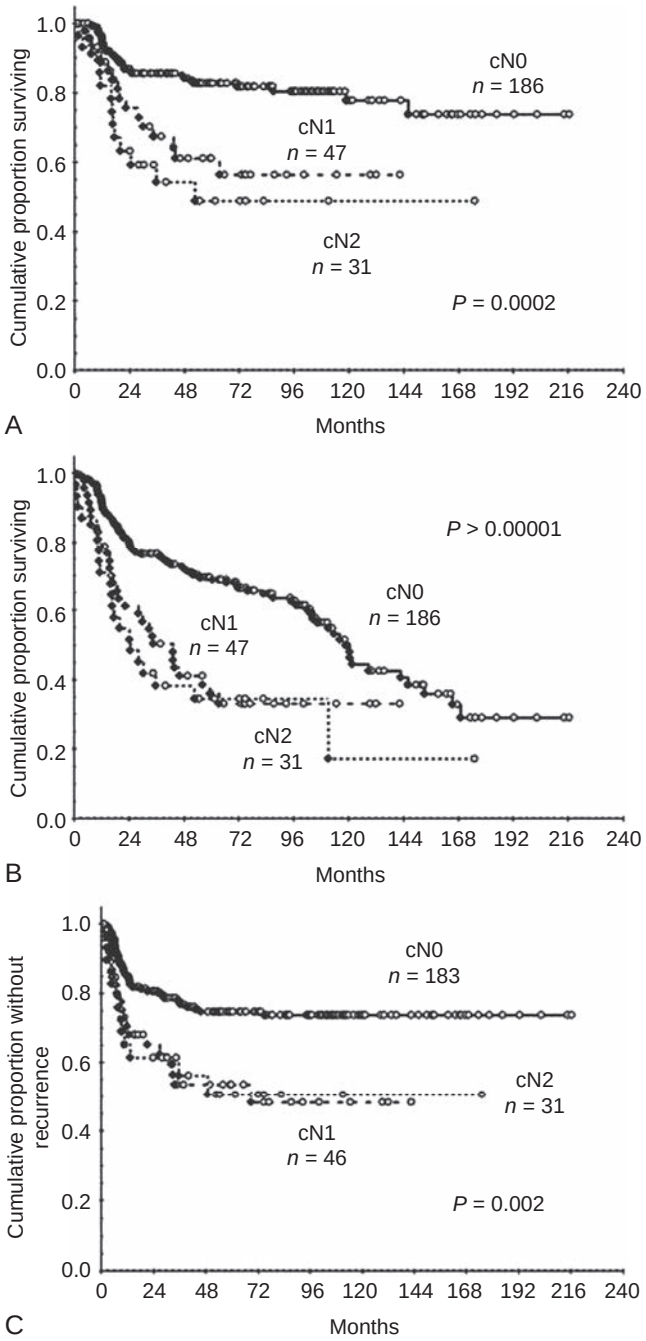
Follow-up

Long-term follow-up of patients after treatment for SCCa of the oral cavity is critical. Appointments should be scheduled based on individual risk of recurrence and the development of second primary tumors. Furthermore, follow-up is dictated by the need for additional treatments associated with morbidity from the surgery and the necessity of providing social and psychological support. These visits should include an annual chest radiograph and measurement of liver enzymes as well as thyroid function tests in patients who have received radiation to the lower neck.

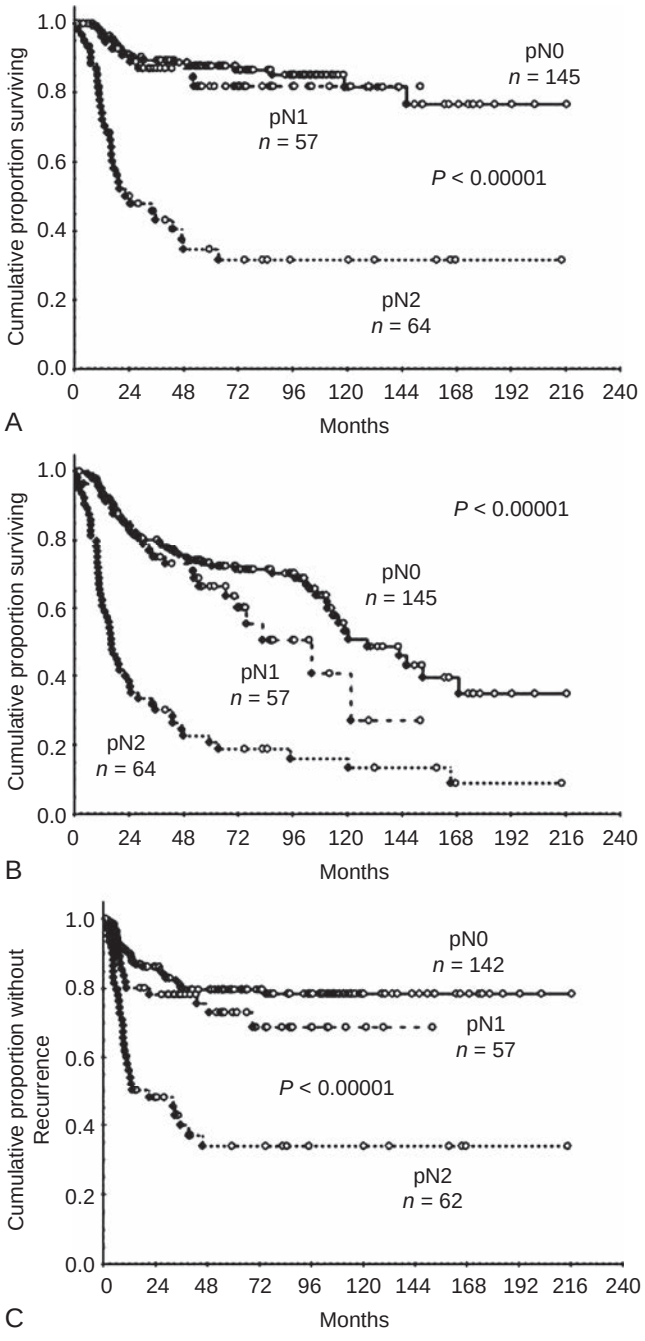
The American Head and Neck Society recommends the following follow-up regimen:

- First year post-treatment: 1 to 3 months
- Second year: 2 to 4 months
- Third year: 3 to 6 months
- Fourth and fifth years: 4 to 6 months
- Beyond 5 years: 12 months

A recent British study on practices of 50 units revealed that all patients were followed monthly for the first year, with 90% having visits every 2 months during the second year. Although variations occurred during the third and fourth years, by the fifth year 6-month visits



• **Figure 28-12** Impact of clinical lymph node stage on **(A)** disease-specific survival, **(B)** overall survival, and **(C)** disease-free interval for patients with squamous cell carcinoma of the oral tongue who received neck dissection. Closed symbols died of disease **(A-B)** and recurrent disease **(C).** Open symbols censored. (Courtesy Greenberg JS, El Naggar AK, Mo V, et al: Disparity in pathologic and clinical lymph node staging in oral tongue carcinoma. Implication for therapeutic decision making, *Cancer* 98[3]:508-515, 2003.)



• **Figure 28-13** Impact of pathologic lymph node stage on **(A)** disease-specific survival, **(B)** overall survival, and **(C)** disease-free interval for patients with squamous cell carcinoma of the oral tongue who received neck dissection. Closed symbols died of disease **(A-B)** and recurrent disease **(C).** Open symbols censored. (Courtesy Greenberg JS, El Naggar AK, Mo V, et al: Disparity in pathologic and clinical lymph node staging in oral tongue carcinoma. Implication for therapeutic decision making, *Cancer* 98[3]:508-515, 2003.)

were universal. Not surprising given the uniformity of results, risk-assessed variations in follow-up were not present.[131]

Ultrasonographic examinations have been added to the armamentarium of imaging devices used for identification of cervical node metastasis for follow-up of patients with head and neck cancer who did not receive neck dissection. In a study published by Hiroshi Yusa and colleagues,[132] 52 patients were examined by ultrasound after the initial primary resection. They accurately diagnosed 24 nodes in 10 patients, while 21 of the nodes were not palpable. Ultrasound examination appears to be useful for follow-up of cervical node metastasis in patients with oral and maxillofacial cancer.

Summary

Squamous cell carcinoma of the oral and maxillofacial region continues to present a challenge in regard to diagnosis, treatment, and patient survival. A number of risk factors have been identified, with others under debate. As our understanding of the genetic changes involved evolves, so may our treatment options. At present, once a patient is diagnosed, a thorough workup must ensue and treatment must be rendered in an expeditious fashion. In the oral cavity, surgery remains the primary modality, with adjuvant therapy (radiation or chemoradiation) as indicated. Close follow-up of patients is required long term in order to identify recurrence or second primary disease and should be tailored based on patient risk factors from the initial cancer as well as the presence of persistent high-risk behaviors.

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29 Melanoma

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Epidemiology

Skin cancer is the most common malignant neoplastic entity affecting humans. These neoplasms can be divided into non-melanoma skin cancers (NMSCs) and malignant melanoma, a malignancy of melanocytes. NMSCs account for 95% of all skin neoplasms and melanomas for the remaining 5%. The American Cancer Society (ACS) estimated that 76,100 cases of melanoma would be diagnosed in the United States in 2014.[1] Approximately 55,000 cases of malignant melanoma were diagnosed in 2004, and 62,190 cases were diagnosed in 2006, indicating a steady increase in incidence. Furthermore from 2006 to 2010, the incidence of melanoma among whites increased by 2.7% per year.[1]

Even though melanoma makes up a small fraction of all skin cancers, it is responsible for the majority (75%) of all skin cancer–related deaths. Malignant melanoma was responsible for approximately 5020 deaths in the United States in 2006, and the ACS estimated 9710 deaths in 2014.[1] Malignant melanoma accounts for approximately 4% of all cancer-related deaths in the United States (Box 29-1). Such staggering statistics make melanoma a significant public health problem in the United States and globally.

The mortality rate and incidence of melanoma have been on the rise since the 1960s; however, in patients whose disease is detected early, 5-year survival appears to be improved.[1] Since the primary mode of therapy (i.e., surgery) has not changed, one can attribute an improvement in disease prognosis to increased public awareness and early detection of these lesions. Unfortunately, this improvement is limited to disease detected at an early stage, for the overall mortality rate secondary to melanoma is still on the rise. This chapter discusses the etiology, risk factors, clinical and histologic characteristics, diagnosis, staging, and management of this potentially fatal skin neoplasm.

Incidence and Etiology

Melanoma is one of a few malignancies in the United States with an increasing incidence. In 1935, the incidence of melanoma was 1:1500; however, by 2008-2010 the incidence had increased to 1:34 in men and 1:53 in women.[1] In considering the epidemiology of melanoma, one must recognize that age is an important risk factor for its development. While the incidence and mortality of melanoma have been increasing steadily, those older than 65 have experienced a decrease in mortality.[2] The lifetime risk of developing melanoma is from birth to death; however, the incidence from birth until the age of 49 is 1:284 men and 1:206 women.[1] The incidence will increase with age reaching an incidence of 1:48 men and 1:113 women for those 70 years of age and older.[1] At present, 25% of individuals affected by this disease are under the age of 40. It is the most common malignancy in women ages 25 to 29 and is second only to breast cancer in women ages 30 to 34.[3] Children make up 1% to 4% of the melanoma patient population, and as has been observed in all patient populations, the incidence of melanoma in children has also increased significantly.[4] Strouse and colleagues reported a 46% increase in the incidence of melanoma in pediatric patients from 1973 to 2001.[5]

Approximately 20% of all melanomas are found in the head and neck region. Fewer than 1% of lesions are found in the oral cavity.[6] These oral lesions, although rare, are associated with a high mortality rate. In general, the torso, back, and head and neck are the most common anatomic sites in men, whereas the extremities are the most common anatomic sites in women.[3] This topographic difference between the two genders has been used to explained the higher incidence of mortality among men in comparison to women; the sites involved in men are considered to have a worse prognosis.[7]

Excessive ultraviolet (UV) light exposure was thought to be the primary etiologic factor in the development of malignant melanomas. The link between Caucasian race and living nearer the equator, such as in Australia or the southeastern United States, is undeniable. However, this link does not provide a biologic explanation for many cases, such as subungual or mucosal melanomas. There is now compelling evidence that, as in all malignant neoplasms,

genetic aberrations play a crucial role in the development of all melanomas. Evidence also links periods of high-intensity UV light exposure, rather than chronic exposure, with the development of melanomas.[8] An exception is the lentigo maligna melanoma. This form of melanoma, as with the NMSCs (i.e., basal cell and squamous cell carcinomas), tends to be associated with more prolonged UV light exposures.

Caucasians are the typical patients who develop malignant melanomas. African-American, Hispanic, and Asian individuals rarely develop the disease. Darker-skinned races tend to have higher mortality rates with melanoma because of the predilection toward developing the acral lentiginous subtype and typically presenting with advanced-stage disease at diagnosis. Women tend to be slightly more affected than men worldwide and have slightly better overall survival than males. The countries with the highest rates of melanoma are Australia and New Zealand, with 37.7 cases per 100,000 men and 29.4 cases per 100,000 women. In comparison, the United States has approximately 6.4 cases per 100,000 men and 11.7 cases per 100,000 women. California, Florida, Texas, New York, and Pennsylvania have the highest estimated rates of new melanoma cases.[1]

Many risk factors for the development of melanoma have been identified (Box 29-2). Generally accepted risk factors are Fitzpatrick skin type 1 or 2 (Table 29-1), red or blonde hair, family history, actinic keratosis, pronounced freckling of the upper back, three or more blistered sunburns before adulthood, and an outdoor job (e.g., lifeguard) for more than 3 years before the age of 20. Individuals with two of these risk factors have an estimated threefold to fourfold increase in incidence of developing a melanoma; those with three or more have an increase incidence of approximately 20-fold.

• Box 29-1 Melanoma Statistics

4% of all cancer deaths
5% of all skin cancers
75% of all skin cancer–related deaths
20% occur in head and neck region
1:34 men, 1:53 women incidence rate in 2008-2010

• Box 29-2 Melanoma Risk Factors

Family history
Fitzpatrick skin type 1 or 2
Three or more blistering sunburns before age 20
Three or more years before age 20 with an outdoor job (e.g., lifeguard)
Actinic keratosis lesions
Pronounced freckling of upper back
Red or blonde hair
Immunosuppression
Older age
Dysplastic nevus syndrome
Congenital nevi >20 mm

These risk factors do not adequately address melanomas in areas not exposed to UV light. These lesions are thought to arise de novo and not as a result of environmental exposure. A family history of melanoma increases the risk by two to eight times. Immunosuppression has also been associated with an increased risk of melanoma development. Older age is also a well-recognized risk factor.[4]

An association between benign melanocytic proliferations (e.g., nevus) and malignant melanoma has clearly been established by Skender-Kalnenas and co-workers.[9] They evaluated 289 cases of thin, malignant melanomas and the association with benign melanocytic proliferations. A nevus was found to be associated with more 50% of lesions, and of these nevi, 56% were dysplastic, 41% were common acquired, and 3% were congenital. The association with melanocytic proliferation was greater with increasing age of the patient.

The majority of melanomas arising in the head and neck region, approximately 70%, have been found to arise in pigmented lesions. This includes pigmented lesions of the oral cavity (Figures 29-1 and 29-2). A change in the character of pigmented lesions, particularly in patients with

TABLE 29-1 Fitzpatrick Skin Type Classification

Type	Characteristics
1	Always burns easily, no immediate pigment darkening, never tans
2	Always burns easily, trace immediate pigment darkening, tans with difficulty and minimally
3	Burns minimally, immediate pigment darkening, tans gradually and uniformly (light brown)
4	Burns minimally, immediate pigment darkening, tans well (moderate brown)
5	Rarely burns, immediate pigment darkening, tans very well (dark brown)
6	Rarely burns, immediate pigment darkening, tans profusely (black)

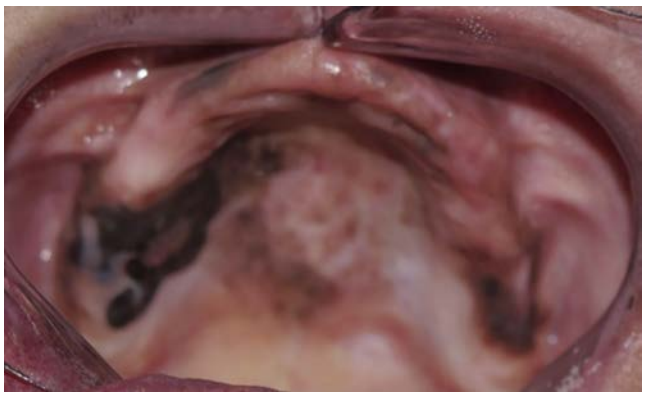


• Figure 29-1 Oral melanoma.

any other risk factors, should raise the level of suspicion for a malignant transformation. All pigmented lesions (Figure 29-3) without an obvious etiology (e.g., amalgam tattoo) in the oral cavity should be biopsied and followed periodically, because the mortality of intraoral melanomas approaches 100%. Congenital nevi larger than 20 mm have a malignant transformation rate of approximately 20%, and lesions associated with dysplastic nevus syndromes have a 100% rate of malignant transformation over an individual's lifetime; removal of these lesions is recommended.[9]



• **Figure 29-2** Oral melanoma.



• **Figure 29-3** Mucosal melanoma involving the hard palate, and bilateral maxillary gingiva.

As a result of the high mortality associated with late melanomas, the index of suspicion with pigmented lesions of the head, neck, and oral cavity should be high. The authors recommend using, and instructing patients to use, the ABCDE and P method of evaluation:

Asymmetry: Irregular "lopsided" lesions
Border: Notched, angled, nonlinear borders
Color: Multiple colors within a lesion or loss of color (amelanotic)
Diameter: Greater than 6 mm lesion or changes in size of existing lesion
Elevation: Changes in height or new-onset nodularity of lesion
Persistence: Lesion that demonstrates persistent erythema, scaling, itching, or ABCDE changes.

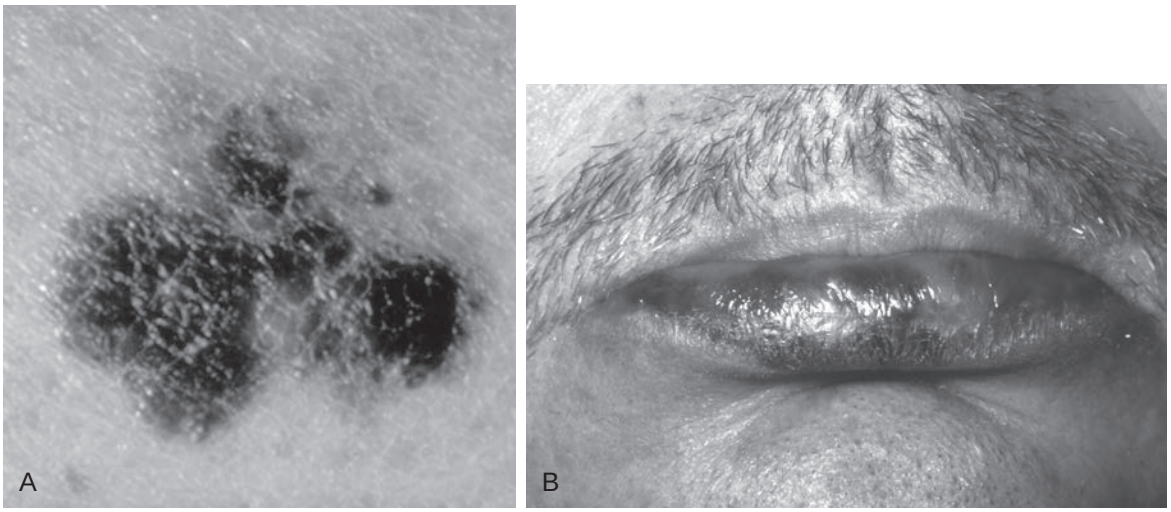
Melanomas have been clinically and histologically subdivided into five types (Table 29-2): superficial spreading (Figure 29-4), nodular (Figure 29-5), lentigo maligna (Figure 29-6), acral lentiginous (Figure 29-7), and desmoplastic. Of all of these melanoma histologic variants, the superficial spreading form is the most common, and lentigo maligna is the least common. Nodular melanoma is considered the most aggressive type of malignant melanoma.

Diagnosis

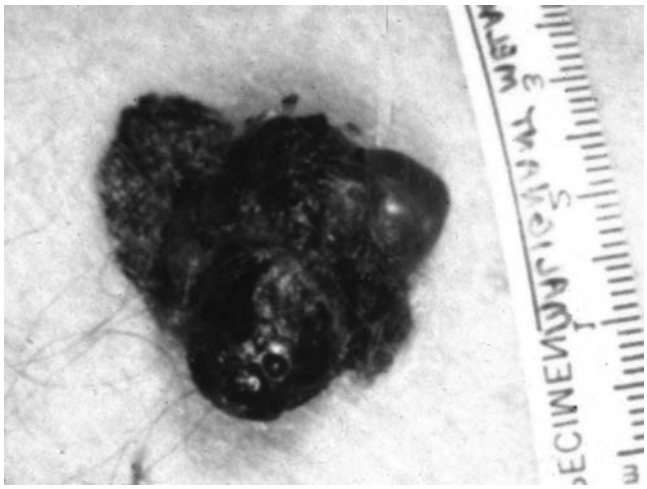
Accurate diagnostic and prognostic information yielded by the pathologic specimen is critical in deciding the patient's treatment options. The "gold standard" for the diagnosis of melanoma remains conventional hematoxylin and eosin (H&E) stained tissue sections (Figure 29-8). The first step in diagnosis of melanoma begins with a biopsy. The ideal biopsy, if the size of lesion permits, is an incisional biopsy with 1- to 3-mm margins and with enough depth to ensure that the lesion is not transected.[10]

TABLE 29-2 Subtypes of Malignant Melanoma

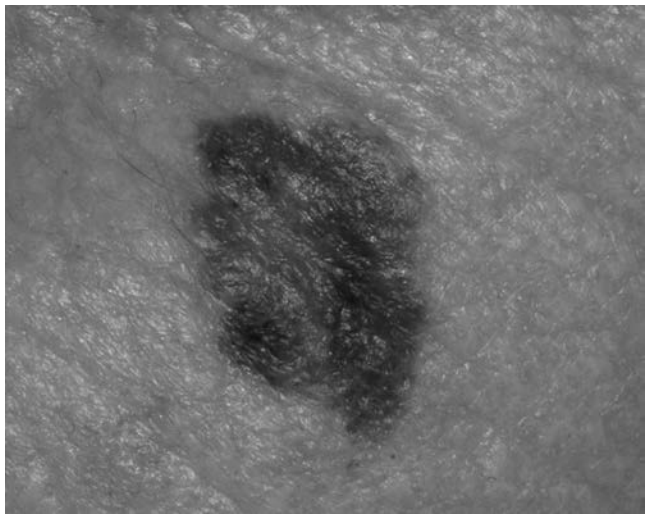
	Prevalence	Age	Clinical Features	Common Sites
Superficial spreading	70% of all; common in light-skinned people	4th-5th decade	Classic ABCDE features; pigmented macule	Head, neck, trunk, back, extremities
Nodular	15% of all	4th-5th decade	Rapid growth; usually from normal skin; poorer prognosis; 5% amelanotic	Head, neck, trunk
Acral lentiginous	10% of all	6th-7th decade	Tan, flat irregular macule; not associated with sun-exposed areas	Plantar, hands, subungal surfaces common
Desmoplastic	Rare; commonly associated with lentigo maligna lesions	6th-7th decade	Sun-exposed areas; pigmented or flesh colored	Head and neck
Lentigo maligna	5%-10% of all; associated with chronic sun exposure	7th-8th decade	Irregular, tan-brown macule	Head and neck; neck and cheeks commonly



• **Figure 29-4** **A,** Superficial spreading melanoma of face. **B,** Superficial spreading melanoma of lips.



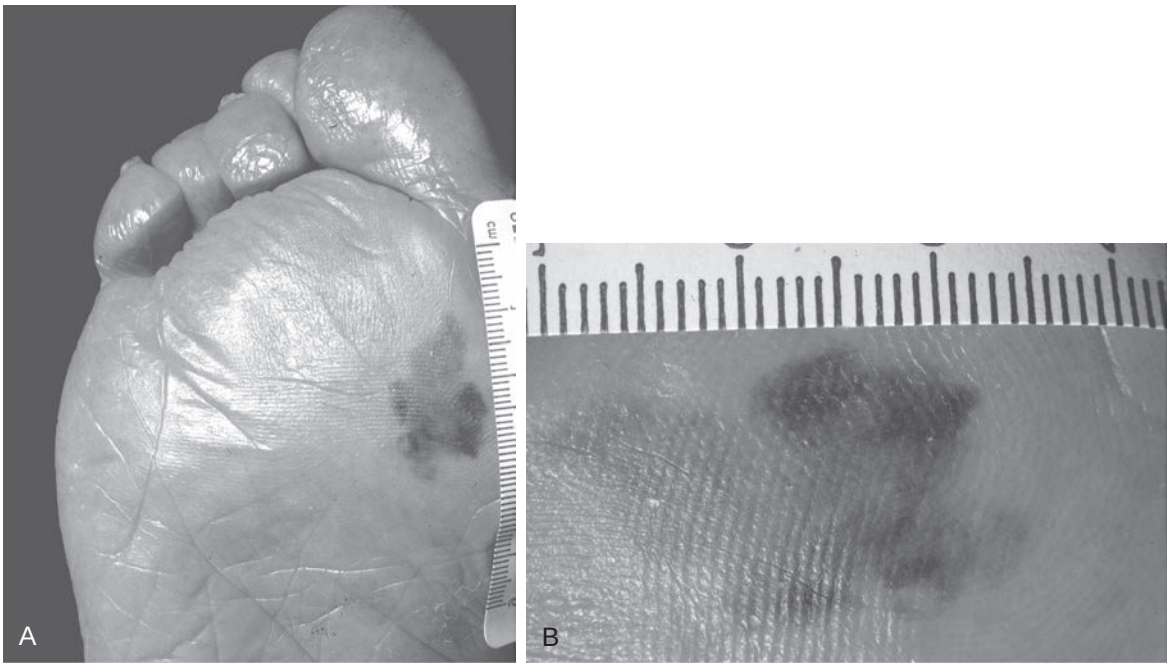
• **Figure 29-5** Nodular melanoma.



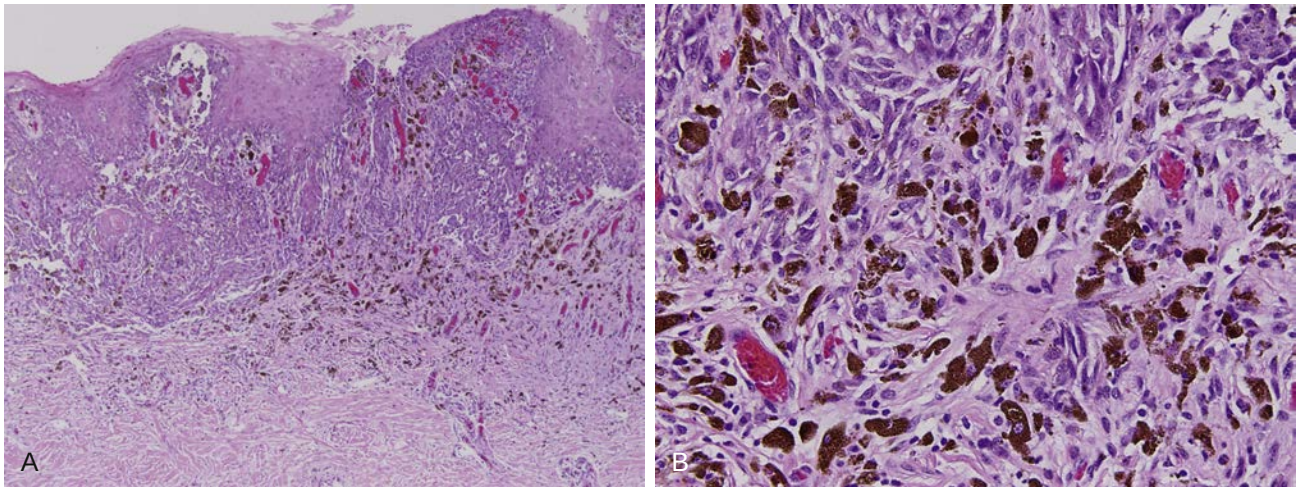
• **Figure 29-6** Lentigo maligna melanoma of cheek.

Typically, the biopsy is performed either by a punch biopsy or scalpel elliptical excision. Performing an excisional rather than incisional biopsy allows for more accurate microscopic staging of the lesion. However, in critical areas of the face or in the presence of large lesions, an incisional biopsy is acceptable.

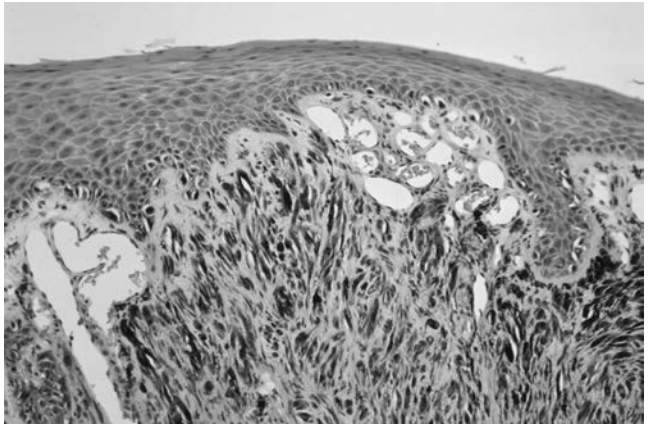
Variation in histologic morphology and similarity to benign melanocytic lesions make the histopathologic diagnosis challenging, even for experienced dermatopathologists. Typically, a diagnosis of melanoma is rendered by consensus among a group of dermatopathologists at their institution.[11] In comparison to other cutaneous and mucosal neoplasms, numerous histologic criteria are used to establish a diagnosis of melanoma, but none alone are adequate enough to establish this diagnosis.[9] The pathologist must include in the pathology report the following information: the melanoma subtype, thickness, anatomic level, presence or absence of microscopic ulceration, positive or negative margins, perineural involvement, perivascular involvement, presence of mitoses, and presence of vertical growth phase (Figure 29-9). Although the staging of cutaneous and mucosal melanoma is discussed later in this chapter, it is worth noting that the previous American Joint Committee on Cancer (AJCC) melanoma TNM staging included only tumor thickness and presence of tumor ulceration in the T category strata, except for T1 lesions, which included Clark's level. However, the revised melanoma staging system released by the AJCC in 2009 included primary tumor mitotic rate, which has replaced Clark's level in the T category strata because of its significance as an adverse predictor of survival (see Table 29-6).[12] The mitotic rate of melanoma has been traditionally evaluated by counting mitotic figures on H&E-stained tissue sections, and averaging the number of mitotic figures per square millimeter (mitoses/mm^2).[13] Today, an area of ongoing scientific research is the incorporation of computer-assisted analysis for calculation of immunolabeled mitoses in order to simplify and standardize this process.[13]



• **Figure 29-7** **A,** Acral lentiginous melanoma of right foot. **B,** Close-up view of **A**.



• **Figure 29-8** **A,** Medium-power hematoxylin and eosin photomicrograph of a mucosal melanoma. **B,** Close-up view of **A**.

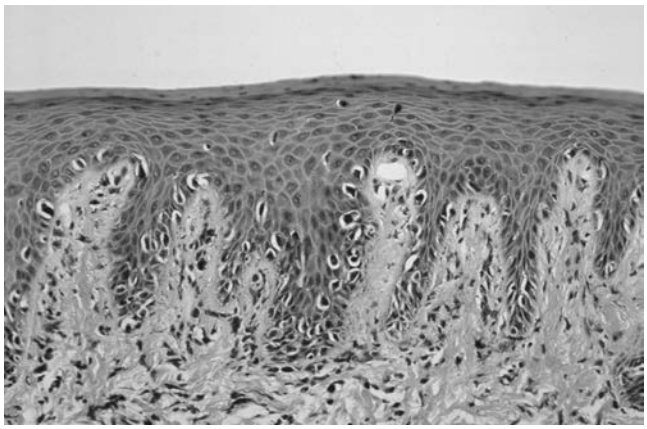


• **Figure 29-9** Medium-power hematoxylin and eosin photomicrograph of a melanoma with vertical growth phase.

Histologically, the features of melanomas are somewhat dependent on the subtype and phase of growth. All melanomas show melanocyte cellular atypia and an altered cellular maturation. Fine intracellular granules, abnormal mitoses, hyperchromatic nuclei, prominent nucleoli, multinucleated giant melanocytes, and abnormal collections of cells ("nests") may all be seen. Various immunohistochemical markers have become useful in the pathologic diagnosis of melanoma (Table 29-3). Of these, S-100 and HMB-45 are the most frequently used melanocytic markers.[14] Anti-HMB-45 is a monoclonal antibody that recognizes the melanosomal glycoprotein gp100; thus positive staining is related to active early melanosome formation.[15] A more sensitive test for the diagnosis of melanoma is the monoclonal antibody to S-100 protein. The sensitivity of

TABLE 29-3 Common Immunohistochemical Markers for Melanoma

	S-100	HMB-45	MART-1/Melan-A and Tyrosinase
Antigen		Cytoplasmic glycoprotein (part of gp 100 premelanosome complex)	Transmembrane protein (melanocyte differentiation antigen)
Cell type	Melanoma cells, nevus components, histiocytes, schwannomas, neurofibromas, nerve sheath tumor cells	Melanoma cells, fetal and neonatal melanocytes, nevus components	Melanocytic cells, perivascular smooth muscle cells, adrenocortical tumors, ovarian tumors
Drawbacks	Not specific for melanoma; cannot differentiate benign and malignant cells	Not specific for melanoma; spindle cell variants do not stain with HMB-45; cannot differentiate benign and malignant cells	Not specific for melanoma; cannot differentiate benign and malignant cells



• **Figure 29-10** Medium-power hematoxylin and eosin photomicrograph of a melanoma with radial growth phase.

S-100 antibody as a melanocytic marker is near 100%. However, the S-100 protein antibody does retain immunoreactivity to tumors that originate from adipocytes, chondrocytes, Schwann cells, and myoepithelial cells.[14] Therefore, the monoclonal antibody against the HMB-45 antigen is more specific for melanocytic neoplasms, with the exception of the spindle cell and desmoplastic melanoma variants.[14]

Microinvasive melanoma and melanoma in situ represent the radial growth phase of these lesions (Figure 29-10). Melanoma in situ is a proliferation of malignant melanocytes restricted to the epidermis. Pagetoid spread (single, atypical cells spread through the epidermis) and atypical, dendritic melanocytes arrayed along the dermoepithelial junction are classic histologic findings seen with melanoma in situ. Melanoma in situ is seen in all major subtypes except the nodular form. Microinvasive melanoma is characterized by epidermal involvement with *microscopic* extension into the papillary dermis. Microinvasiveness can be defined as follows: the largest dermal nest of cells is smaller than the largest epidermal nest of cells; and no dermal mitoses are present. Frequently a lymphocytic infiltrate is also present as well.[16]

When a melanoma breaches the basement membrane and involves the underlying dermis, it is said to be in a vertical growth phase (see Figure 29-9). In this phase the lesion has metastatic potential and thus a poorer prognosis. The vertical phase is characterized by at least one dermal mitosis or one or more dermal cell nests larger than the largest epidermal cell nest. Table 29-4 describes the basic histologic features of the various subtypes of malignant melanoma.

The growth characteristics of melanomas typically manifest with a long horizontal radial growth phase. These early lesions tend to spread within the epithelium without violating the basement membrane and penetrating into the underlying tissues. Late lesions tend to penetrate the basement membranes, grow vertically, and invade deeper tissues. This vertical growth phase was noted by early investigators to have profound significance in predicting overall survival and in directing treatment of the disease. In 1969 and 1970, Clark and Breslow, respectively, developed histologic classifications based on the depth of the lesion alone[17,18] (Table 29-5). Clark's anatomically based system has been replaced in the current staging protocols in favor of Breslow's millimetric depth system. Breslow's classification, which measures from the granular cell layer to the depth of the tumor, has been shown to have better predictive value and less variability between observers. Melanoma depth has also been shown to have a strong relationship with regional lymph node metastasis and distant metastatic disease. These prognostic implications of lesion depth make it one of the major prognostic indicators of melanoma, and thus it is currently a major part of the AJCC staging system for melanoma.[12]

Several lesions can be mistaken for melanoma. These include pigmented basal cell carcinomas, seborrheic keratosis, nevi, lentigines, and dermatofibromas. Clinicians should have a high index of suspicion for melanoma, and excisional biopsies should be performed. Improved rates of survival were demonstrated in patients who had excisional (8.9%) versus incisional (25%) biopsies.[19] Delay in definitive treatment, altered local host factors, and an increased time for lesion dissemination have been postulated as reasons for the

TABLE 29-4 Histologic Features of Melanoma

	Superficial Spreading	Lentigo Maligna	Acral Lentiginous	Nodular	Desmoplastic
Radial growth pattern	Pagetoid	Lentiginous	Lentiginous	Not present	Not present
Characteristic radial phase cell type	Epithelioid	Spindle cell, epithelioid	Spindle cell, epithelioid, dendritic	N/A	N/A
Epidermal characteristics in radial phase	Normal or hyperplastic	Atrophic	Hyperplastic	N/A	N/A
Characteristic vertical phase cell type	Epithelioid	Spindle cell, epithelioid	Spindle cell, epithelioid	Epithelioid	Fibroblastic, spindle cell

TABLE 29-5 Depth Classifications and Associated Survival Rates

Clark's Level	Clark's Classification	Breslow's Depth (mm)	Clark's 10-yr Survival	Breslow's 10-yr Survival
Within epithelium	Level I	N/A	96%	N/A
Penetrates papillary dermis	Level II	0.0-0.75 mm	96%	98%
Fills papillary dermis	Level III	0.76-1.69 mm	90%	89%
Penetrates reticular dermis	Level IV	1.70-3.59 mm	67%	67%
Invades subcutaneous tissue	Level V	>3.6 mm	26%	43%

decreased survival rate. Shave biopsies should not be performed, because they do not indicate the depth of lesion involvement. As previously stated, biopsies with 2- to 3-mm margins of surrounding tissue extending down to the underlying fascia are preferred. Incisional or punch biopsies should only be considered with very large lesions.

Definitive excision of the lesion and the extent is a source of debate. There have been five multicenter prospective randomized clinical trials which have evaluated the relationship between excision margin status and risk of local recurrence, as well as the impact of margin status on survival in patients with cutaneous melanoma.[20] These trials include the World

randomized cohort of 612 melanoma patients. In this trial, patients were stratified into either a Breslow depth < 1 mm or a Breslow depth 1 to 2 mm. The investigators compared 1-cm versus 3 to 5 cm excision margins. With a greater than 15-year follow-up, the investigators did not identify a statistically significant difference in distant recurrence rates and survival rates based on these margins of excision. Of note, patients managed with a 1-cm margin of excision had

melanoma that are 2 mm or greater in thickness. The investigators in this study identified that for tumors that were 2

mm or greater in thickness a 1-cm margin was associated with a statistically significant increase in locoregional recurre

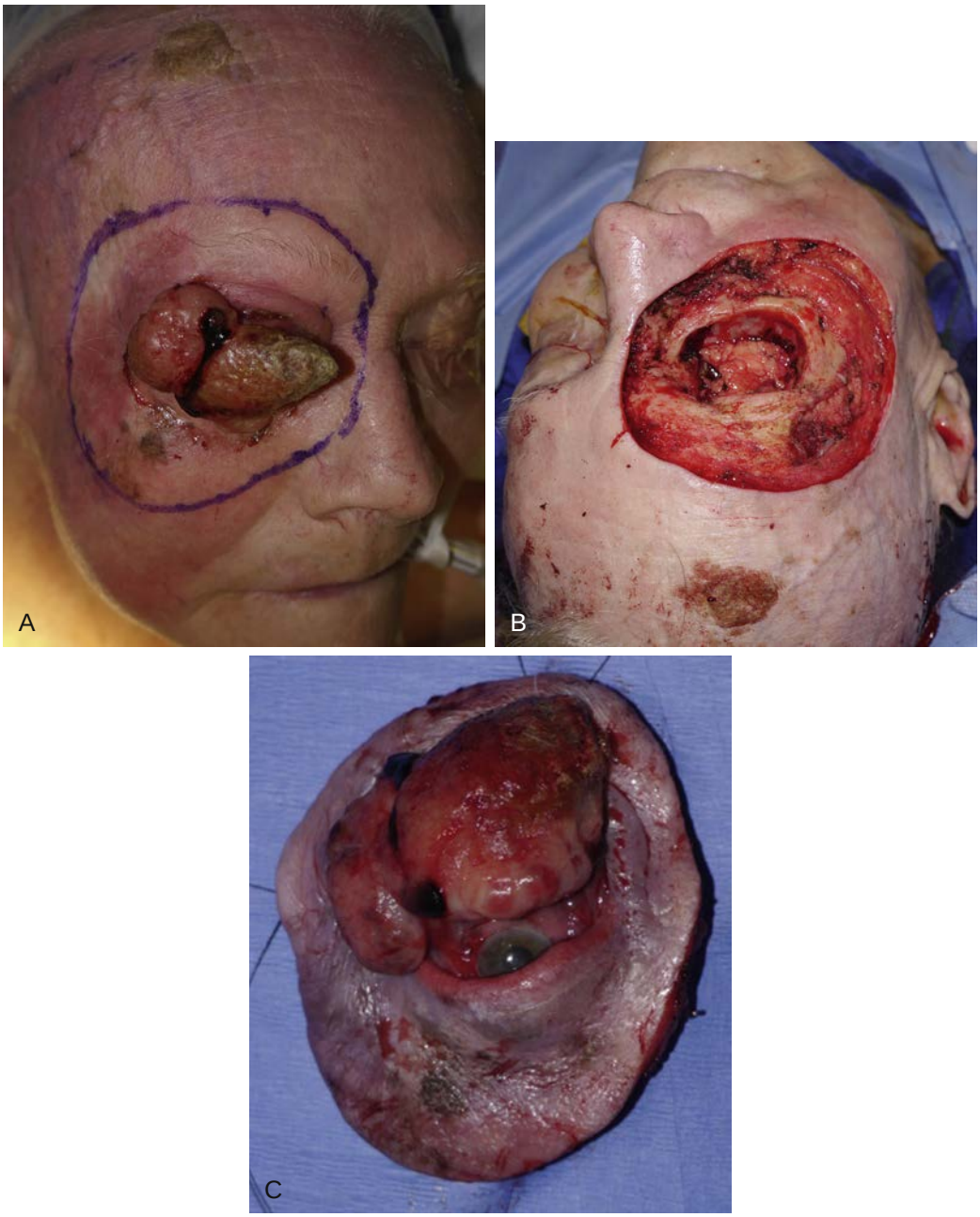
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neck with tumors ≤2 mm Breslow thickness; 2-cm versus 5-cm excision margins were compared. This multicenter trial could not identify a statistically significant advantage

stratified by tumor thickness and presence/absence of ulceration. The investigators reported that the 10-year survival

posed,

local recurrence is not affected by excision margins, but is by lesion thickness. The WHO proposes that 1-cm margins should be used for lesions less than 1 mm in thickness, and



• **Figure 29-11** **A,** Patient with upper eyelid cutaneous melanoma with a tumor thickness of 8 mm underwent resection with a 3-cm margin of excision including exenteration. **B,** Final defect. **C,** Clinical photo of specimen. (Photos courtesy Dr. Melvyn Yeoh, Shreveport, LA.)

3-cm margins should be used for lesions greater than 1 mm (Figure 29-11).[21] The authors feel that 1- to 2-cm margins, with appreciation of facial aesthetic subunits and adjacent vital structures, are adequate in all except scalp lesions. Scalp lesions have been shown to have higher rates of in-transit metastasis, and it is recommended to take wider margins (3-4 cm) with these resections.

Management of Regional Disease

The treatment of choice for melanoma is surgical excision. In most cases wide local excision adequately controls local disease. Melanoma is believed to initially metastasize via spread to regional lymphatics. At the time of initial diagnosis, 82% of patients have localized disease and 11% of patients are found to have spread to regional sites.[27,28] Accurate assessment of the regional node status is a major prognostic factor for overall survival and locoregional control; it also plays an important role in directing therapy. The management of regional lymphatics is a topic of considerable debate in the literature—in particular, management of patients with a clinically negative neck.

In patients with clinically positive lymph nodes, or a positive sentinel lymph node biopsy (SLNB), the suggested

therapy is a therapeutic lymphadenectomy (removal of *all* nodes in the involved drainage basin). This approach may be curative or at least decrease the morbidity associated with a regional recurrence. The morbidity of the dissection and the ability of the patient to tolerate the procedure must be taken into account before a therapeutic neck dissection. In the case of head and neck cutaneous melanoma, a positive SLNB will allow for appropriate escalation of treatment, such as regional lymph node dissection, addition of adjuvant therapies, and/or enrollment in a clinical trial. Performing an SLNB is not indicated for patients presenting with a lymph node with clinical features highly suggestive for regional disease. In these cases, a fine-needle aspirate is typically performed, and also for patients with disseminated disease.[29]

Elective lymph node dissection (ELND) is based on the same physiologic and anatomic rationale as the therapeutic neck dissection. However, prospective randomized trials involve regional lymphatics, the potential morbidity of neck dissections, and the success of sentinel lymph node biopsies have effectively limited the usefulness of elective neck dissections.

SLNB has been used successfully in the treatment of melanoma and is currently the standard of care for evaluating the regional lymphatics in thin lesions and with clinically negative necks.[34,35] Most centers use the following indications for SLNB: Breslow thickness 1.0 mm, Clark level IV, ulceration or regression, subungual location, and no clinical or radiographic evidence of lymph node metastasis. The concept of SLNB is based on studies showing that lymphatic drainage is predictable and the initial nodes involved fall within a specific nodal basin. In theory, if the sentinel node(s) have not been involved with metastatic disease, the other remaining "downstream" nodes in that basin will not harbor disease. A therapeutic lymphadenectomy is completed if a patient is found to have a positive sentinel node.

Sentinel node mapping requires a coordinated effort by the surgeon, pathologist, and nuclear medicine physician. Currently, the most predictable way to identify sentinel nodes is by using a combined vital blue dye (sulfan blue) and technetium-99m sulfur colloid mapping technique. The periphery of the lesion is injected with the vital dye, lymphoscintigraphy is performed, and the markers are given time to distribute into the regional nodes. A conservative incision is made to access the nodal basin identified by the prior lymphoscintigraphy. The incision is placed so the surgeon is able to access the neck or parotid region for a therapeutic lymphadenectomy, if the sentinel node biopsy is positive. Intraoperatively, dye staining of the lymphatics and verification with a gamma probe are used to identify the sentinel node(s). The pathologist then performs serial sections on the collected lymph nodes. The protocol used to evaluate sentinel nodes varies according to the institution. However, some combination of serial sectioning, hematoxylin and eosin staining, and immunohistochemical stains is generally used. Serial sectioning is work-intensive for the pathologist and, although better than standard node evaluation techniques, still examines only less than 1% of the submitted node. Recently, molecular analysis techniques have been investigated and have been found to increase the accuracy of SLNB techniques while decreasing the workload involved with serial sectioning. These techniques will likely play a more important role in the future of SLNB analysis, but they should not be used currently in management decisions and escalation of treatment.

Positivity with SLNB has been reported to occur in 17% to 19% of cases of trunk or extremity melanoma, and 10% of head and neck cases. It is important to mention that in cases of head and neck melanoma, SLNB allows for identification of microscopic nodal disease and subsequent escalation of treatment.[36] The identification of microscopic nodal disease via SLNB has been shown to improve regional disease control. However, a Surveillance Epidemiology and End Results (SEER) database cohort analysis of 7266 patients published in 2014 was unable to demonstrate a significant association between SLNB and improved disease-specific survival for patients with head and neck melanoma.[28]

Staging of Melanoma

It is important that all providers use the same criteria and definitions in the literature and in a patient's management. The nomenclature and criteria for discussing melanomas have been provided by the AJCC.[12] Staging is important in the stratification of disease, in the prognostication of mortality, and in directing therapy. It was recognized that improvements in the staging of melanoma could be made by applying evidence-based methods to create and then validate a staging system for melanoma. Buzaid and associates[37] published a paper pointing out the inadequacies of the preexisting AJCC staging system for melanoma. The Melanoma Staging Committee of the AJCC was formed in 1998.[37] It was made up of experts from all relevant medical specialties and included leaders from most of the major melanoma treatment centers. An additional modification of the existing staging system was included in the 7th edition of the AJCC Cancer Staging Manual in their paper published in 2009.[12] The previous staging system in the 6th edition of the AJCC Cancer Staging Manual emphasized that thickness and ulceration are the predominant predictors of survival and that depth of invasion matters only in thin (≤1 mm) lesions. In the 7th edition of the AJCC Cancer Staging Manual, primary tumor mitotic rate has replaced Clark's level of invasion as the main criterion differentiation subtant metastasis and the presence of elevated lactate dehydrogenase (LDH) levels were also found to be prognostic and

TABLE 29-6 T Classification of Melanoma

Tumor Thickness	Tumor Ulceration Status/ Mitoses
T1 ≤1.0 mm	a: Without ulceration and mitosis <1/mm^2
	b: With ulceration or mitoses ≥1/mm^2
T2 1.01-2.0 mm	a: Without ulceration
	b: With ulceration
T3 2.01-4.0 mm	a: Without ulceration
	b: With ulceration
T4 >4.0 mm	a: Without ulceration
	b: With ulceration

TABLE 29-7 N Classification of Melanoma

Nodal Metastases	Nodal Mass
	a, micrometastasis*; b, macrometastasis†; c, in-transit/satellite(s) with (–) nodes
N0	
0 nodes	n/a
N1	
1 node	a, b
N2	
2-3 nodes	a, b
N3	
≥4 nodes, matted nodes, in-transit or satellite(s) with (+) nodes	a, b, c

*Micrometastasis diagnosed after sentinel node biopsy or elective lymphadenectomy.
†Macrometastasis with clinically detectable nodes, confirmed with therapeutic lymphadenectomy or with gross extracapsular spread.

TABLE 29-8 M Classification of Melanoma

Metastasis Site	Serum LDH
M0	
0 sites	N/A
M1a	
Distant skin, subcutaneous tissue or node metastasis	Normal
M1b	
Lung metastases	Normal
M1c	
Any other visceral metastases	Normal
Any distant metastasis	Elevated

TABLE 29-9

Clinical Stage	T Classification	N Classification	M Classification
0	T in situ	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
III	Any T	Any N	M0
IV	Any T	Any N	Any M

*Includes microstaging of primary melanoma and metastasis evaluation; *after* completed primary excision and clinical evaluation for metastasis.

were included in the staging system.[10,38,39] Patients with an elevated LDH are all categorized as M1c irrespective of all other M-category strata. Tables 29-6 through 29-10 describe the current AJCC (TNM) staging system for cutaneous malignant melanoma.

Today, the role of positron emission tomography (PET), and other advanced imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI), for staging of malignant melanoma has yet to be defined. Wasif and colleagues evaluated use of staging studies in 25,643 patients with cutaneous melanoma using the SEER database.[36] Based on their analysis, in the year 2000, 4.2% of patients with early-stage cutaneous melanoma had a cross-sectional imaging study performed, and in 2007 this had increased to 12.2%. The 2012 National Comprehensive Cancer Network (NCCN) guidelines for staging of cutaneous melanoma do not recommend any cross-sectional imaging studies for stage I through IIC disease. They do, however, state that a chest x-ray is optional for patients with stage IIB or IIC disease.[37] Based on their recommendation, cross-sectional imaging studies (e.g., PET, MRI, CT) are optional for patients with stage III or stage IV disease. Similarly, the American Academy of Dermatology does not recommend any imaging study for patients with a primary melanoma with a thickness less than 4 mm.[10,36] PET has been found to have a lower sensitivity for the detection of occult nodal disease when compared to SLNB.[10,36] In summary, cross-sectional imaging studies should be reserved for patients with advanced-stage disease (stage III/IV).

TABLE 29-10 Pathologic Staging of Melanoma

Pathologic Stage	T Classification	N Classification	M Classification
0	T in situ	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a		
IIA	T2b	N0	M0
	T3a		
IIB	T3b	N0	M0
	T4a		
IIC	T4b	N0	M0
IIIA	T1→4a	N1a	M0
	T1→4a	N2a	M0
IIIB	T1→4b	N1a	M0
	T1→4b	N2a	M0
	T1→4a	N1b	M0
	T1→4a	N2b	M0
	T1→4a	N2c	M0
	T1→4b	N2c	M0
IIIC	T1→4b	N1b	M0
	T1→4b	N2b	M0
	Any T	N3	M0
IV	Any T	Any N	Any M

Includes microstaging of primary melanoma and nodes after lymphadenectomy; Stage 0 and IA do not require pathologic evaluation of nodes.

In summary, appropriate therapy is based on accurate staging and, in the case of malignant melanoma, consists of assessment of histologic features of the primary tumor and measurement of serum LDH level. As with any neoplastic disease process, assessment of the patient's performance status will aid in risk stratification of patients for surgery and other adjuvant therapies.

Treatment

As mentioned previously, surgery is the mainstay of current melanoma treatment. Wide local excision of small, thin lesions is curative in many cases. SLNB with therapeutic lymphadenectomy, when indicated, is the current standard of care for the surgical management of melanoma in the head and neck. There is some question as to the efficacy of this approach in extremity melanomas, related to the morbidity of groin or axillary lymphadenectomy, without a benefit in overall survival. The current literature also debates the therapeutic value of many current treatments, including sentinel node biopsy (as a staging intervention), radiation therapy, chemotherapy, molecular targeted therapy, and interferon alfa therapy.

SLNB is not used as a therapeutic modality in itself. It is currently used to direct therapy (surgical vs. adjuvant). Gutzmer and colleagues[40] described three theories as to how SLNB itself may affect prognosis. The first, which improves prognosis, is that micrometastatic disease is removed from the regional nodal basin. This implies that early metastatic disease is primarily within the lymphatics, and the disease then spreads to distant sites after some time. The second, which does not change overall prognosis, is that lymphatic and hematogenous metastasis occur simultaneously and that lymphatic micrometastasis found in SLNB indicates aggressiveness of the tumor (aka the marker hypothesis). The last theory, which worsens prognosis, is that malignant cells are removed from an immunologically active environment, therefore impairing the body's response to the malignant cells. The results of their paper showed an improvement in locoregional control, but no advantage in death from distant metastasis. Their conclusions favored the marker hypothesis.

The Multicenter Selective Lymphadenectomy Trial (MSLT-I) raised the question of whether SLNB was beneficial in terms of survival.[41] The trial randomized patients with intermediate-thickness melanoma (1.2–3.5 mm) to undergo SLNB and therapeutic lymphadenectomy. The remaining patients had a wide local excision and observation. Regional recurrences were then treated with therapeutic lymphadenectomy. The trial showed that SLNB is accurate in identifying patients who may benefit from adjuvant therapy.[41] Regardless of any positive or negative therapeutic effects, SLNB has been shown to be invaluable in prognosis and is the standard of care in the evaluation of nodal disease in melanoma.

Melanomas have been traditionally thought to be a radioresistant tumor. The facts dispute this assumption. Although not recommended as a primary treatment modality, the use of adjuvant radiation therapy for regional disease is well supported in the literature. The use of radiation does improve local control of disease. However, there have been no compelling data showing an increase in overall survival.[42,43] The ideal radiation dose schedule has yet to be defined. Ballo and co-workers[43] have used a hypofractionated schedule in their practice consisting of 30 Gy in five 6-Gy fractions twice per week for 2.5 weeks. The authors explain that patients who present with extracapsular extension, disease in more than 3 nodes, nodes ≥3 cm, recurrent disease, and cervical location are more appropriate candidates for adjuvant radiotherapy.

Systemic therapy in the management of malignant melanoma is essentially in an adjuvant or palliative role. The role of conventional chemotherapy has yet to be defined, and also has yet to show any significant survival benefits. Dacarbazine and temozolomide are the chemotherapeutic agents of choice. Dacarbazine (DTIC, Bayer Pharmaceuticals, West Haven, CT) is an intravenous DNA alkylating agent, whereas temozolomide (Temodar, Merck & Co., White House Station, NJ) is an oral DNA alkylating agent. Both of these agents have shown poor response rates when used for single-agent therapy. A phase III clinical trial reported by Middleton and colleagues demonstrated equal efficacy of dacarbazine and temozolomide from a survival perspective; however, because temozolomide is an oral alternative that has been shown to have a better overall response, one can argue for selective temozolomide over dacarbazine.[44] Nevertheless, one must not forget that for cases of advanced-stage disease or metastatic melanoma, immunotherapy (see later discussion) offers better outcomes than do conventional chemotherapeutic agents.

Today, immunotherapy and cytotoxic chemotherapy are the pharmacologic agents of choice for patients with advanced disease (stage III/IV) or those with disseminated disease.[45] Interferon alfa-2b is the primary systemic agent in use today for adjuvant therapy in patients with advanced disease. There is debate as to the effectiveness of this agent; and concluded there was a benefit in disease-free survival, but that there was no change in overall survival. Because of data such as these and the toxicities (e.g., fatigue, cognitive dysfunction, depression, suicide risk) associated with HDI, some practitioners may not recommend interferon therapy. In the United States, although debated, interferon alfa-2b is currently recommended for use in high-risk melanoma as an adjuvant therapy. The rationale for the use of HDI following disease resection is based on histologic and animal model evidence that interferon alfa-2b induces tumor regression via an indirect immunomodulatory mechanism.[49,50] These studies and others have shown that the effect of alfa-2b interferon is based on modulation of the host immune system, rather than via a direct antitumor mechanism.[51] IL-2, a cytokine-based agent, is used to stimulate the proliferation and activity of T cells in hopes of inducing tumor regression.[52,53] Today, recombinant IL-2 is recommended as a first-line agent for unresectable stage IV melanoma with a good performance status and no evidence of or treated central nervous system (CNS) disease, irrespective of BRAF mutation status.[52] This intravenous agent is marketed under the trade name Proleukin (aldesleukin, Prometheus Laboratories, San Diego).

Because of the rise in the incidence of melanoma, current statistics such as a 20% 5-year survival for patients with advanced melanoma and unresectable tumors, and the resistance of melanoma to radiation therapy and conventional chemotherapy, there has been significant scientific effort to identify pharmacologic agents that can directly induce or substitute the host's antitumor immune mechanism.[51] In the previous edition of this chapter, the treatment of melanoma with systemic therapy was limited to interferon alfa-2b for adjuvant therapy, and interleukin-2 (IL-2) and the aforementioned DNA alkylating agents (i.e., dacarbazine and temozolomide) for metastatic disease.[43]

However, today there are three new systemic agents that are approved for the treatment of melanoma: ipilimumab, an anti-CTLA4 monoclonal antibody, pegylated-interferon-alpha 2b for adjuvant therapy; BRAF inhibitor for patients with metastatic melanoma harboring $BRAF^{V600}$ mutation; and trametinib, a specific inhibitor of mitogen-activated protein kinase (MEK).

In the previous edition of this text, we described an ongoing phase III clinical trial involving the aforementioned anti-CTLA4 monoclonal antibody, ipilimumab, which was administered with or without a glycoprotein 100 (gp100) peptide vaccine for patients with unresectable stage II or IV melanoma. In 2010, Hodi and colleagues reported in the *New England Journal of Medicine* the results of this phase III trial.[54] Of the 676 patients enlisted in the trial, the median overall survival was 10 months among patients receiving ipilimumab plus gp100, as compared to 6.4 months for patients receiving gp100 alone. In 2011 the FDA approved ipilimumab (Yervoy, Bristol-Myers Squibb, New York) for treatment of metastatic melanoma.[55] Today, ipilimumab is recommended as a first-line agent in the treatment of unresectable BRAF mutation–negative tumors in patients with a poor performance status and untreated CNS disease.[51] For the case of BRAF mutation–negative tumors in a patient with a good performance status with absent/treated CNS disease, ipilimumab is considered a second-line agent, second to IL-2.[51]

Pegylated interferon alpha-2b (pIFN alfa-2b) is interferon alfa-2b that is conjugated to polyethylene glycol in order to reduce its rate of absorption and rate of clearance, while also increasing its immunogenicity.[52] In 2011 the FDA approved subcutaneous pegylated interferon alfa-2b (Sylatron, Merck & Co., Whitehouse Station, NJ) as a treatment for melanoma with microscopic nodal involvement after surgical resection. The Society for Immunotherapy of Cancer consensus statement on tumor immunotherapy, released in 2013, recommends standard interferon alpha-2b for patients with macroscopic nodal disease.[52] In summary, pegylated interferon alfa-2b could be considered in patients with microscopic nodal disease after surgical resection, whereas standard interferon alfa-2b should be used in patients with macroscopic nodal disease (N1b and N2-N3 disease).[45,51]

About half of melanomas harbor a mutation in BRAF; the most common genotypes are $BRAF^{V600E}$ and $BRAF^{V600K}$.[56,57] Detection of $BRAF^{V600}$ mutations has become routine in the evaluation of patients with advanced

disease or metastatic melanoma. Historically the presence of metastatic CNS disease is associated with lack of benefit from systemic therapies; however, today mainly BRAF inhibitors have shown evidence of benefit from systemic therapy if the tumor is BRAF mutation positive.[51] Today, two compounds are available within the selective BRAF inhibitor class: vemurafenib (Zelboraf, Genentech, South San Francisco, CA) and dabrafenib (Tafinlar, GlaxoSmithKline, London). The aforementioned mutations are point mutations causing $BRAF^{V600E}$ and $BRAF^{V600K}$ kinases to be constitutively active, resulting in sustained MAPK signaling and perpetual cell growth.[57] The BREAK-1 (phase I),[58] BREAK-2 (phase II),[59] BREAK-3 (phase III),[60] and BREAK-MB (phase II)[61] clinical trials have proven the safety of dabrafenib in patients with metastatic melanoma. Furthermore, a benefit of dabrafenib was identified for patients with unresectable stage III/IV BRAF mutation positive tumors in improving progression-free and overall patient survival. For instance, in the BREAK-3 trial an objective response rate with dabrafenib was determined to occur in 53% of patients, whereas with dacarbazine only 19% of patients had an objective response to treatment. Furthermore, these trials identified a higher response rate in the $BRAF^{V600E}$ positive tumors. Similarly, trametinib (GSK1120212, GlaxoSmithKline Pharmaceuticals, Philadelphia, PA), an oral MEK inhibitor, has also been found to improve overall survival in patients with metastatic melanoma with a BRAF mutation as a single agent when compared with conventional chemotherapy, dacarbazine.[62] In summary, today oncologists have at their disposal several pharmaceutical agents to combat disseminated melanoma. One must also not overlook the necessity and value of recommending a clinical trial for patients with unresectable disease.

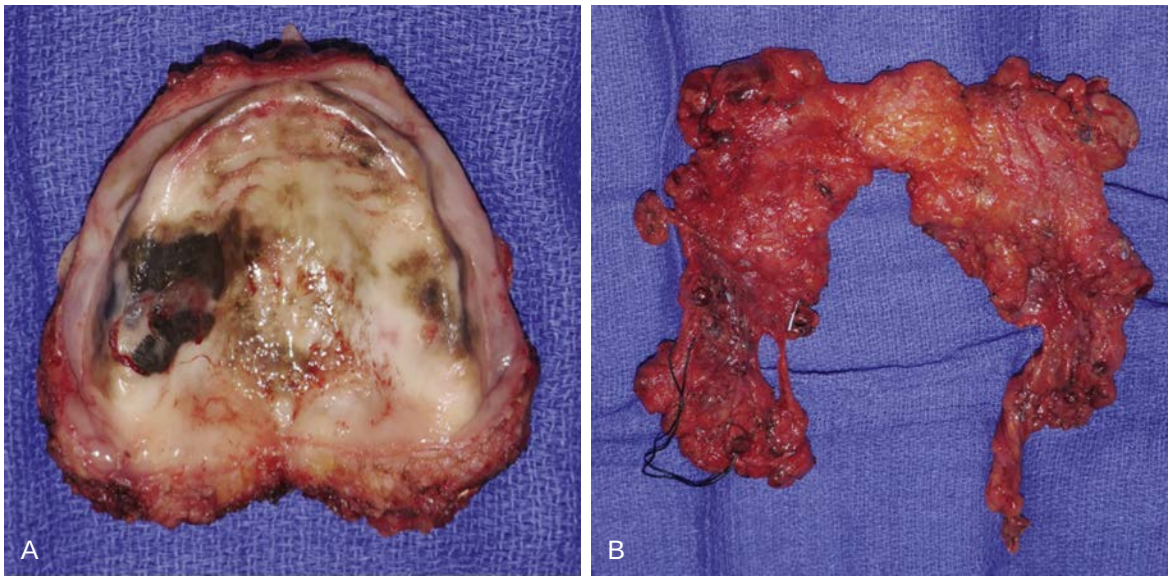
Oral Mucosal Malignant Melanoma

As previously discussed, melanoma is a cancer of melanocytes. Within the skin, melanocytes are located within the stratum basale of the epidermis, and their function is to produce melanin, a vital pigment that serves to protect the skin from damage from ultraviolet rays. However, melanocytes have been identified in extracutaneous tissues, including the nasal cavity, paranasal sinuses, oral cavity, larynx, tracheobronchial tree, uvea, esophagus, gallbladder, rectum, anal canal, vagina, and cervix.[63] Given that these anatomic sites are sun-shielded, the true function of melanocytes within these tissues is not well understood. Some studies have described non-pigment functions of melanocytes that include phagocytosis, antigen presentation, and cytokine production.[63-65] Therefore, the current thought is that melanocytes could play a role in the innate immune system within mucosal surfaces, as well as the skin. Similar to skin melanocytes, these extracutaneous melanocytes have the potential to become cancerous. However, mucosal malignant melanomas are still considered rare neoplasms, representing 1.4% of all melanomas.[63] The head and neck is the most common location of mucosal melanomas, accounting for 25% to 50% of cases, with the nasal cavity being the most common head and neck subsite.[66] Although these lesions are rare, they are unfortunately associated with a high mortality rate (5-year survival is around 25% irrespective of tumor stage), which is indicative of their highly aggressive biologic behavior.

TABLE 29-11 AJCC-TNM Classification and Clinical Staging of Mucosal Melanoma

Primary Tumor			
T3	Mucosal disease		
T4a	Moderately advanced disease. Tumor involving bone, deep soft tissue, cartilage, or overlying skin		
T4b	Very advanced disease. Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures		
Regional Lymph Nodes			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastases		
N1	Regional lymph node metastases present		
Distant Metastasis			
M0	No distant metastasis		
M1	Distant metastasis present		
Clinical Stage			
Stage III	T3	N0	M0
Stage IVA	T4a	N0	M0
	T3-T4a	N1	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Oral mucosal malignant melanoma is typically detected on routine oral evaluation. It is worth noting that whereas fewer than 2% of cutaneous melanomas are amelanotic, within the oral cavity 25% to 75% of cases are amelanotic.[66,67] With regard to the distribution of oral and sinonasal mucosal melanoma, 48% of lesions will occur in the oral cavity and 52% in the sinonasal region.[68,69] With sinonasal mucosal melanoma, 84% of cases will involve the nasal cavity. Within the oral cavity, Hicks and colleagues reviewed 703 cases of oral mucosal melanoma and reported that 32% of cases involved the palate, making the palate the most commonly involved subsite followed by maxillary gingiva.[69] The diagnosis of mucosal melanoma of the head and neck, unlike its cutaneous counterpart, should include an incisional biopsy. The reason we recommend an incisional biopsy is that the depth of invasion and microscopic features of a mucosal melanoma are not part of the staging process (Table 29-11). Therefore, preserving the periphery of the lesion could aid in determining surgical margins at the time of tumor extirpation. Furthermore, histologic diagnosis is



• **Figure 29-12** **A,** Specimen following bilateral subtotal maxillectomy for T3 mucosal melanoma (no bony invasion) with 3-cm surgical margin. **B,** Specimen following bilateral selective neck dissection (level I-IV).

complicated by the fact that only 50% to 70% of oral cavity melanomas stain positive for melanin.[70] Therefore, immunohistochemistry staining for S-100, MART-1, and HBM-45 is frequently performed to aid in histologic diagnosis.

Unfortunately, because of the rarity of this malignancy, there are no set guidelines or randomized clinical trials to aid in the management of these patients. Furthermore, from a public health perspective, unlike cutaneous melanoma, there is no known risk factor for mucosal melanomas to aid in disease prevention.

Because of the aggressive biologic behavior of this neoplasm and its poor overall survival, treatment consists of surgery, adjuvant radiation, and adjuvant chemotherapy/immunotherapy. Patients should be treated with multimodality therapy unless the extent of disease renders tumor unresectable, or the patient's performance status contraindicates surgery or adjuvant therapies. Nonetheless, as with all other forms of malignant melanoma, surgery typically offers the best outcome for the patient. However, because of the complexity of the local anatomy of the maxillo-mandibular complex, especially the maxilla, tumors that are diagnosed at a later stage could be deemed unresectable. Unlike cutaneous melanoma, surgeons treating oral mucosal melanoma do not have any randomized clinical trials to guide their decision making in choosing the size of surgical margin, and indication for SLNB versus ELND. The authors feel that a wide surgical margin (≥3 cm) should be safe enough (Figure 29-12). A liberal margin is imperative because frozen-section analysis is unreliable when dealing with mucosal melanoma, a result of the necessity for immunohistochemistry in histologic analysis. Furthermore, there is evidence to suggest that a negative margin offers survival benefit to these patients. Similarly, the role of lymph node dissection is not known. The incidence of nodal disease at first presentation for oral mucosal melanoma ranges from 25% to 48%.[71] Therefore, in the authors' practice, patients with oral mucosal melanoma will undergo an ELND, with the goal of appropriate staging and directing adjuvant radiation therapy. If the patient is able to tolerate adjuvant radiation therapy to the cervical lymph nodes, one could consider this option in patients with extracapsular extension and/or presence of two or more involved lymph nodes. Six percent to 14% of patients will present with distant metastasis.[71] Furthermore, there have been documented cases of distant metastasis of mucosal melanoma without lymph node involvement in other anatomic sites (i.e., anorectal); therefore, consideration should be given to obtaining an initial PET scan to assess for regional and distant disease.

Wushou and colleagues performed one of the more comprehensive and up-to-date reviews on oral mucosal malignant melanoma and identified a 4.69-fold increase in mortality in patients 60 years of age or younger.[68] These investigators also reported a 1.52-fold increase in mortality in patients managed with surgery alone, and a 12.84-fold increase in mortality in patients treated with nonsurgical modalities. These data highlight the importance of surgery in the management of oral mucosal malignant melanoma, and the need for adjuvant therapy. Even though both cutaneous and mucosal melanomas are considered radioresistant, it is common practice to recommend adjuvant radiation to the primary tumor site because of subclinical disease.[72]

As previously mentioned, 50% of malignant melanomas will be positive for BRAF mutation; however, in the case of all mucosal melanomas, only 9% will harbor this mutation.[73] Yet roughly 25% of all mucosal melanomas will harbor mutations in c-Kit.[73] In patients with c-Kit gene mutation, imatinib (Gleevec, Novartis Pharmaceuticals, Basel) could be beneficial. As in the case of cutaneous melanoma, vemurafenib and dabrafenib could be considered in patients with BRAF gene mutation. Del Vecchio

and colleagues evaluated the role of ipilimumab in 855 patients with unresectable cutaneous, ocular, and mucosal melanoma who had failed all other therapeutic options.[74] Within their cohort, 71 patients had metastatic mucosal melanoma, and with a medial follow-up of 21.8 months, they reported a response rate of 12% with immune-related disease control rate of 36%, and an overall survival of 6.4 months. The role of systemic therapies is less defined with mucosal melanomas. Adjuvant chemotherapeutics such as dacarbazine, platinum analogues, nitrosoureas, and IL-2 have shown a poor response rate.[72] Therefore, the role of chemotherapeutics in mucosal melanoma is primarily adjuvant or palliative. In conclusion, oral mucosal melanoma is a disease with a very poor prognosis; therefore, these patients should be managed with tumor extirpation with wide surgical margins with consideration for ELND, adjuvant radiation therapy, and conventional or novel systemic melanoma therapies.

Summary

Malignant melanoma is an increasingly common, potentially deadly entity that the oral and maxillofacial surgeon must be able to recognize. This disease is on the rise in pediatric and adult patient populations and has become a global health burden. Just within the United States, new cases of invasive melanoma will cost close to $2 billion annually.[53] It is imperative to fully understand the treatment and prognostic factors associated with this disease. Proper management requires a high index of suspicion and use of proper biopsy and excision techniques, as well as understanding the role of surgery in identifying and controlling locoregional and distant disease. Current issues in the management of malignant melanomas include an emphasis on sentinel node biopsy, as well as a treatment stratification based on the new AJCC staging system. Ongoing clinical trials will hopefully allow for better diagnostic and prognostic information, which will improve the management of this formidable disease.

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30 Lymphoma

KETAN PATEL, AVANTI MEHROTRA, DEEPAK KADEMANI

Introduction

sixth most common malignancy and the second most common neoplasm of the head and neck after squamous cell carcinoma and accounts for 50% to 59% of head and neck neoplasms in children.[1,2] They constitute approximately 3% to 5% of all known malignancies and are generally divided into two morphologically distinct types: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).[3-6] These malignancies typically arise within the lymphatic tissues and can progress to extranodal disease as in NHL. Cervical lymph node involvement can be present in any type of lymphoma. HL extends by means of contiguous nodal spread, whereas NHL tends to disseminate hematogenously and is typically a systemic diagnosis. Within the head and neck, Waldeyer ring is the most common site of involvement,[7-9] accounting for more than half of all extranodal head and neck lymphomas. Oral involvement by lymphoma may represent a localized disease process but is more often part of a systemic process that secondarily involves the cervical lymph nodes.

Lymphoma arising within the oral cavity accounts for less than 5% of all oral malignancies, and approximately 85% of these lesions involve the pharyngeal tonsil and the palate (Figure 30-1). Extralymphatic sites include the salivar

log

Several classification systems have been used to classify lymphomas, including the World Health Organization (WHO) classification, which is based on the principles defined in the Revised European-American Classification of Lymphoid Neoplasm (REAL). Both the WHO and REAL classifications divide lymphomas based on cell of origin into two large categories: Hodgkin Lymphoma and Non Hodgkin Lymphoma (NHL).

HL is subdivided into Classical Hodgkin and Nodular Lymphocyte Predominant HL (NLPHL).

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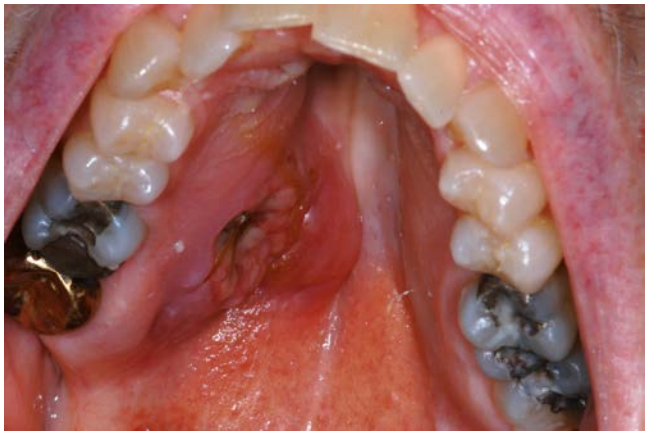
divided into B-cell NHL and T-NK (natural killer)-cell lymphoma, which are then further subdivided[3,4,10-12] (Box 30-1).

Diagnosis

Patients often present with a neck mass to oral and maxillofacial surgeons (Figure 30-2). Therefore, it is critical when assessing neck masses to have a well-developed algorithm for their evaluation (Figure 30-3). This will enable earlier-stage diagnosis and expeditious treatment.

Nodal presentation of a lymphoma typically presents with a neck mass of small to medium-sized lymph nodes with a rubbery consistency that progressively become larger. Lymph nodes larger than 1 cm that persist for more than 4 to 6 weeks in the absence of infection should be evaluated histologically.[13] There are several specific criteria for biopsy of suspected lymphoma. It is preferable that the largest accessible lymph node be removed for histologic diagnosis. Excisional biopsy provides the highest yield diagnostically. The excised lymph node should preferably be intact and undistorted. Fine-needle aspiration (FNA) may on occasion be diagnostic when augmented with immunophenotyping studies and is a useful diagnostic modality for intra-abdominal, thoracic, or retroperitoneal lymph nodes. FNA is often used to obtain tissue for surveillance in the post-treatment setting.[9,13]

The diagnosis of lymphoma is based on the histopathologic examination of enlarged cervical lymph nodes or from extralymphatic tissue. Immunophenotyping of lymphomas, by either immunohistochemistry or flow cytometry, is critical for accurate classification of a lymphoma. The majority of B-cell lymphomas express the pan-B cell antigen CD20, whereas T-cell lymphomas express the T-cell antigen CD3. Both sets are positive for the leukocyte common antigen CD45. Hodgkin lymphoma lacks the B-cell and T-cell antigens. The classical Hodgkin pathognomic cell is the Reed-Sternberg cell that typically expresses CD15 and CD30.



• **Figure 30-1** Non-Hodgkin lymphoma (follicular type) presenting as an intraoral palatal mass with mucosal ulceration.

• BOX 30-1 Classifications of Lymphomas

Hodgkin Lymphoma

- Classical Hodgkin lymphoma
- Nodular sclerosis
- Mixed cellularity
- Lymphocyte-rich
- Lymphocyte-depleted
- Nodular lymphocyte predominant Hodgkin lymphoma

Non-Hodgkin Lymphoma

- Precursor B-cell neoplasms
- Mature B-cell neoplasms
- Small cell lymphoma/chronic lymphocytic leukemia
- Extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT-lymphoma)
- Follicular
- Mantle cell
- Diffuse large cell
- Burkitt (African and endemic)
- Others
- Precursor T-cell
- Mature NK/T-cell
- Extranodal NK/T-cell lymphoma, nasal type
- Anaplastic large cell
- Mycosis fungoides
- Others

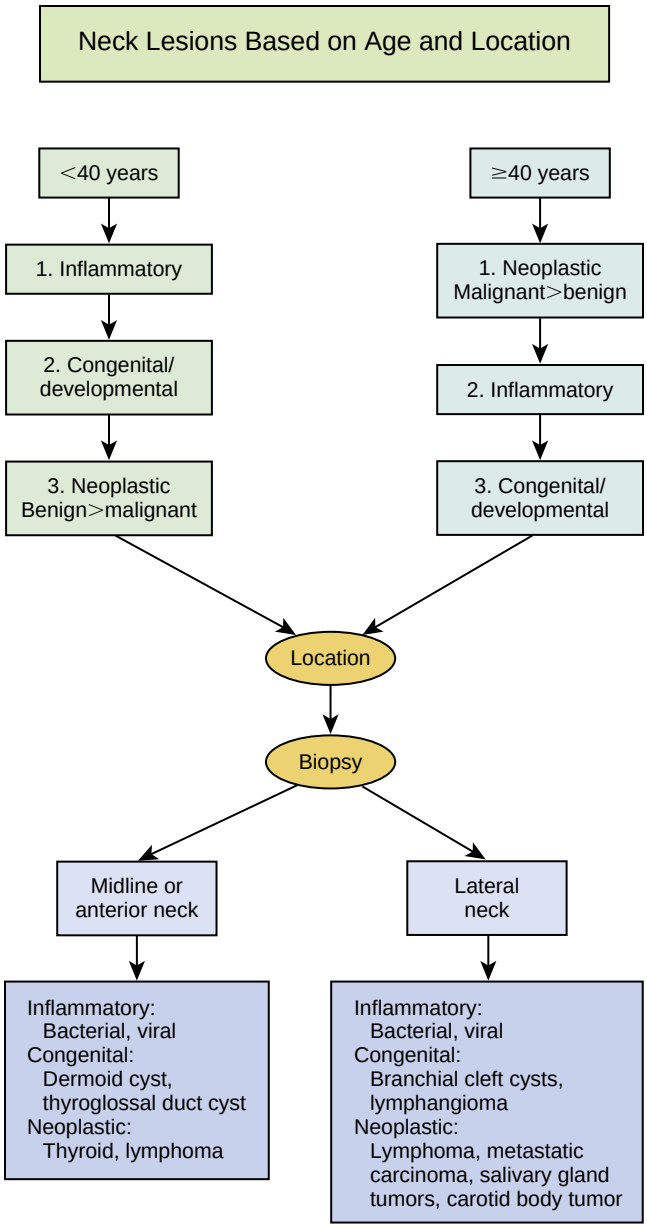
The clinical staging of NHL and HL is based on a combination of clinical, radiologic, and surgical findings. In order to appropriately stage lymphoma, a complete medical history, physical examination, urinalysis, blood chemistries, complete blood count with differential, and bone marrow biopsy are required. Imaging modalities are also required, and this centers on obtaining a computed tomography (CT) scan with intravenous contrast, which should include the head and neck, mediastinum, abdomen, and pelvis. Positron emission tomography (PET)-CT scan is now used whenever possible for initial staging. A bone marrow biopsy is typically performed from the iliac crest, because approximately 18% of non-HLs involve the bone marrow.[13-16] If central nervous system (CNS) involvement is suspected, a lumbar puncture is indicated. Lumbar puncture with cerebrospinal fluid flow cytometry is performed in high-risk cases of DLBCL involving the head and neck area, paranasal sinuses, or bone marrow and in testicular and extranodal



• **Figure 30-2** Elderly female patient with palpable cervical and parotid tail enlargement. Diagnosed as diffuse large cell non-Hodgkin lymphoma.

for targeting novel therapies.

The Ann Arbor staging system (see Figure 30-3) is applicable to both HL and NHL and provides the basis for staging.[9,12,13,15,17] The Ann Arbor system depends on the number of lymph node regions involved, the presence of extranodal disease, the presence of disease above and below the diaphragm, and the existence of concomitant constitutional symptoms (*category A* for those patients without systemic symptoms; *category B* for patients with defined systemic symptoms including fever, chills, night sweats, and greater than 10% weight loss). These symptoms are more commonly associated with HL and are prognostically significant if present for both NHL and HL. In addition to routine histologic examination, the presence of genetic and chromosomal abnormalities is common in lymphoma. Aneuploidy occurs in HL; translocations such as *c-myc* gene may be seen in Burkitt lymphoma, and *bcl-2* may often be found in follicular lymphomas. Infection such as Epstein-Barr virus, HIV-1, *Helicobacter pylori,* hepatitis B and C, and human herpesvirus 8 may all be implicated in the pathogenesis of lymphoma.[3,12,15,18-21] The presence of chronic inflammation also increases the risk of developing

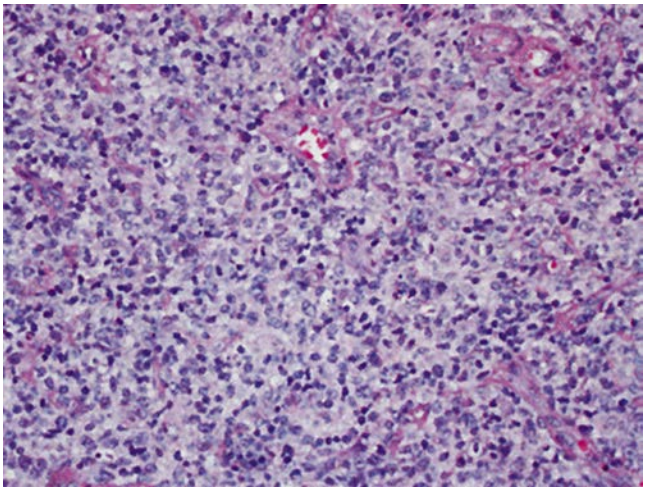


• **Figure 30-3** Evaluation of a neck mass. (Adapted from Bagheri S: *Clinical review of oral and maxillofacial surgery*, St Louis, 2008, Mosby.)

lymphoma as is seen with mucosa-associated lymphoid tissue (MALT) lymphoma in patients with Sjögren syndrome and rheumatoid arthritis.[16,21-27]

Hodgkin Lymphoma

HL is a disorder that is localized to the lymph nodes in more than 90% of cases. HL can be divided into two forms: classical HL (CHL) and nodular lymphocyte predominant HL (NLPHL). CHL is further subtyped into nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted forms. Distinguishing CHL from NLPHL is the most important breakpoint because of their differing clinical presentation, behavior, and immunohistologic features. The majority of cases (95%) are of the classical form, with



• **Figure 30-4** Large collection of Hodgkin cells. Multinucleated Reed-Sternberg cells are also present.

the nodular sclerosis subtype accounting for 70% of these cases.[13,28] This type of classic lymphoma has a bimodal age distribution, with a peak incidence between 20 and 25 years and a second peak in the eighth decade. In the majority of cases (98%), the malignant cells of CHL arise from a mature B-cell.[28] The uninucleated forms are referred to as Hodgkin cells or Reed-Sternberg cell variants, whereas the multinucleated, diagnostic cells are referred to Reed-Sternberg cells (Figure 30-4). All Hodgkin cells in CHL have a similar immunophenotype: *CD15 +ve, CD30 +ve, and CD20 –ve.* Approximately 5% of HL cases are of the NLPHL type, which may occur at any age with a peak between 30 and 50 years old.[28] Like CHL, NLPHL also arises from a mature B cell. However, the neoplastic cells in this type are characterized as large cells with convoluted nuclei. Hence, they are referred to as popcorn or L&H cells (lymphocytic and/or histiocytic Reed-Sternberg cell variants). In contrast to classic RS cells, L&H cells are typically *CD30 –ve, CD45 +ve, and CD20 +ve.*[12] HL is very uncommon in children less than 5 years of age.[12]

HL accounts for approximately 14% of all lymphomas, making it significantly less common than NHL.[3,6,10,15] HL presents rarely as extranodal disease (1% to 4%), whereas NHL occurs in extranodal sites in up to a third of cases.[13,29] Classically, HL occurs in a single lymph node that then progressively involves contiguous lymph node structures. This pattern is in contrast to NHL, where noncontiguous spread to lymphatic structures or extranodal sites is more commonly seen. Clinically, HL causes generalized symptoms or laboratory abnormalities in 41% of patients, as compared with 27% of patients with NHL.[9] The distinction between HL and NHL can only be made histopathologically, because clinical and radiographic

patients with HL versus 33% of patients with NHL presenting with cervical lymphadenopathy.

Non-Hodgkin Lymphoma (NHL)

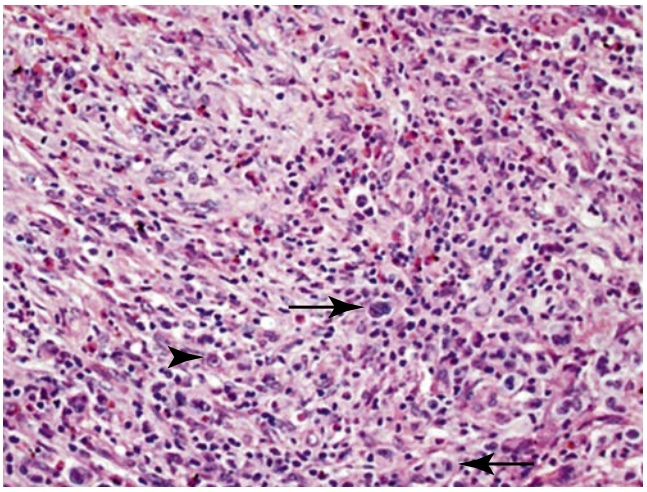
forms. Mature B-cell lymphomas constitute more than 85% of NHL worldwide.[28] Some forms include follicular lymphoma, B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma, diffuse large B-cell lymphoma, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, extranodal marginal zone B-cell lymphoma of MALT lymphoma, mantle-cell lymphoma, and Burkitt lymphoma. All of these lymphomas share expression of the pan-B-cell marker CD20. In addition, many of them also have other specific immunophenotypic profiles that allow for definitive classification. Plasma cell proliferations, such as myeloma or plasmacytoma, also fall under the category of mature B-cell neoplasms, but these are typically CD20(–).

The gastrointestinal system is the most frequently involved extranodal site, which occurs in over 50% of patients.[16,20,30-33] This is followed by the head and neck, which is affected in 11% to 33% of patients.[33] NHL of the head and neck arises in lymph nodes in 65% of cases and in extranodal sites in 25% to 30%.[16] NHL of the head and neck occurs predominantly in patients between the ages of 50 and 60. NHL may spread to regional and distant lymphatic sites as well as parenchymal organs including liver, spleen, lung and bone marrow.

Follicular lymphoma (FL) occurs in an older population, has a relatively indolent course, and constitutes approximately 40% of NHL in adults. It typically manifests as painless lymphadenopathy, splenomegaly, and bone marrow involvement. This lymphoma has a follicular center cell origin and histologically has nodular effacement of the lymph node. The lymphoma cells are CD20, CD10, BCL6, and BCL2(+). BCL2 is an anti-apoptosis gene, which is expressed in FL and allows for distinction from reactive follicular hyperplasia, which is BCL2(–).[28]

Extranodal marginal zone B-cell lymphoma of MALT lymphoma also displays an indolent clinical evolution. This type of lymphoma is commonly seen within the head and neck and in particular extralymphatic sites such as the thyroid and salivary glands and is commonly associated with other autoimmune diseases such as Hashimoto thyroiditis and Sjögren syndrome.[24,25,30,34-38] This lymphoma forms characteristic lymphoepithelial lesions in which the neoplastic lymphocytes infiltrate and injure ducts and glands of the involved organ (Figure 30-5).

Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL in the head and neck, constituting over 50% of cases. This form of lymphoma has a median age of occurrence of 60 and most often presents as a rapidly enlarging single or extranodal mass.[2,39] Waldeyer ring is the most commonly involved site in the head and neck for DLBCL, which can also affect the paranasal sinuses and oral cavity but is relatively rare in the orbital adnexa. Histologically, the lymphoma cells are CD20(+) B-cells whose nuclei are larger than the nuclei of a macrophage or



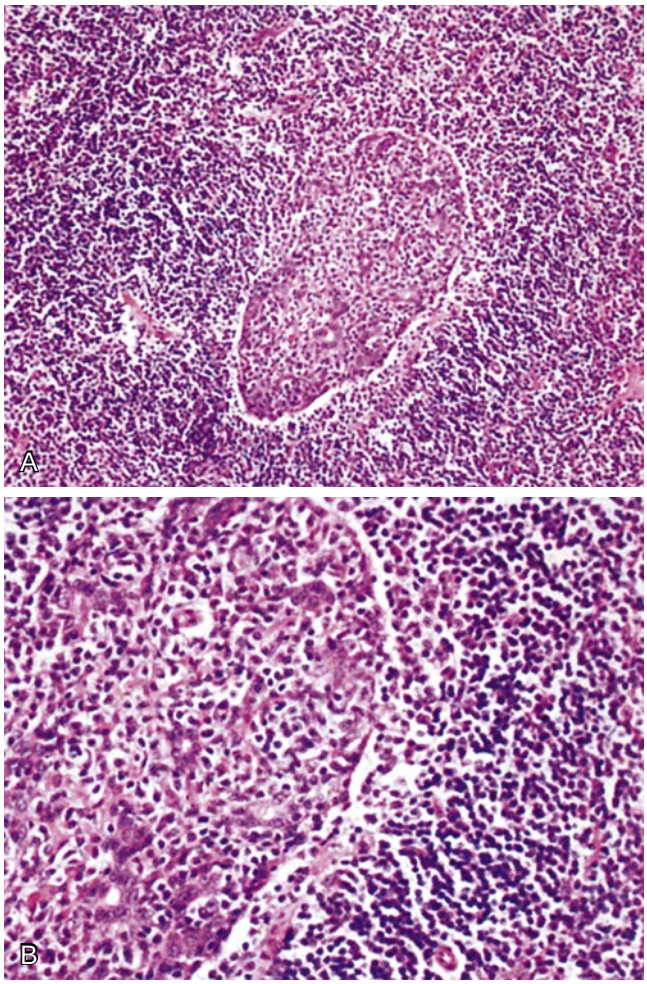
• **Figure 30-5** Diffuse large B-cell lymphoma. Medium-high power view showing sheet of large, atypical cells with moderate amounts of amphophilic cytoplasm. Small, reactive lymphocytes are interspersed. Scattered Reed-Sternberg cells *(arrows)* and uninucleated Hodgkin cells *(arrowhead)* present in the typical inflammatory background of classical Hodgkin lymphoma. Numerous eosinophils and plasma cells are a common finding.

endothelial cells. This lymphoma typically causes a diffuse effacement of the lymph node architecture (Figure 30-6). Some cases of DLBCL represent transformation of a more indolent lymphoma, such as FL or B-cell CLL/SLL. Gene expression profiling and identifying genetic subtype of DLBCL by molecular tying is rather important. DLBCL that have c-myc translocation portend poorer prognosis and have lesser response to therapy.[40] An even more aggressive form of DLBCL is when there is coexpression of c-myc and bcl-2 protein by IHC.[41] The term "double-hit" lymphoma is now used for DLBCL that have translocations of both c-myc gene at (8q24) and bcl 2 gene at (18q21).[39,42]

Burkitt lymphoma, an aggressive form of B-cell lymphoma, has three notable forms: endemic (African), sporadic, and immunodeficiency associated.[32] Endemic BL involves the maxillofacial region in 50% of cases. Sporadic BL more often tends to involve the intra-abdominal contents. Immunodeficiency-associated BL often involves lymph nodes and bone marrow.

Angiocentric Lymphoma

Some lymphomas that involve the sinonasal tract show a peculiar angiocentric/angiodestructive growth pattern. These processes have historically gone by various confusing terms, including polymorphic reticulosis, lethal midline granuloma, lymphomatoid granulomatosis, and malignant midline reticulosis.[28] Histologically there is ulceration and a mixed inflammatory infiltrate, not the typical monotonous proliferation seen in other lymphomas. In addition to T-cell lymphoma, which would be CD3(+), and EBV-associated B-cell lymphoma (CD20+), extranodal NK/T-cell lymphoma, nasal type, can cause this pattern.

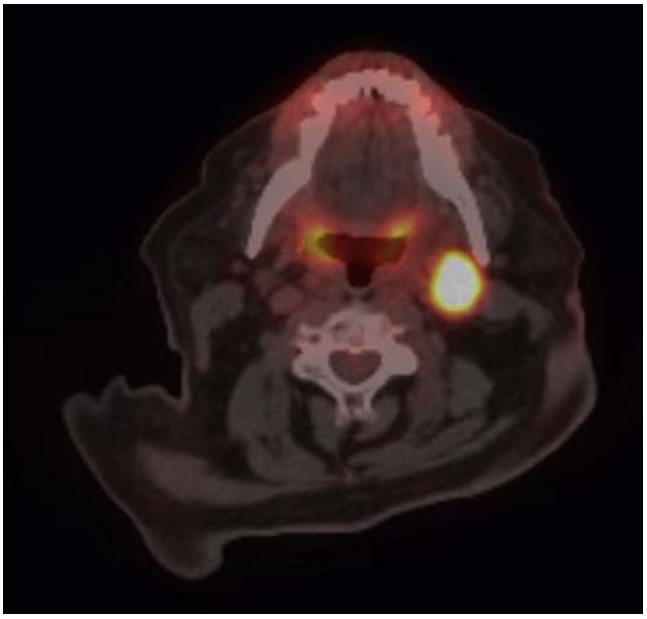


• **Figure 30-6** Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). **A,** Aggregates of small to medium-sized lymphocytes with moderate amounts of cytoplasm. The lymphoma cells characteristically infiltrate the epithelial glands and ducts, forming lymphoepithelial lesions. **B,** Higher-power view of a lymphoepithelial lesion *(left half of field)*.

Nasal-type NK/T-cell lymphoma is almost always associated with EBV and typically is surface CD3(–) (as opposed to most T-cell lymphomas) and CD56(+). This lymphoma is thought to arise from activated NK cells or cytotoxic T-cells. Nasal-type NK/T-cell lymphoma has a variable prognosis, but often behaves in an aggressive manner.[28]

Post-transplant Lymphoproliferative Disorder

Patients who have undergone a solid organ transplant or allogeneic stem-cell transplant for hematologic malignancies are placed on immunosuppressive medications such as cyclosporine and mycophenolate to prevent transplant rejection or to reduce graft-versus-host disease. These patients are at an increased risk of development of lymphomas. This can frequently occur in the buccal mucosa or any lymphoid aggregate in the head and neck region. The disorder can range from a mild lymphoproliferative disorder, to low-grade lymphoma, to aggressive high-grade lymphoma. These are mostly EBV associated as well. Treatment involves reduction of immunosuppression, which places them at risk of transplant rejection. However, this is quite effective in the treatment of the lymphoma.



• **Figure 30-7** Positron emission tomography/computed tomography (PET/CT) scan of a diffuse large cell lymphoma with fluorodeoxyglucose-avid node in left neck.

Radiographic Evaluation

CT scan with intravenous contrast is the primary modality for radiologic assessment of enlarged lymph nodes associated with head and neck lymphoma. Enlarged cervical lymph nodes are typically isodense with muscle and usually appear as a homogeneous conglomerate mass. More recently, PET/CT has become the modality for the initial staging for lymphomas (Figure 30-7). Necrosis is not a prominent primary feature of lymphoma. Aggressive lymphoid lesions may have extracapsular lymph node extension with invasion of adjacent soft tissue structures. It is not uncommon for cervical lymph nodes to form a large matted mass, mimicking an extranodal primary malignancy.[43-45]

An extranodal lymphoma typically manifests as a firm submucosal mass, often lobulated; however, it classically presents with an intact overlying mucosa, unlike squamous cell carcinomas of the head and neck. Osteolytic bone lesions can be displayed by aggressive high-grade lesions similar to other malignant processes. Low-grade lymphomas such as MALT lymphoma are rarely associated with bone destruction. Magnetic resonance imaging (MRI) typically manifests low signal intensity on T1-weighted images, with intermediate signal intensity on T2-weighted images. However, the mainstay of diagnosis continues to be CT scan

with intravenous contrast with formal immunophenotypic analysis of lymphoid tissue and bone marrow biopsy.[45-47]

There are several specific sites within the head and neck that may develop lymphomatous disease and deserve special discussion. Waldeyer ring comprises a network of lymphoid tissue within the nasopharynx, which includes the nasopharynx, base of tongue, and pharyngeal tonsils. It is the most common site of extranodal lymphoma within the head and neck and accounts for more than 60% of extranodal lymphoma. The majority of Waldeyer ring–associated lymphoma is seen in patients in the sixth to seventh decade of life and has a 10% association with concomitant gastrointestinal tract lymphoma.[8,24,37] DLBCL is the most frequently seen morphologic variety of lymphoma in 50% to 60% of cases, and most patients present with early stage I or stage II disease.[13] HL has rarely been reported in the Waldeyer ring or nasopharynx. Radiographic examination typically demonstrates a large bulky mass involving one or all three lymphoid sites within Waldeyer ring. The most commonly affected site within Waldeyer ring is the pharyngeal tonsil, seen in 37% to 52% of cases, followed by the nasopharynx and least commonly the base of the tongue.[48,49] On radiographic examination, these lesions typically present as an isolated isodense mass to muscle with submucosal extension with relatively normal overlying mucosal tissue. Mucosal ulceration as seen in squamous cell carcinoma is not a typical feature.

Lymphomas of the oral cavity constitute 2% of extranodal lymphomas.[26] The majority of site involvement includes the palate, maxilla, and gingival tissues. Oral cavity lymphoma is more frequently seen in patients with immunosuppressive diseases and in particular those who have HIV infection.[50,51] More than 50% of lymphomas within the oral cavity are of the DLBCL variety, with follicular lymphoma and MALT lymphoma being the next most common, respectively.[52] The tumor may originate within the soft tissue structures as a localized exophytic bulky mass or may have osteolytic lesions as is typically seen with Burkitt lymphoma.[26,53]

Lymphoma is the second most common malignancy of the paranasal sinuses after squamous cell carcinoma.[35,54] In extranodal NHL of the head and neck, approximately 6% to 13% occur in the paranasal sinuses.[35,54] The most common variant is DLBCL. T-cell lymphoma invariably involves the nasal cavity, which is the primary site for this form of malignancy. Paranasal sinus lymphomas are considered moderately aggressive and commonly will extend into the orbital vaults. They are clinically and radiographically indistinguishable from the more commonly seen epidermoid tumors of the head and neck. Direct involvement of the nasal vault from paranasal sinus tumors is not unusual. However, a small percentage of lymphomas arise primarily in the nasal cavity. These are typically extranodal NK/T-cell lymphomas. The median age of presentation is 50, with a typical male predominance.[55] Lymphoma localized to the nasal vault will typically cause osteolytic bone destruction with concomitant extension into the paranasal sinuses, alveolar bone, or hard palate with soft tissue extension into the masticator, buccinator, pharyngotemporal, and infratemporal fossa, nasopharynx orbit, or intracranial vault. NK/T-cell lymphoma typically exhibits an aggressive clinical course with early multi-organ involvement and poor patient survival. Extranodal nasal NK/T-cell lymphoma is much more prevalent in Asia than in Latin America or Europe and has a high association with Epstein-Barr virus.[55-57]

Salivary gland lymphomas comprise 2% to 5% of all salivary gland neoplasms, with the parotid gland involved in more than 70% of cases.[58-60] Histopathologically, these are typically B-cell lymphomas, with the MALT-type occurring in one third of cases, follicular lymphoma in one third, and DLBCL in the remaining one third. MALT-type lymphomas are typically seen in the parotid parenchyma, whereas follicular lymphomas are more commonly seen within intraparotid lymph nodes.[58-60] Twenty percent of patients have an association with other immunotypical diseases such as Sjögren syndrome, as is seen with MALT lymphoma.[29] An important diagnostic and prognostic finding is the presence of extra salivary gland involvement to adjacent cervical lymph nodes, which is seen in 20% to 45% of cases.[29]

NHL may involve the mandible or maxilla. The peak incidence is between 25 and 40 years of age, with clinical manifestation representing persistent facial swelling, loose teeth, and gingival bleeding. The majority of maxillofacial lymphomas are DLBCL.[43,46] HL as a primary lesion is infrequently seen in the maxillofacial structures. However, 20% of cases with systemic involvement are associated with bony involvement, which may include the maxillofacial structures secondarily. Bone lesions are typically osteolytic in 70% of cases, sclerotic in 4.3%, and mixed in 16%.[26,61] Periosteal reaction can be seen with a variable soft tissue mass. Burkitt lymphoma will often present with primary disease being localized to the maxillofacial structures. Jaw lesions are seen in up to 50% of patients, most often occurring at the angle of the mandible. Typical radiographic features include loss of lamina dura with an associated osteolytic lesion with concomitant periosteal reaction.[62]

PET scan is now an important part of initial staging of lymphomas. Lymphoma masses are usually associated with increased hypermetabolic uptake. PET scan is used to monitor response as well. Resolution of hypermetabolic uptake on PET scan (negative PET scan even though mass may still be present) midway through chemotherapy is an extremely important prognostic factor and portends good prognosis. In Hodgkin lymphoma, PET scans are obtained after the initial two cycles of chemotherapy for prognostic information.

After the treatment is completed, disease may be followed by surveillance. Maximum recurrences occur within the first year, and most of the remaining recurrences happen within the second year after completion of treatment. Thus, having normal scan results at 1 year and 2 years after treatment is considered an important landmark in the course of treatment of lymphomas.

Treatment

Lymphomas are typically treated with medical management with chemotherapy or radiotherapy or else a combination of these, rather than primary surgical management. In most instances, for early stage I/II disease, treatment involves a reduced schedule of chemotherapy followed by radiation. However, for advanced-stage disease, treatment is chemotherapy. In advanced-stage disease, radiation therapy is added only for bulky disease. Radioimmunotherapy is yet another modality used for relapsed disease. It is a combination of monoclonal antibody labeled with a radioisotope such as yttrium-90 or iodine-131.

Several chemotherapeutic options are available for systemic management of lymphoreticular diseases. This is mostly a combination of targeted therapy (usually a monoclonal antibody) along with conventional cytotoxic chemotherapy. Some important regimens for NHL are:

- R-CHOP: rituximab-cyclophosphamide, hydroxyadriamycin, vincristine, and prednisone
- BR: bendamustine-rituximab
- RICE: rituximab-ifosfamide, carboplatin, etoposide
- R-DHAP: rituximab-dexamethasone, cytarabine, cisplatin
- R-CVP: rituximab-cyclophosphamide, vincristine, prednisone
- R-Hyper-CVAD: rituximab-cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine
- R-CODOX-M/ IVAC: rituximab-cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, cytarabine
- R-EPOCH: rituximab-etoposide, vincristine, infusional doxorubicin, cyclophosphamide, prednisone

Chemotherapy for NHL is very successful and produces excellent local, regional, and systemic control of the disease. The International Prognostic Index (IPI) helps predict prognosis and outcomes. The IPI scoring system incorporates age, clinical factors (ECOG performance status and serum lactate dehydrogenase concentration), and stage of the disease. This is therefore, used as a guide to establish a treatment plan as well. Depending on the IPI score, relapse and cure rates for different disease states are determined.

When patients relapse after first-line treatment, they are treated with salvage high-dose chemotherapy followed by autologous stem-cell transplantation. Certain types of NHL deserve some additional discussion. Indolent B-cell NHL (for example, follicular lymphoma, marginal zone lymphoma, low-grade mantle-cell lymphoma, or splenic marginal zone lymphomas) may be managed with observation for a certain period of time. They are followed along and treatment is undertaken only when progressive disease is identified or if the patient develops considerable constitutional symptoms. Sometimes, this happens years after initial diagnosis. For these asymptomatic, low-grade, indolent NHLs, cure is not possible. Thus, delaying therapy until symptom development or disease progression is no significant detriment to overall survival outcome.[63]

Mantle cell lymphoma can have different courses. Some are very aggressive and need aggressive chemotherapy. Intensive chemotherapy regimens such as hyper-CVAD regimen (fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) seem to improve initial response rate and remission.[64] However, this regimen is highly toxic, which can be associated with significant morbidity and mortality. Patients with mantle-cell lymphoma will often undergo autologous stem-cell transplantation during the first remission because of poor outcomes with less intensive treatment regimens. However, there is another subset of patients with mantle-cell lymphoma who have a more indolent course and have outcomes similar to those of patients with follicular lymphomas.

Burkitt lymphoma is a highly aggressive B-cell lymphoma associated with EBV and is traditionally associated with a dismal prognosis, with the majority of patients dying within 1 year of diagnosis. However, the use of intensive chemotherapy regimens has significantly improved patient survival. The use of the R-CODOX-M regimen (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate), as described by Magrath and colleagues,[65] has shown the potential to cure the majority of adults with Burkitt lymphoma. The use of stem-cell transplantation in the initial management of patients with Burkitt lymphoma has not been shown to increase patient survival. Patients with relapse are rarely salvaged with any treatment approach.

MALT lymphomas are low-grade lymphomas. The majority of MALT lymphomas occur within the gastrointestinal tract and are associated with *H. pylori* infection. Frequently in patients with early-stage disease, eradication of *H. pylori* leads to tumor regression. Patients who do not respond to initial eradication of *H. pylori* or do not have documented *H. pylori* infection with gastric MALT lymphoma may be treated with combined chemo-radiotherapy. Patients with localized MALT lymphoma to the head and neck again are managed primarily with chemo-radiotherapy with localized field radiotherapy, with surgical dissection limited to local regional recurrence.[66,67]

T-cell non-Hodgkin lymphomas are also treated with the same regimens. However, these do not express the target CD20 on the surface. Thus, targeted therapy with rituximab is not used for T-cell NHL. Response to chemotherapy in T-cell NHL is not as robust. Regimens used include:

- CHOP: cyclophosphamide, hydroxyadriamycin, vincristine (Oncovin), prednisone
- Pralatrexate
- Anti-CD30 antibody: brentuximab vedotin

Hodgkin lymphoma is treated with different chemotherapy regimens. The early stage is treated with fewer cycles of chemotherapy in combination with radiation to follow. Advanced-stage disease is treated with chemotherapy alone.

Radiation therapy is employed for early-stage disease and for bulky disease. Commonly used chemotherapy regimens are:

- ABVD: adriamycin, bleomycin, vinblastine, dacarbazine
- BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
- Stanford V: mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone

Cure rates are high even in advanced-stage disease in younger patients, being more than 85%.[68]

For relapse disease, high-dose chemotherapy followed by autologous stem-cell transplant is a very effective salvage therapy. Anti-CD30 targeted therapy with brentuximab has shown excellent control for relapsing disease. Thus, long-term consequences of therapy need to be kept in mind when choosing treatment for these patients. Radiation therapy typically involves field radiation and is effective for local control. It does increase the risk of second malignancies in these patients. The risk for solid tumors increases from 2% at 10 years to 13% at 19 years. Potential long-term side effects of chemotherapy include myelodysplasia, cardiomyopathy, and pulmonary toxicity.

agents such as rituximab is added. For aggressive, advanced disease or disease not responding to reduction of immunosuppression, chemotherapy with CHOP or R-CHOP can be used with an excellent success rate.

• BOX 30-2 Ann Arbor Staging System for Lymphoma

Stage I

Involvement of a single lymph node or localized involvement of a single extralymphatic organ or site.

Stage II

Involvement of two or more lymph node regions on the ipsilateral side of the diaphragm.

Localized involvement of the extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (IIE).

Stage III

Involvement of lymph node regions on bilateral sides of the diaphragm, which may be accompanied by localized involvement of an associated extralymphatic organ or site.

Stage IV

Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node involvement.

Letter Designations

A—Asymptomatic
B—Constitutional symptoms: Fever >38° C, drenching night sweats, >10% weight loss within 6 months
E—Extranodal
X—Bulky disease; tumor diameter is greater than >10 cm

Discussion

prognosis than patients with squamous cell carcinoma of the head and neck. The 5-year survival rate for HL is 73% and 65% for extranodal NHL head and neck lymphoma. HL accounts for approximately 30% of all malignant lymphomas. The typical presenting feature of lymphoma for both HL and NHL is the development of a mass within the head and neck or pain. There are several classification systems for lymphomatous disease, including the WHO and REAL classification systems. The Ann Arbor staging classification system is widely used in North America and is based on the anatomic extent of tumor involvement (Box 30-2). Patients presenting with stage I or stage II disease have a more favorable prognosis compared with patients presenting with advanced stage III or stage IV disease. The natural history and prognosis of HL are based on the histologic type, stage, and the presence or absence of systemic symptoms. The 5-year survival for all tumor types managed with chemo-radiotherapy is greater than 80%.

NHL is a neoplastic proliferation of lymphoid cells that is often disseminated and can be prognostically differentiated into several immunophenotypes as well as into low-, intermediate-, and high-grade lesions. Disease that is low- or intermediate-grade has a more favorable prognosis and, when localized, may well respond to localized field radiotherapy alone. Localized stage I and stage II low-grade NHLs are primarily treated with radiotherapy. Surgery is primarily used as a diagnostic modality. In deeply invasive disease or with documented evidence of systemic involvement, the addition of chemotherapy has improved patient survival.

The overall prognosis of patients with lymphoma is associated with histologic type and stage of disease at presentation. The IPI scoring system is rather helpful in predicting prognosis. Low-grade lesions have a 5-year survival of over 80% compared with 52% for those with high-grade histologic types. Stage is also an important prognostic feature, with 83% of patients with stage I disease surviving more than 5 years compared with only 49% of patients with stage II and higher.[15,65] Although post-treatment remission often occurs in treatment of low-grade lymphomas, the disease can often have an indolent course with a significant risk of transformation to a more aggressive lesion.

Oropharyngeal and oral cavity lymphomas are the second most common malignant disease in the oral cavity. It is critical for health care providers, and in particular maxillofacial surgeons, to be able to identify a well-defined algorithm for the management of neck masses and to recognize and initiate appropriate early management of lymphoreticular disease in order to improve overall survival.

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31

Non-melanoma Skin Cancer of the Head and Neck

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Introduction

Non-melanoma skin cancer (NMSC) is the most common malignancy in the United States, with more than 2 million patients treated each year.[1] More than $426 million is spent yearly on skin cancer treatment, with the majority of care provided in an office setting.[2] When defined as impaired ability to work and lost future earning potential due to premature death, an estimated $10.2 billion in yearly lost productivity has been calculated to result from skin cancers, excluding melanoma.[3] Available research on cost reveals a broad range of expenditures depending on the care setting and the treatment modality. Office settings offer the lowest average cost per episode of care ($492),[4] whereas inpatient treatment can result in more than a 10-fold increase in cost.[5] Although the true economic impact of NMSC treatment is likely underestimated, Medicare data show NMSC to be one of the five most costly cancers to treat. Further analysis suggests this high cost is due to the high frequency of diagnosis rather than the actual cost of each cancer treatment.[6] Given its increasing incidence, NMSC expenditures will only increase, and along with prevention, effective and efficient management is paramount. Although this chapter focuses on the diagnosis and treatment of the most common non-melanoma cutaneous malignancies—basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)—other select skin cancers are included for completeness. In general, oncologic principles for the management of these cancers can be applied to other malignancies affecting the skin.

Epidemiology and Etiology

The increasing incidence of NMSC is multifactorial and may be attributed to increased photodamage from sun exposure, ozone depletion, increased longevity, and improved detection.[7] White populations show increased risk, especially with lighter skin type, blue eyes, freckles, and red/blonde hair. NMSC is uncommon in Black, Asian, and Hispanic populations. Blacks do not appear to be as affected by increased sun exposure, as their skin cancers tend to be in areas not exposed to sunlight. Indoor tanning among adolescents is common in the Unites States (21% of high school females engaged in indoor tanning in 2011) and increases the risk of basal cell carcinoma by 40% and squamous cell carcinoma by 102%.[8]

The role of ionizing radiation is further highlighted by the significant geographic variability in the incidence of NMSC. Certain areas of Australia show NMSC development in over 2% of the population, which is a 10-fold increase over European and United States cohorts of similar ancestry. Younger people are affected more frequently in Australia and the southwestern United States. Proximity to the equator influences rates of NMSC for White populations, with the incidence of squamous cell carcinoma doubling for every 10 degrees in latitude closer to the equator.[9]

In addition to ionizing radiation, several other risk factors deserve mention. Secondary NMSC can result from previous radiation treatment. The Childhood Cancer Survivor Study found a 6.3-fold increase in risk of developing NMSC within the radiation field, with 42% of these cases occurring in the head and neck. The median age at diagnosis of their first NMSC was 31, and almost half of patients had multiple recurrences.[10] Long-term immunosuppression increases the risk of skin cancer. A 2015 review noted kidney transplant recipients have a 65- to 250-fold greater risk than the general population of developing NMSC.[11,12] Similar increases in risk have been noted for heart, lung, liver, and pancreas transplant patients.[12-15] Skin cancer risk associated with transplantation is increased for sun-exposed skin even for patients living in regions of relatively low sun exposure, with lip cancer among the most common.[12] Interestingly, immunosuppression caused by HIV carries a 2-fold higher risk for skin SCC, but not BCCn.[16]

One of the most important risk factors for the development of a skin cancer is a history of prior skin cancer. The

5-year cumulative risk for development of a NMSC in a patient with a prior NMSC is 40%. Risk further increases over time as additional skin cancers are diagnosed in the same person. For a patient with a prior NMSC who develops a second skin cancer, there is an 82% risk that yet another NMSC will develop over the next 5 years.[17] In patients with a history of BCC, the risk for developing an SCC is 6%. Regardless of primary treatment modality, patients with skin cancer require structured follow-up, given their high risk for development of second primaries.

Pathology and Epidemiology

Epithelial Cancers

Basal Cell Carcinoma

The most common NMSC is basal cell carcinoma (BCC), which makes up approximately 80% of NMSCs.[18] Basal cell carcinomas arise from the basal cells of the epidermis and skin appendages. Although rarely associated with metastasis, they are capable of extensive local tissue destruction and, uncommonly, may invade deeper structures, including cartilage, bone, and muscle. Basal cell cancers are most commonly located in the head and neck, with the skin of the periorbital, perioral, and auricular areas being especially at risk (Figure 31-1). Rarely, large, neglected lesions can be fatal through local invasion of vital structures or distant metastasis.

Basal cell carcinomas are the most common skin cancer found in Whites, Asians, and Hispanics. In Black populations, BCC is the second most common skin cancer after SCC.[19] Although exposure to ultraviolet radiation is the major cause of BCC, other risk factors for BCC include age, skin type, radiation exposure, immunosuppression, and exposure to certain chemicals. Men have a 2-fold higher incidence than females, which may be related to their increased involvement in outdoor occupations and leisure activities and consequent increased exposure to solar radiation.[18] In addition to the association of basal cell carcinoma with basal cell nevus syndrome (Gorlin syndrome), other syndromes, including albinism and xeroderma pigmentosum, are also associated with BCC.[20,21] Although once considered infrequent before the age of 40, basal cell cancers are appearing in younger patients, likely secondary to increased sun exposure and tanning.[8]

Presentation

Basal cell carcinomas can be subdivided into four types, listed here in decreasing order of incidence: nodular (or nodulo-ulcerative), sclerosing (or morphea), basosquamous, and multicentric (superficial) type. Friedrich and colleagues reviewed 216 patients with BCCs that primarily affected the middle third of the face. Of the 216 patients, 124 were treated with surgery. Friedrich found that 83% of the BCCs were solid (or nodular), 10% were sclerosing, 4% were metatypical (basosquamous), and 3% were multicentric.[22] The nodular type usually appears as a firm, translucent (pearly) papule with telangiectatic blood vessels. Pigmentation can be present and can lead to a concern for melanoma, which should be taken into consideration when planning a biopsy (see biopsy techniques in Figure 31-5). Late stages are accompanied by crusting and a central ulcerated depression as the central portion becomes necrotic from lack of blood supply. This results in the classic "rodent ulcer" recognized by most clinicians as a BCC. Histologically, the lesions contain nests and strands extending perpendicular to the basement membrane. Squamous differentiation can occur within the lesion, leading to the basosquamous variety (Figure 31-2), which behaves in a more aggressive fashion that is more analogous to a squamous cell cancer with an increased incidence of recurrence and metastases.[23] The sclerosing variant may appear as a scar or fibrotic skin and lack elevation. It is made up of nests and cords of tumor cells within a dense fibrosis. Its borders are often indistinct, and microscopic extension into the surrounding dermis can lead to positive margins and an increased chance of recurrence following excision. As these lesions enlarge, the sclerosing type can develop central depressions, giving them the appearance of a scar. Finally, the superficial or multicentric form typically presents as a red, scaling



• **Figure 31-1** Basal cell carcinoma of the upper lip.



• **Figure 31-2** Basosquamous cell carcinoma of the ear.

lesion, and although it occurs on the skin of the head and neck, it is more common on the trunk and extremities. As these lesions enlarge, they can assume the appearance of a nonspecific dermatitis.[18]

Metastatic basal cell carcinoma is extremely uncommon, with fewer than 400 cases reported, and an estimated incidence of 0.0028% to 0.55% of cases. Metastasis can occur by both lymphatic and hematogenous spread. Metastasis to lymphatic basins seems to be associated with longer survival than hematologic spread to distant organs, which include bone, liver, and lung.[24] Given its rarity, management of metastatic BCC is not standardized. The most promising research currently focuses on inhibition of the Hedgehog signaling pathway. Vismodegib was approved in 2012 by the FDA as the first Hedgehog signaling pathway inhibitor to treat metastatic or recurrent locally advanced basal cell carcinoma in adults who cannot be treated with surgery or radiation.[25]

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is the second most common cutaneous malignancy and accounts for approximately 20% of skin cancers. Approximately 200,000 to 300,000 cases are diagnosed yearly, and 2000 people die each year from this disease.[26] SCC arises from the common precursor cell, the keratinocyte. Compared to most BCCs, SCCs are typically more aggressive and are more commonly associated with metastases and locoregional recurrence following treatment. Like BCC, cutaneous squamous cell cancer is strongly associated with exposure to UV radiation, and there is a direct correlation between cumulative solar exposure and risk for development of cutaneous SCC. A history of childhood sunburn and long-term exposure to solar radiation is common.[9]

Similarly, chronic immunosuppression in solid organ transplant patients is also associated with an increased incidence of squamous cell cancers. These cancers typically arise in sun-exposed areas, suggesting that UV radiation and immunosuppression combine to increase overall risk.[12] Additional etiologic factors include human papillomavirus (HPV-5, -16, and -18), exposure to certain chemicals (organic hydrocarbons and arsenic-containing compounds), and long-standing inflammatory conditions, such as fistulas and ulcers (e.g., Marjolin ulcer).[26]

Presentation

Squamous cell cancers are the most common skin cancer in Blacks and Asian Indians and the second most common cutaneous malignancy in Caucasians.[27] SCC is predominantly a cancer of the older patient (average age at diagnosis 70), and males predominate, again likely related to increased outdoor activities. The vast majority occur in the head and neck, with the skin of the upper face being especially susceptible. Squamous cell cancers typically arise in an area of actinic keratosis (AK) that appears as hyperkeratotic plaques. Approximately 10% of actinic keratoses will ultimately transform to squamous cell cancer.[28] Ulceration, possibly accompanied by bleeding, may develop with thickening of the plaque.

There are several varieties of squamous cell cancer worth noting. The vast majority are typical SCCs, which can be subdivided into well, moderate, and poorly differentiated based on the amount of keratin production (keratin pearls), and on how closely the tumor mimics normal skin histologically. A well-differentiated SCC typically contains an abundance of keratin pearl formation surrounded by well-formed keratinocytes lacking nuclei. Conversely, poorly differentiated tumors lack keratin formation, and the nucleated keratinocytes are haphazardly arranged and have a high mitotic index. Histologic evaluation may also take note of a dense inflammatory infiltrate, which is often associated with improved local control rates.

Keratoacanthoma (KA) is a controversial lesion that some consider a very well-differentiated squamous cell cancer. Keratoacanthomas are common lesions that, like BCC and SCC, usually occur on sun-exposed areas. They typically present as red, raised lesions with hyperkeratotic centers and are often difficult to distinguish from an SCC clinically. Characteristic rapid growth is usually followed by spontaneous involution in the majority of cases. Pronounced scarring can occur in some cases. Although a clinical history of rapid growth coupled with the clinical appearance can provide clues to the diagnosis, these lesions should be excised and examined histologically for confirmation of diagnosis and margin assessment. Rarely, keratoacanthomas can be associated with more aggressive behavior, including recurrence and metastasis, although the latter is controversial. Most clinicians recommend that KAs be treated as well-differentiated SCCs with surgical excision and margin analysis.[29-31]

Carcinomas of Skin Appendages

Microcystic Adnexal Carcinoma

Microcystic adnexal carcinoma arises from the sweat ducts and most commonly affects the skin of the head and neck, with more than half of cases occurring on the upper or lower lip. It usually presents in middle-aged and elderly Caucasians, and there does not seem to be a male or female predilection. Lack of symptoms and slow growth often result in late diagnosis. Perineural invasion, however, is common (as high as 80%), and patients who are symptomatic often present with complaints of numbness or pain.[32] As many as 60% of patients will experience metastatic spread. Deep infiltration with extension well beyond the clinical margin can be present and lead to a high recurrence rate (up to 70%) following traditional surgical excision.[33] For this reason, consideration should be given to Mohs micrographic excision (see discussion later) if available. Frozen section analysis during traditional surgical excision can also be of assistance. Radiation therapy plays little role in primary management, as these tumors are considered somewhat radiation resistant. It is usually reserved for palliation.[32] Benign tumors from adnexal structures can occur but can be clinically indistinguishable from malignant tumors (Figure 31-3).



• **Figure 31-3** Syringocystadenoma of the scalp.

Sebaceous Gland Carcinoma

Sebaceous gland carcinoma (SGC) is the most common eyelid malignancy in Asians and is most commonly associated with the meibomian glands of the upper eyelid.[34] Lower lid involvement and origin from the glands of Zeis is less common. Although extraocular SGC can occur in the head and neck, cases are rare. Its clinical presentation can lead it to be mistaken for a chalazion or other benign inflammatory condition affecting the eyelid.

Surgical excision is the treatment of choice, but recurrences are common. Deep orbital involvement makes complete excision difficult, and orbital exenteration should be considered. Mohs micrographic excision has been used with some success. Regional and distant metastases are not unusual and are usually associated with large size and recurrent tumors.[35] Although radiation treatment is typically reserved for a palliative role in most cases, some authors have suggested its use as an adjunct to surgical excision in an attempt to decrease local recurrence.[36]

Nonepithelial Cancers

Merkel Cell Carcinoma

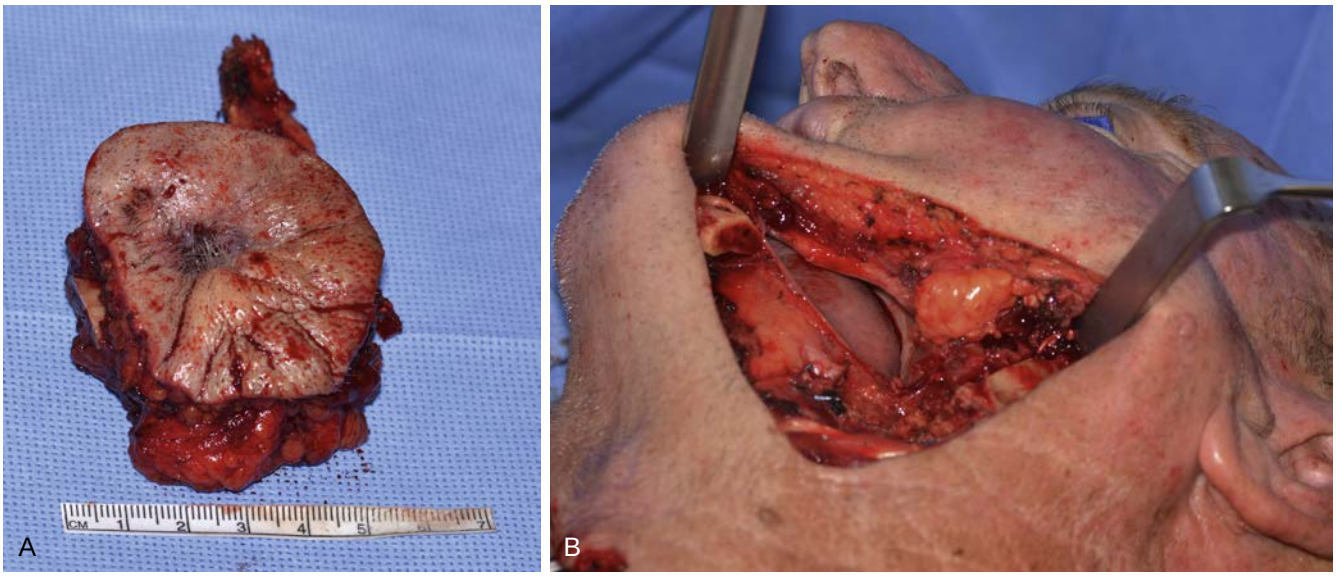
First described by Toker in 1972, Merkel cell carcinoma (cutaneous neuroendocrine carcinoma) is a rare neuroendocrine malignancy known for its rapid growth, high recurrence rate, and propensity to metastasize to regional lymph nodes.[37,38] Merkel cell carcinomas are usually associated with male and female Caucasians of advanced age, and 50% are located in the head and neck.[39] Although suspected, sun exposure has not been established as a definite etiologic factor in their development. Clinically, Merkel cell carcinoma typically presents as an indiscreet red or violaceous papule or plaque that grows rapidly. Originally thought to be of indolent behavior, it is now recognized that Merkel cell cancers are aggressive tumors with a high incidence of local recurrence, as well as metastases. Regional and distant metastasis rates as high as 75% have been reported.[29]

The rarity of Merkel cell cancer (MCC) precludes large trials to develop and compare treatment regimens, and therefore, treatment recommendations based on clinical experience are the norm. Most authors recommend aggressive treatment, including elective management of the at-risk lymph node basins. More recently, interest in sentinel lymph node biopsy has developed, and authors have reported on its utility in the management of MCC.[30,31,39] The behavior of MCC is often compared to that of melanoma, and some authors advocate wide excision margins (2 to 3 cm) to include the subcutaneous tissue and underlying fascia.[31] Others have suggested Mohs micrographic excision (see discussion later) as an acceptable alternative to wide excisions with arbitrary margins. Despite the aforementioned recommendations of most clinicians, there remains considerable controversy regarding the need for elective dissection of the nodal basins at risk. Recommendations vary, but some authors have suggested node dissection in cases of size greater than 1.5 cm or clinically apparent nodes. Multimodality therapy combining surgery and irradiation is indicated in most cases of this potentially lethal cutaneous cancer. MCC is radiosensitive, and in most cases, adjunctive radiation therapy should be considered to the primary site, as well as to the at-risk nodal basins to improve local and regional control.[40,41] Interestingly, Merkel cell carcinoma is one of the few cutaneous malignancies in which chemotherapy can play a significant role. MCC is chemosensitive, and chemotherapy has been used with some success in palliating patients deemed non-operative. Although chemotherapy has been shown to lead to significant remission rates (up to 70%), an improved overall survival rate has not been demonstrated.[31]

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFP) is a malignant tumor known for its indolent growth but propensity to recur following excision. It is rare, accounting for less than 0.1% of all malignancies. It primarily affects middle-aged patients (age 20 to 50 years), but it may present at any age and has a slight male predominance. Some authors report an increased incidence in African Americans.[42]

The majority of DFP occurs on the trunk, with only 10% to 15% occurring on the head and neck.[43] They usually present as a skin-toned or brown plaque that produces multiple protuberant nodules, although a solitary nodule can occur. DFP has an indolent growth phase initially, which is then followed by a more rapid growth in which the multiple nodules are usually noticed by the patient and medical care is sought. Invasion into the subcutaneous tissue is common, and long-standing lesions can invade fascia, muscle, and even bone.[42] Diagnosis is made following a biopsy, which is best obtained from a nodular area and extending into the subcutaneous tissue. Treatment of DFP is adequate surgical excision and annual follow-up. The hallmark of DFP is its propensity to recur following surgical excision. The tumor produces multiple, irregular extensions into the surrounding tissue, leading to extension well beyond the clinical margin. Early recommendations for conservative margins led to a disappointingly high recurrence rate. Currently, recommendations include peripheral margins of 3 to 4 cm that include the deep fascia,



• **Figure 31-4** **A,** Specimen of basal cell carcinoma of the cheek invading into the mandible resulting in a pathologic fracture. **B,** A segmental mandibulectomy was performed, which created a defect communicating with the oral cavity.

which results in recurrence rates from 20% to 60%.[35,43] Unfortunately, these margins are often difficult in the head and neck. Alternatively, Mohs micrographic excision (see discussion later) has been suggested to offer a more complete evaluation of the surgical margin and preserve uninvolved tissue. Mohs' technique has been recommended for primary excision in critical areas and in cases of recurrent tumor.[35,42] Recurrences, which usually occur in the first 3 years, are more common in lesions excised from the head and neck compared to other sites.[42] Death can occur and is usually the result of uncontrolled growth following multiple attempts at excision followed by direct extension into critical anatomic structures. Radiation therapy has been used in some cases as an adjunct to surgical excision and also in cases that are not amenable to surgical excision. The role of chemotherapy is only in cases of distant metastatic disease.[44]

Aggressive Skin Cancer of the Head and Neck

The vast majority of skin cancers affecting the skin of the head and neck are basal and squamous cell cancers, and most patients present with localized disease in which appropriate surgical excision will effect a cure. There is a significant subset of patients, however, who will present with a skin cancer that displays aggressive behavior and fails to respond to standard therapy, with multiple recurrences leading to substantial morbidity and, rarely, death. The challenge to the surgeon is to predict which tumors warrant more workup, such as imaging with computed tomography (CT) or magnetic resonance imaging (MRI) (see discussion later), or more aggressive therapy, such as lymph node sampling or consideration of adjunctive radiation therapy. Ideally, the ability to predict which cancers will behave more aggressively would spare the vast majority of patients additional unwarranted costs and the morbidity associated with a more aggressive approach. Although far from exact, there are several predictors of biologic aggressiveness that can be used to judge behavior in some cases of basal and squamous cell cancers, including location, diameter, depth, differentiation, perineural invasion, and patient characteristics.

Topographically, certain locations are associated with a more aggressive clinical course. This is described as the so-called "H-zone," which includes the eyelids, canthi, nose, nasolabial folds, upper lip, periauricular skin (including the preauricular skin of the cheek), and frontozygomatic region of the forehead.[45] For reasons incompletely understood, tumors arising in these locations tend to have a more vertical, as opposed to horizontal, growth pattern and therefore tend to invade more deeply. Additional factors suggested as contributing to the more aggressive behavior seen with tumors arising in these areas include embryonic fusion planes, density of nerve endings, and proximity to muscles of facial expression, cartilage, and bone. Cancers arising near the medial canthus can invade the orbit with involvement of the lacrimal apparatus and periorbital fat, making eradication without orbital exenteration difficult. Periauricular cancers can spread deeply along the cartilage of the helix, making a clear, deep margin difficult without temporal bone excision.[46]

The surface dimension of skin cancers has a well-accepted influence on prognosis, and for that reason it is included in the staging of these cancers. Both BCCs and SCCs larger than 2 cm have a much higher potential for recurrence following excision.[47,48] Depth of invasion may be equally or even more important than surface dimension in predicting behavior, with deeper invasion (greater than 4 mm) associated with an increased risk of local recurrence, as well as regional and distant metastases.[47-49] Neglected skin cancers can eventually invade facial bones (Figure 31-4).

Tumor histology has a direct bearing on behavior. Poorly differentiated SCCs and sclerosing BCCs have a distinctly more aggressive behavior. Other histologic variables appear to correlate with more aggressive behavior, with the most important being perineural invasion (PNI) or neurotropism, which is defined as invasion in, around, and through peripheral nerves. The loose connective tissue of the perineural space offers a well-known conduit for the conduction of cancerous cells. Although early investigators believed tumor cells traveled within lymphatics surrounding the nerve, currently it is known that tumor cells simply follow a path of least resistance in the natural cleavage plane that exists beneath the perineurium and endoneurium. Perineural invasion can either be noted clinically with a nerve deficit or be noted on biopsy or specimen examination.[50] SCCs more commonly demonstrate perineural invasion compared to BCCs, but involvement by either is an ominous finding. Sensory nerves are more commonly affected compared to motor, and most often the second and third divisions of the trigeminal nerve are affected in cutaneous malignancies affecting the face. Most patients with perineural invasion are asymptomatic, but patients may present with pain, burning sensation, anesthesia, or facial paralysis.[51] Clinically evident perineural invasion is associated with decreased 5-year local control rates compared to microscopic perineural invasion.[52] Cranial nerve deficits rarely improve following therapy. Histologic perineural invasion is associated with a 45% incidence of local recurrence, a 10% to 35% incidence of regional metastasis, and a 65% 5-year survival.[50,53] At 2 years, 46% of patients with PNI were dead of disease or alive with recurrence, in contrast to 9.1% of patients without PNI who were dead of disease or alive with recurrence.[54]

Perineural invasion is also associated with an increased risk of nodal metastases. The concept of "skip lesions" along the nerve is controversial and may be due to difficulty with histologic interpretation or a processing error. In examining nerve margins for tumor clearance, however, it is suggested that clearance of signs of perineural inflammation be used as an end-point rather than clearance of tumor cells. Patients with perineural invasion, especially those with clinically evident deficits, should be considered for more aggressive therapy, including sampling of at-risk nodal basins and consideration of adjunct radiation therapy if a major (named) nerve is involved.[49,50]

Certain patient characteristics may also serve as a guide to the potential for more aggressive tumor behavior. The effect of immunocompromise on the incidence and outcomes of cutaneous malignancy is well recognized. Transplant recipients are regarded as high risk for the development of NMSC, and their outcome following standard treatment is worse. Southwell and colleagues, along with others, have demonstrated a significantly higher incidence of recurrence and decreased survival in patients with immunocompromise.[55]

Most importantly, a recurrence following standard therapy is an indication of biologic aggressiveness and portends a worse outcome. Recurrent tumors are indicated for more aggressive therapy, and recurrence is often an indication for Mohs micrographic excision (see discussion later), which results in a significantly lower recurrence in these patients compared to traditional surgical excision or radiation.[56,57] It is hoped that the future will bring improved genetic markers for biologic aggressiveness to aid in therapy selection and prognosis.

Screening and Clinical Exam

Most skin cancers are not symptomatic. Given the relative low mortality associated with NMSC involving the head and neck, the primary benefit from early detection is the potential for less morbidity and disfigurement with excision. Although screening for malignancies has come under increasing scrutiny,[58] the American Cancer Society still recommends a cancer-related checkup every 3 years for asymptomatic men and women 20 to 39 years of age, and yearly for men and women age 40 and older. This includes examination of the skin. Clinical history, including environmental exposures that place patients at increased risk, may warrant more frequent checkups.[59] Although screening for skin cancers would seem relatively easy, considering the ability to visualize the area of concern, studies have failed to demonstrate the effectiveness of routine screening. In a review of the literature, Helfand and associates[60] found that although skin examination was accurate (sensitivity of 94% and specificity of 98% in one of the largest prospective studies evaluated), there was little support for formal, routine screening. They did find some support for screening of high-risk populations and suggested that strategies be developed to identify and screen those at highest risk. Because their review was not limited to NMSC of the head and neck, it would be difficult to know if screening and early detection do help minimize disfigurement in treatment of this subset.[60] Surgeons often deal with neglected cancers that reach large sizes, and it is difficult to know if these patients would avail themselves of screening opportunities even if they were available.

Physical Exam

Anatomy

The skin is made up of three layers: an outer epidermis, middle dermis, and subcutaneous layer. The outer layer consists of an outer keratinized layer with an underlying stratified squamous epithelium and innermost layer of germinative cells and melanocytes. The dermis is made up of connective tissue fibers embedded in an amorphous matrix of mucoproteins and mucopolysaccharides. The subcutis consists of adipose tissue with an underlying fascial layer. Supporting adnexal structures, including hair follicles, sebaceous glands, and sweat glands, reside in the deep dermis and subcutis. The many cell types that collectively make up the variety of malig-

Skin Types

Exposure to ultraviolet radiation plays an important role in the development of most skin cancers. Likewise, a

TABLE 31-1 Fitzpatrick's Sun Reactive Skin Types

Skin Type	Skin Color	Tanning Response
I	Caucasian	Always burns, never tans
II	Caucasian	Usually burns, tans with difficulty
III	Caucasian	Sometimes mild burn, average tan
IV	Brown	Rarely burns, tans easily
V	Dark brown	Very rarely burns, tans very easily
VI	Black	No burn, tans very easily

patient's skin type predisposes to damage from exposure to solar radiation. Fitzpatrick[61] described a scale (Table 31-1) based on skin reactivity to 30 minutes of sun exposure in the Northern Hemisphere. Although the Fitzpatrick scale is commonly used in the assessment of a patient's suitability for certain aesthetic skin resurfacing procedures, it is also useful for evaluating a patient's risk for the development of cutaneous malignancies that arise secondary to UV exposure.[61] Glogau's photoaging scale (Box 31-1) is also useful to quantify an individual's cumulative damage from solar exposure.[62]

Little wrinkling or scarring
No keratoses
Requires little or no makeup

Early wrinkling, mild scarring
Sallow color with early actinic keratoses
Little makeup

Persistent wrinkling or moderate acne scarring
Discoloration with telangiectasias and actinic keratoses
Always wears makeup

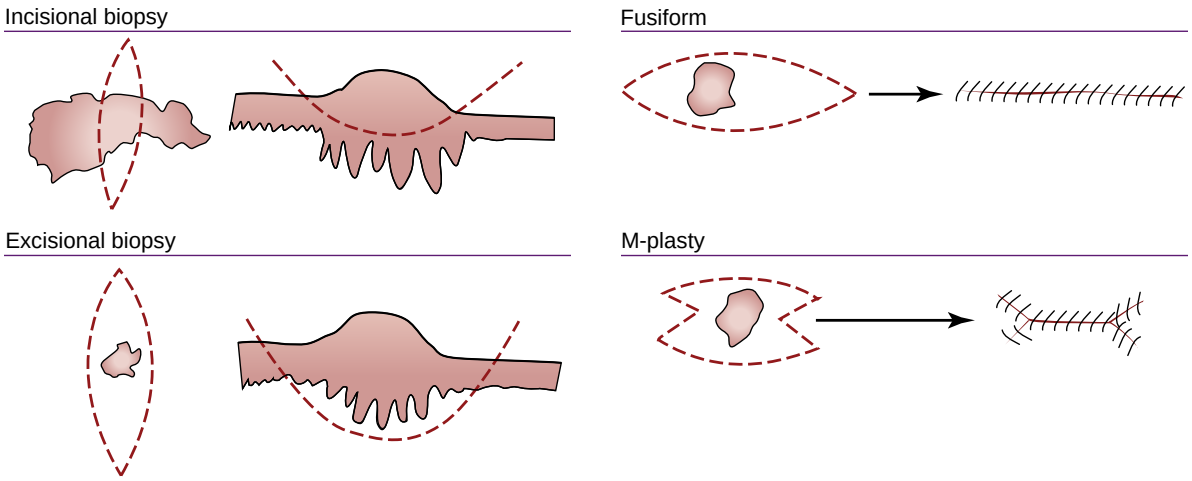
Wrinkling: photoaging, gravitational and dynamic
Actinic keratoses with or without skin cancers or severe acne scarring
Makeup with poor coverage

Nodes

Skin cancers typically spread by local extension; as noted previously, metastasis to regional lymph nodes is rare and represents an ominous finding. Lymph node involvement is usually associated with large, deeply invasive, or recurrent tumors. Distant metastasis is more rare, with the most common visceral site involved being the lung, especially for squamous cell cancers. The exact rate of lymph node metastasis from NMSC of the head and neck is unknown. O'Brien and his colleagues[63] reported on patterns of lymph node spread from cutaneous squamous cell cancer of the head and neck among 209 patients with known regional metastases. Among 209 patients, 171 (82%) had clinical parotid involvement, and of these, 28 had clinical neck disease. Whereas 143 patients had parotid disease alone, 38 (18%) had neck disease only. Level II was most commonly involved in the neck. Common sites of origin for metastases were usually lateral and included the cheek, pinna, and temple. Lesions from the anterior inferior face tend to metastasize to levels I, II, and III, whereas metastases from the nose tend to involve level I.[64] Involvement of parotid nodes can lead to facial nerve paralysis. At-risk patients presenting with a parotid mass, with or without facial nerve paralysis, should be carefully screened for potential skin cancer primary sites.

Biopsy

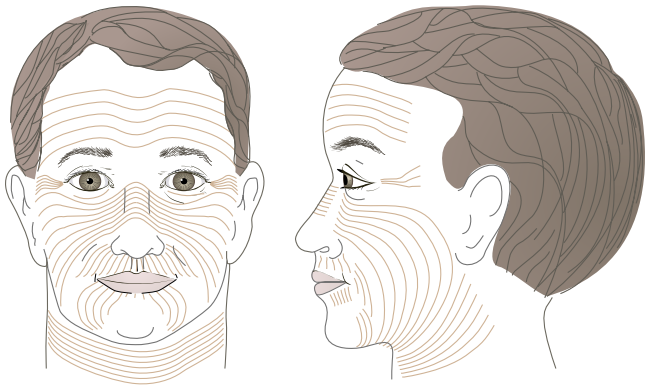
The goal of a biopsy is to remove a representative piece of tissue to allow histologic diagnosis. There are a variety of techniques available for obtaining tissue for histologic diagnosis, but all generally fall into two categories: incisional biopsy, including shave and punch biopsy techniques; and excisional biopsy (Figure 31-5).[65] The decision to perform an incisional or excisional biopsy should take into account the size and location of the lesion, as well as the surgeon's clinical impression of the lesion's behavior (benign or malignant). Incisional biopsies remove a portion of the lesion for histopathologic analysis before definitive treatment. A portion of adjacent tissue can be removed to allow the pathologist an opportunity to examine the transition between normal and abnormal tissue. Removal of tissue from this transition zone is more important in some vesiculobullous and pustular entities. It should be avoided in cases of suspected malignancy where there is a concern for seeding adjacent tissue, requiring a larger excision in the future. Obviously necrotic areas should be avoided for biopsy. Incisional biopsies are typically indicated in larger lesions, where complete removal is not appropriate without knowledge of the histologic diagnosis. Incisional biopsies are also indicated in areas where maximal preservation of tissue is important (e.g., eyelids) and histologic confirmation of diagnosis is necessary before planning definitive treatment. Incisional biopsies can take the form of shave or punch biopsy. Shave biopsy is best suited for raised lesions of suspected epidermal origin, such as basal cell carcinoma, early squamous cell carcinomas, and actinic keratosis. Although it can be used to remove benign nevi, it should not be used in cases of suspected melanoma in which the depth of the lesion guides therapeutic choices. It can also be a good technique for sampling bullous lesions because it allows the blister roof to remain attached. The technique is best performed with the patient in a comfortable position and the surrounding tissue under slight tension. The tissue can also be elevated with infiltration of local anesthetic directly deep, but not directly into, to the lesion. Excessive traction on



• **Figure 31-5** Biopsy techniques.

the surrounding tissue should be avoided because this can lead to a depressed scar. Bleeding is controlled with pressure, electrocautery, or application of a hemostatic agent, such as silver nitrate. Advantages of shave biopsy include less trauma and scarring at the biopsy site. The most important disadvantage is the potential that there will be inadequate tissue for diagnosis. Attempts to perform shave biopsies in larger squamous cell or verrucoid cancers, for example, can lead to sampling only superficial keratinaceous or necrotic debris. Sellheyer and colleagues[66] sought to compare the practice of shave versus excisional biopsy among plastic surgeons and dermatologists and found that dermatologists were more likely to perform shave biopsies of actinic keratosis (AK) and plastic surgeons were more likely to perform excisional biopsies. They suggested that shave biopsies were more appropriate in cases of diagnostically uncertain cutaneous lesions. They argued that this was especially true in cases of actinic keratosis, where shave biopsies provided a more cosmetic outcome and allowed treatment of confirmed AKs with cryosurgery or other topical therapy, sparing the morbidity of excision. Many surgeons would argue, neous malignancies, including squamous cell and basal cell cancers, carries prognostic information (as discussed earlier) that is not available from shave biopsies. For this reason, in the authors' opinion, shave biopsy should be reserved for suspected benign or smaller malignant lesions. Full-thickness biopsies that extend into the subcutis are preferred for all other lesions.

An alternative biopsy technique is the punch biopsy, which can be either incisional or excisional, depending on 4 mm being the most commonly employed. The technique



• **Figure 31-6** Relaxed skin tension lines (RSTLs) of the head and neck region.

should be held perpendicular to the skin surface, and tension can be placed on the surrounding tissue perpendicular to the resting skin tension lines (RSTLs) (Figure 31-6), which allows the final wound to take an oval shape parallel to the RSTLs, and more aesthetic healing. Once adequate depth is reached, the resulting core of tissue is amputated with a scalpel blade or scissors, taking care not to crush the specimen. The biopsy wound can be closed or left to heal by secondary intention.[65] Incisional biopsies can also be performed with a scalpel blade. Typically, fusiform incisions are designed to allow closure parallel to RSTLs. Incisional scalpel biopsies may be indicated when a larger piece of tissue is needed, or if the lesion in question lies deeper in the subcutaneous tissue. They are also helpful when tissue adjacent to the lesion is needed, as noted previously. If melanoma is suspected, the biopsy should be taken from the thickest portion, because depth and thickness serve as important prognostic indicators and guide selection of further therapy.

Excisional biopsies are typically reserved for smaller lesions, typically less than 2 cm. Fusiform type excisions with a length to width ratio of 3:1 are outlined parallel to the RSTLs. A margin of healthy-appearing tissue 2 to 3 mm wide at its closest point should be taken. A scalpel blade is

then used to excise the tissue, taking care not to crush or distort the specimen. Undermining of the adjacent tissue may be required for tension-free closure, but should be avoided if there is a question of incomplete removal so as to avoid seeding and distortion of adjacent tissue. If questionable, wounds may be dressed, and definitive closure delayed until final margins are available. The specimen should be oriented with a suture or ink. Advantages of excisional biopsy include providing the pathologist with the complete specimen for review and the possible convenience of a single surgery. The main disadvantage is that the pathology and margin status are unknown at the time of excision, and patients should be advised that final pathology may dictate further therapy.

In addition to choosing the appropriate technique for sampling the lesion, the surgeon must also decide on the most appropriate media in which to send the material to the pathologist. Although the vast majority of specimens are submitted for routine pathology in formalin, special circumstances may dictate that all or a portion of the specimen be submitted fresh or in alternative media. This decision is often made in concert with the histologist and is based on the need for special stains or studies, such as flow cytometry.

Imaging

Although advances in imaging have arguably had the greatest impact on the surgical care of head and neck cancer patients in general, imaging is rarely part of the workup of the routine patient with cutaneous malignancy of the face and neck. Clinical exam alone provides enough information in the majority of cases. Surgeons may consider imaging, however, in cases of deeply infiltrating, recurrent, or multiple lesions. Involvement of critical areas (eyelid or conchal bowl, for example) or higher potential for lymph node involvement (see discussions under management of lymph nodes and predictors of biologic aggressiveness) can also be indicators for cross-sectional imaging. In the past, surgeons dealing with larger skin malignancies were confronted with operating on tumors with only a clinical examination of the surface characteristics. Currently, excellent three-dimensional representations are available with which to plan surgery and allow more conformal radiation treatment.

In the 1980s computed tomography (CT) scan became a part of the evaluation of this subset of patients with more advanced cutaneous malignancies in an attempt to examine the extent of the primary involvement of adjacent anatomic structures and to search for evidence of regional nodal metastases. CT scans with 3-mm cuts and soft tissue windows are effective for evaluating depth of invasion and potential lymph node metastasis. Specific criteria, such as size, loss of fatty hilum, central necrosis and spherical shape, are available for defining nodes as suspicious for metastatic involvement.[67] Additional indications for CT imaging include long-standing scalp lesions or other lesions suspicious for bone involvement, which should be imaged with finer (1 mm) cuts with bone windows through the area of concern.

In the 1990s, magnetic resonance imaging (MRI) began to challenge the CT scan. Its exquisite anatomic detail and lack of radiation, however, are associated with higher cost and a lengthy, uncomfortable exam. At this point, MRI is reserved for evaluation of tumors with extensive soft tissue involvement and is especially helpful in evaluating potential perineural extension.[67] Also, newer techniques that modulate the magnetic field in an attempt to examine changes in the bone marrow hold promise for evaluating bone involvement that may offer better sensitivity than CT with fine cuts. Tumor invasion into the marrow space is accompanied by a lower intermediate signal and is best seen on T1-weighted sequences.[68]

The role of positron emission tomography/computed tomography (PET/CT) has yet to be fully defined in NMSC. Although this whole-body imaging modality has become a standard procedure in detecting malignancy in many areas of clinical oncology, data to support PET in routine staging of NMSC are still emerging. Isolated case reports document the use of PET in basal cell carcinoma[69,70] and squamous cell carcinoma[71,72] but few large studies exist to make useful conclusions. Cho et al[73] retrospectively reviewed 12 cases of cutaneous squamous cell carcinoma and noted that PET/CT detected the primary lesion in nine cases, lymph node involvement in three cases, and distant organ involvement in one case. All these areas were confirmed positive by histology, although PET-negative areas were not confirmed to be negative by histology. The authors noted that all patients with regional or distant metastatic disease had high-risk primaries as determined by size, location, poorly differentiated histology, and immune status of the patient. Fosko et al[74] published a series of six patients with head and neck basal cell carcinomas larger than 1 cm and noted that three of the primary lesions were not detected by PET/CT, including an aggressive 3.1-cm recurrent BCC with extensive perineural spread. Although the majority of cutaneous malignancies are SCC and BCC, PET imaging has been advocated in uncommon forms of skin cancer such as Merkel cell carcinoma,[75] apocrine sweat gland carcinoma,[76] primary cutaneous lymphoma,[77] and melanoma.[78-80]

Staging of Skin Cancer

Accuracy in staging of cancer is critical for comparison of treatment modalities and for following outcomes. The staging of non-melanoma skin cancers follows the tumor, node, and metastases (TNM) system proposed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (IUAC).[81] The staging system undergoes constant review and updating, and the rules for staging of skin cancer are specific. Most cutaneous basal cell carcinomas are not staged, leading to the primary application of the non-melanoma staging to squamous cell carcinomas. Clinicians should be familiar with changes in the staging system and strive for consistency in staging. Technological advances lead to stage migration; for example, improved ability to detect earlier metastatic disease with CT scans leads to more patients being diagnosed with late-stage disease. Clinical staging of skin cancer is based on all clinical data available

before initiation of treatment, which at a minimum includes data from the physical exam. If available, imaging data are included. It does not include information gained during the surgical procedure. If surgery is performed, a pathologic staging is possible based on examination of the surgical specimen. This is designated by inserting the letter *p* in front of the TNM stage. Standard staging of non-melanoma skin cancer of the face excludes the eyelid, which has its own staging criteria based on different prognostic variables.

A summary of the current staging follows:

Primary Tumor

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor less than 2 cm in greatest dimension with less than 2 high-risk features
- T2: Tumor more than 2 cm or Tumor any size with 2 or more high-risk features
- T3: Tumor with invasion of maxilla, mandible, orbit, or temporal bone
- T4: Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base

If there are multiple synchronous tumors, the lesion with the highest T stage is used and the number of separate tumors is indicated in parentheses. For example, if the largest lesion is 3 cm and there are 3 other lesions, all of which are smaller, the clinical T stage would be T2(3).

Regional Lymph Nodes

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
- N2a: Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension
- N2b: Metastases in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension
- N2c: Metastases in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension
- N3: Metastasis in a lymph node, >6 cm in greatest dimension

Distant Metastases

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

- Stage 0: TisN0M0
- Stage I: T1N0M0
- Stage II: T2N0M0
  - T3N0M0
- Stage III: T4N0M0
  - Any TN1M0
- Stage IV: Any TN2M0
  - Any T
  - Any NM1

Also, additional descriptors are available to better define the system: an *m* suffix (T(m)NM) designates multiple primary sites, a *y* prefix (yTNM) indicates that staging was performed during or following multimodality treatment, an *r* prefix (rTNM) indicates a recurrent tumor staged after a disease-free interval, and an *a* prefix (aTNM) designates a stage determined at autopsy.

The current staging system offers clinicians a consistent system to classify tumors for comparison of treatment strategies and evaluating prognosis. Certain factors known to affect prognosis are taken into account. There are, however, shortcomings. The current system does not take into account several known factors that influence skin cancer behavior and survival. The most important factor neglected in the current system is the tumor-host relationship and factors that influence it, such as nutrition, immunologic factors, and performance status. Head and neck skin cancer patients typically are older and suffer from multiple other medical conditions. Certainly the TNM staging system will continue to undergo revisions to enhance its utility. Unfortunately, with these revisions, the simplicity of the system will be difficult to maintain. O'Brien[63,82] has suggested that the staging system should be altered to include the location of nodal disease (e.g., neck vs. parotid). The authors found that involvement of neck nodes was worse than involvement of parotid nodes. They also noted that involvement of neck nodes was a predictor of survival and that involvement of multiple nodes was associated with a worse outcome.

The seventh edition of the *AJCC Staging Manual*[81] introduces new parameters previously not incorporated into staging criteria for cutaneous squamous cell carcinoma. The T stage now accounts for high-risk features that are outlined in Table 31-2. The presence of two or more of these high-risk features elevates a T1 tumor to a T2. This highlights potentially more aggressive tumors regardless of size. Although this is a helpful addition, some clinicians have been critical of the omission of additional high-risk features such as basosquamous morphology, lymphovascular invasion, or inflammatory response.[83] Nodal involvement has been expanded to note size of nodes, number of nodes, and laterality. These updates should improve data

TABLE 31-2 High-Risk Features for Primary Tumor (T) Staging for Cutaneous Squamous Cell Carcinoma

Depth/invasion	>2 mm thickness (Breslow thickness)
	Clark level ≥IV
	Perineural invasion
Anatomic location	Primary site ear
	Primary site hair-bearing lip
Differentiation	Poorly differentiated or undifferentiated

collection and guide prognosis, but some authors believe additional characteristics should be included in the staging, including hypopigmentation. Cure rates in actinic keratosis are around 99%, and in smaller BCC and SCC (<2 cm) cure rates are also satisfactory (94% to 99%).[86-88]

sively.[84,85] Extracapsular extension in nodal basins is not included in the N-staging, although this is a known poor prognostic factor.[83]

Treatment

Surgery

Once the diagnosis is made and the indicated workup completed, the clinician must decide on treatment. Surgery is the mainstay of therapy for the vast majority of cutaneous head and neck malignancies. Because basal cell and squamous cell cancers make up the vast majority of skin cancers, our discussion focuses on the surgical principles involved in their treatment.

Cryotherapy

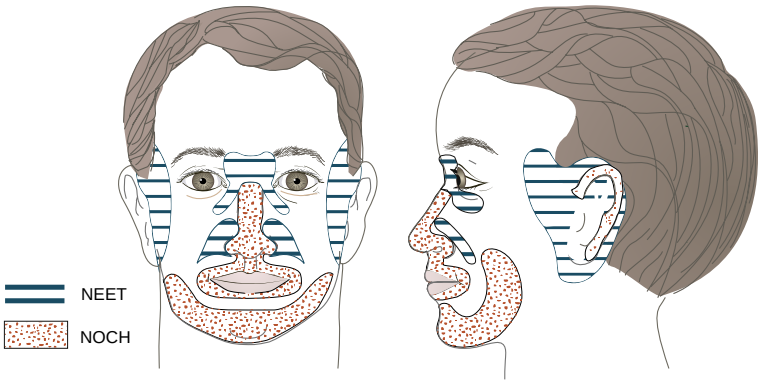
Although not specifically a surgical therapy, cryotherapy creates a wound more akin to traditional surgery than other medical therapies and is therefore considered here. Indeed cryotherapy (or cryosurgery) can be used in lieu of surgical excision in cases of actinic keratosis and some early BCC and SCC. The most common technique includes the application of liquid nitrogen with a spray device that cools the skin to −50° C and to a depth of 1 to 3.5 mm.[86] Multiple applications may be used, but most commonly two applications are performed. An area of surrounding skin should be frozen as well to ensure clearance of cancerous cells. The diameter of the surrounding "halo" that is visualized around the application area correlates roughly with the depth of the freeze. Use of local anesthetic is optional in most cases, as the cooling has an anesthetic effect. A local anesthetic can be infiltrated, however, if the thaw phase causes undue discomfort. Cryotherapy does not provide a specimen for histologic examination and is generally reserved for actinic keratosis and very early BCC and SCC with well-defined borders. An additional disadvantage is the potential for unfavorable

Curettage/Electrodesiccation

Curettage of skin lesions followed by electrocautery or chemical cautery is used with success on many smaller skin lesions of the trunk and extremities, but it is rarely indicated on the skin of the face, where the potential for unfavorable scarring precludes its use in most cases. The technique involves removal of the lesion using sequentially smaller curettes and relies on the tactile sensation of the surgeon to identify when normal tissue has been reached and the tumor has been removed. It is used by many dermatologists as a first-line treatment of smaller BCCs.[89] Some authors have recommended curettage alone without the electrodesiccation in an attempt to avoid some of the hypertrophic scarring associated with the use of electrodesiccation. Alterations in pigmentation can still result in an unacceptable scar. If it is performed on the face, its use should be restricted to those areas known to heal well by secondary intention—the so-called NEET areas: concave surfaces of the nose, ear, eye, and temple. In contrast, it should be avoided on the NOCH surfaces: convex surfaces of the nose, lips, cheeks, and chin (Figure 31-7).[90] Curettage is best suited for the treatment of thick actinic keratosis and smaller, exophytic squamous and basal cell cancers (typically less than 1 to 2 cm). Cure rates are high (>90%) with selection of appropriate lesions. As with cryotherapy, no specimen is generated for histopathologic exam.[86,91]

Laser Excision, Ablation, and Resurfacing

A variety of lasers are available for use by surgeons to ablate and excise lesions; lasers also can act as an energy source for activating photosensitizers, which are administered to patients and selectively taken up by tumor cells. The biologic effect of a laser is dependent on its absorption by the target tissue, and the wavelength determines the ultimate effect. A variety of laser media are available, including CO_2, argon, ruby, and Nd:YAG, to alter the absorption characteristics of the beam. In addition, altering the size of the beam as well as the delivery mode—continuous, pulsed, or



• **Figure 31-7** Areas of the face that can heal by secondary intention.

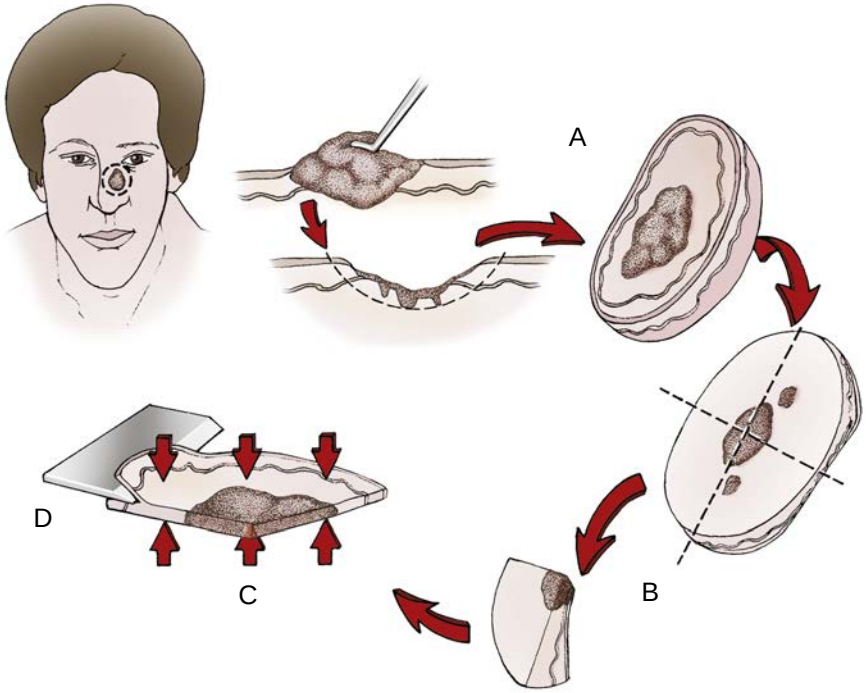
Q switched—changes the effect on the tissue as well. Lasers can be used in a continuous, focused mode for excisions with minimal thermal injury to surrounding tissue and excellent hemostasis. Larger beam sizes in a variety of energy modes can be used to ablate larger areas with minimal thermal injury to the underlying tissue, allowing for more rapid and complete healing by secondary epithelialization. Laser ablation is often indicated for resurfacing large areas of skin with actinic photodamage as an alternative to chemical peeling or other medical therapies. Hantash and colleagues[92] compared carbon dioxide laser resurfacing, topical 5% fluorouracil, and 30% trichloroacetic acid (TCA) peel for the prevention of squamous and basal cell carcinomas in patients with actinic keratosis and a history of non-melanoma skin cancer associated with severe photoaging. All demonstrated a statistically similar reduction in the number of actinic keratoses (range 83% to 92%), a lower incidence cond pri-

Mohs Micrographic Surgery

The current technique of Mohs micrographic surgery evolved from Dr. Frederic E. Mohs' chemosurgery technique, which he developed while working with Professor M. F. Guyer in the Department of Zoology at the University of Wisconsin.[93] Dr. Mohs was evaluating the effects of zinc chloride on cancerous tissue when he discovered that in addition to tissue necrosis, zinc chloride resulted in fixation of the tissue, which provided an excellent specimen for histologic examination. A paste was ultimately developed, which contained a binder *(Sanguinaria canadensis)*, a matrix (Stibnite; Hummel Chemical Co., South Plainfield, NJ), and zinc chloride 45% by weight. In 1941, Mohs presented his technique of chemosurgery. This technique involved application of the fixative for a prescribed time (maximum tissue penetration occurs at 18 hours following application), followed by removal and microscopic examination of the fixed tissue. Depth of penetration was controlled by altering the thickness and surface area on which the paste was applied. Successive layers were removed until tumor clearance was accomplished.[93,94] An important part of the procedure was the specific way in which Dr. Mohs oriented his specimen, which in theory allowed examination of 100% of the margin. Others argue that the most important component of the technique is that the surgeon performing the excision is also evaluating the margins. This decreases the potential for communication error, especially regarding specimen orientation, that may occur between surgeon and pathologist, because in this case they are one and the same.[95] At the time of his original work, frozen section analysis of margins was not available, and although labor intensive, the fixed tissue technique allowed for significantly improved cure rates compared to traditional surgical excision. Several modifications of the technique occurred, including elimination of the fixative in most cases, and in 1953 Dr. Mohs presented his technique modified for use with fresh tissue and frozen analysis of margins. Careful orientation of the specimen was the same, and the entire margin was still evaluated, which offered advantages over traditional surgical excision and margin analysis.

Although it is beyond the scope of this chapter to discuss the nuances of processing tissue for histologic examination, some discussion of margins is necessary to understand the advantage of Mohs surgery. A clinical margin refers to the edge of the lesion as appreciated clinically. A surgical margin is defined as the tissue edge of the specimen. Margins can be assessed as clear, close, or involved. Close margins are often defined differently by various pathologists, and surgeons should discuss the meaning of a "close" margin with the pathologist in order to decide whether or not further treatment, most commonly re-excision, is warranted. Tumor shrinkage of up to 40% can occur when a specimen is removed and processed, leading to a close margin when the excision seemed adequate clinically.[96] When a specimen is removed and oriented for the pathologist, there are several techniques for processing it for analysis. Traditionally, specimens are bisected or cross-sectioned in a vertical plane for examination. Alternatively, the specimen may be "bread-loafed" and cross-sectioned for greater visualization of the tumor and margins. The most comprehensive processing technique involves peripheral sectioning of all four sides of the tumor with or without a deep layer. Despite these variations, often less than 0.1% to 1% of the tumor margin is analyzed in the vertical sectioning techniques of traditional pathologic processing. It is impossible to examine the entire margin in a vertical technique because complete serial sectioning of a 1-cm tumor would require 2000 5-µm sections. By necessity, skip sectioning is performed. Asymmetric tumor growth can lead to tumor extensions between areas examined in a vertical technique.[95] By contrast, Mohs' micrographic excision technique is a horizontal and oblique sectioning technique, which theoretically allows examination of 100% of the deep and lateral tumor margins.

Mohs micrographic surgery is typically accomplished with the patient receiving a local anesthetic. The tumor is initially debulked using scalpel excision or curettes. This is followed by a lateral, beveled excision (45 degrees) joining a more horizontal excision of the deeper portion of the tumor bed. The specimen is carefully oriented with an accurate specimen map (Figure 31-8). Larger specimens may be divided by cross-sectioning, which is reflected on the specimen map. Inking edges with different colored inks can also aid in orientation. The specimen is inverted and mounted on the cryostat. Frozen margins are processed and examined from the undersurface of the specimen. These frozen sections are then evaluated and residual tumor is documented on the specimen map. Further layers are taken from the areas that were positive for tumor. The process is continued until a clear layer is reached. Typically this takes two or three layers.[97] Mohs' micrographic technique is best suited for tumors that grow in a contiguous fashion. Discontinuous tumor extension (emboli, for example) limits its utility because a clear margin may not ensure complete tumor removal—"skip" tumors may remain.



• **Figure 31-8** Mohs micrographic surgery. **A,** Tumor may be debulked with a curette and the remaining defect is excised. **B,** The specimen is oriented and frozen sections are obtained. **C,D,** The specimen is inverted on a cryostat to obtain full view of the deep margins by slicing with a microtome.

Reported indications for Mohs' micrographic technique include aggressive tumors (poor histologic characteristics), recurrent tumors, high-risk anatomic locations (H-zone of the face; see discussion earlier), and areas in which preservation of uninvolved tissue is of paramount importance for aesthetics or function (eyelids, for example) (Box 31-2).[98]

• BOX 31-2 Selected Indications for Mohs' Micrographic Surgery

Recurrent tumor
Tumor larger than 2 cm in diameter
Aggressive pathology or histologic features (perineural invasion, poorly differentiated squamous cell carcinoma, morphea-form basal cell carcinoma)
Tumors in certain anatomic locations where maximal preservation of tissue is desired (eyelid, canthus, ear, lip, nose)
Ill-defined borders
Tumors located in areas associated with aggressive behavior (H-zone)

Traditional Surgical Excision

Traditional surgical excision (TSE) involves removal of an arbitrary margin of healthy tissue in an attempt to encompass the tumor. This is followed by analysis of the margins with either intraoperative frozen sections or postsurgical permanent sections. The initial margin outlined around the lesion should take into account the size and histology of the lesion. Although there is no "gold standard" for initial margins, the literature does offer recommendations based on recurrence rates and positive margins following excision using various margins. For example, an initial peripheral margin of 4 mm will clear 98% of nodular basal cell cancers, whereas a 2-mm margin will clear only 75%. More generous margins, 8 to 10 mm, have been suggested for more aggressive BCC, such as the morphea-form subtype. For smaller BCCs (5 mm or less), initial margins of 3 mm may be acceptable.[99-102] Initial margins of 4 to 6 mm, which will clear the tumor in 95% of cases, are suggested for small to medium SCCs. More advanced lesions require margins of 10 to 20 mm. The depth of excision should include the subcutaneous tissue immediately subjacent to the tumor in most cases of squamous and basal cell cancers. Underlying fascia or periosteum is included in tumors with deep extension or fixation, and routinely in other histologies, such as DFP and Merkel cell carcinoma.[103]

Surgeons can use intraoperative examination of margins similar to Mohs' technique. Strong and his colleagues[104] describe their use of intraoperative peripheral in-continuity tissue examination in which 4-mm margins are taken for basal cell cancers and 6-mm margins are taken for squamous cell cancers. This is followed by orientation of the specimen and processing that allows frozen section examination of the margins similar to Mohs micrographic surgery. It requires excellent communication with the interpreting pathologist. The accuracy of intraoperative frozen section analysis for cutaneous malignancies of the head and neck is high (85% to 98.3%), but must be weighed against the resources necessary to carry out these procedures, and the low incidence of positive frozen margins requiring further excision.[105,106]

Treatment following positive margins on the final pathology report must be tailored to the individual patient. Most surgeons would recommend re-excision of squamous cell cancers with positive margins.[107] Treatment of positive margins in basal cell cancer excision is more controversial. Although some authors have suggested a watch and wait approach, most surgeons would opt for further excision if possible, with strong consideration given to Mohs' technique.[57,107,108] In some cases, however, re-excision may not be possible. Patients may refuse further surgery, or extensive flap coverage accomplished before final margin status may make accurate re-excision impossible. For this latter reason, surgeons may opt for delayed repair of the defect with careful analysis of permanent sections before committing to complex repair techniques. Positive margins can be an indication of biologic aggressiveness. In cases of initial positive margins, consideration should be given to postoperative radiation therapy even if re-excision has been performed. In addition, the need for a structured follow-up regimen should be stressed to the patient.

Traditional Surgical Excision versus Mohs Micrographic Surgery

There is ongoing debate regarding the choice of surgical technique for cutaneous malignancies of the head and neck. Kropp and colleagues noted that the 5-year overall survival in patients with head and neck skin cancer treated with Mohs excision was 86%, as compared to traditional surgical excision resulting in a 76% 5-year survival.[109] Despite the advantages of Mohs surgery discussed previously, there are well-known disadvantages, including the labor and time intensiveness of the technique, which can drive up costs of excision. Cost comparisons between Mohs micrographic surgery and traditional surgical excision (TSE) have been difficult, and results contradictory.[110,111] Bialy and colleagues[112] performed an interesting study comparing TSE and Mohs excision, and found that the costs were comparable when the Mohs technique was compared to TSE with frozen section control of margins or when compared to cases that included further treatment for inadequate margins. They cautioned, however, that choice of repair technique often influenced costs more than the method of excision. Dermatologic surgeons experienced in the Mohs technique often allow certain wounds to heal by secondary intention instead of performing coverage by local flap or grafting. Also, their excisions take place in an outpatient clinic. Patients undergoing surgery using local anesthesia may not tolerate excision of larger tumors, which often require multiple layers and lengthy procedures. This can build in a case selection bias when investigators attempt to compare the two techniques as larger, more complex tumors are more likely to undergo traditional surgical excision. Mohs surgery can be performed using a general anesthetic, but costs are increased significantly.[112] Given the sheer number of cutaneous malignancies, some have argued that Mohs surgery should be reserved for specific indications (see Box 31-2), and that traditional surgical excision is faster and allows for an acceptable cure rate. Finally, the decision to perform Mohs' excision technique versus traditional surgical excision may be determined by availability. Patients in many areas simply do not have access to a surgeon or dermatologist with training and competence in Mohs' surgical technique. Properly performed traditional surgical excision, with or without frozen section control, remains an option for most lesions in the head and neck.

Lymph Node Involvement in Cutaneous Malignancy

Regional lymph node metastases from cutaneous malignancies of the head and neck, although rare, must be considered. Lymph node metastases are an ominous finding and are usually associated with a poor outcome. Although clinically apparent nodal involvement is a clear indication for therapy, surgeons continue to search for predictors that would indicate the need for elective evaluation, including sampling of nodal basins at risk, in cutaneous malignancy, and without known regional metastasis. There are currently no accepted guidelines, and surgeons must rely on data gathered mostly from retrospective analysis and their own experience. Factors associated with regional metastases include recurrent lesions, thickness greater than 4 mm, and size greater than 2 cm. In addition, clinical perineural invasion is associated with a higher risk of nodal disease, and according to some authors, therapy should include treatment of first-echelon nodes (see earlier discussion on indicators of aggressive behavior in skin cancer).[54,113]

The lymph nodes in the parotid area deserve special attention because they serve as first-echelon nodes for many facial cutaneous malignancies.[114] As many as 20% of malignant parotid masses represent spread from cutaneous malignancy.[115] In Australia, metastatic cutaneous cancer is the most common parotid malignancy, with SCC occurring most frequently.[64] Metastatic parotid involvement by cutaneous SCC indicates the need to address the ipsilateral neck. In 73 patients with metastatic SCC involving the parotid, O'Brien found a high incidence of clinical and occult neck disease, 26% and 35%, respectively.[82] Based on a follow-up study, reported by Vauterin,[63] they recommended elective treatment of the neck with a supraomohyoid neck dissection, including the external jugular nodes, in patients with parotid involvement and a clinically negative neck. In cases of posterior lesions, level V should be included as well. In patients with clinical neck involvement, they recommended a comprehensive neck dissection.[103] One of the challenges facing surgeons is predicting which nodal basin would harbor occult disease if it is present. Lymphatic drainage of the face is not always predictable, and lymphoscintigraphy and sentinel node biopsy (SNB) techniques used in melanoma have demonstrated that drainage patterns can vary from predicted routes, and extended dissections may be needed to address occult disease.[116]

The sentinel node technique, previously validated in melanoma and breast cancer, has been investigated for use

in head and neck cancer, including non-melanoma skin cancer.[117-119] Theoretically, it allows the identification and removal of the lymph node that would first receive metastases from a given site. The technique involves injecting the area surrounding the primary site with a radioactive labeled tracer, usually ^{99m}Tc-sulfur colloid. Various molecular weights can be chosen depending on the transit time desired. At this point a radiograph can be taken to localize the sentinel node, which is the first node that receives lymph flow from the area of the tumor. The patient is then taken to the operating room, where the surgeon may inject a blue dye around the tumor. Again, this will drain to the first-echelon node, staining it blue, and assist the surgeon in identification during surgery. Also, the surgeon can use a gamma detection counter probe to identify the node with the highest concentration of radioactive colloid. This node is then removed. If it is positive, further treatment, such as radiation or more extended nodal dissection, may be indicated. Although its utility in cutaneous melanoma has been demonstrated, with accuracy of 82% to 100% and very few false negatives, the technique has shown only modest utility in non-melanoma skin cancers.[117,118] Basal cell cancers have a very low propensity for metastases, and therefore sentinel node biopsy does not seem to be warranted. Cutaneous squamous cell cancer, however, carries a higher risk for regional metastasis. Some studies have reported rates as high as 16% in cutaneous head and neck sites.[119] Sentinel node sampling may play a role in evaluation of patients whose cutaneous squamous cell cancer demonstrates poor histologic variables or those who present with large, deep lesions.[117,120] The sentinel-node technique can help overcome some of the inherent difficulties in nodal dissection for cutaneous malignancies, such as identifying which nodal basin is most likely draining the involved site, and therefore allow a more focused removal of the at-risk nodes. It may be especially indicated in Merkel cell cancers, which are known for their propensity to metastasize to regional nodes.[117,121] Devaney offered an excellent review of the current role of sentinel node biopsy for head and neck tumors, including cutaneous malignancies, and concludes that we will likely see further refinements and applications of the technique to a variety of head and neck cancers.[122] At this time, elective treatment of the neck with traditional or sentinel-node technique is not warranted without clinical evidence of involvement of regional lymph nodes, parotid, or neck.

Repair

The ability to repair or refer for repair a variety of wounds is an integral part of the management of skin cancers. The majority of wounds can be managed using healing by secondary intention, primary repair, or local flaps. Regional and even distant flaps may be necessary in a minority of cases. With experience, most surgeons develop their own preferences and "go-to" repair techniques. Here we review some of the general principles involved in repair of facial defects following excision of skin lesions. Before surgery, surgeons should have a reconstructive plan, which will be altered as necessary following excision, at which time the most appropriate method of repair is selected based on patient and defect characteristics. Consideration of the repair options preoperatively will help orient the excision in the appropriate manner, whether for primary closure or flap repair. An attempt should be made to orient the excision in such a way as to allow its closure along resting skin tension lines (see Figure 31-6). Likewise, if a local flap is required, proper planning can allow closure of the defect created by flap development along RSTLs as well. Although primary repair is convenient and possible in many cases, patients with large tumors or those with indications of biologic aggressive behavior (see earlier) may be best served with delayed repair. Delayed repair offers several advantages, including time for assessment of margins with permanent technique and an opportunity to assess the defect and choose the best technique for repair. Friedrich[22] examined 124 patients who underwent surgical treatment for 216 basal cell carcinomas, the majority of which were located in the middle third of the face. Further resections were indicated in 71% after histologic examination of the margins. Because of the complexity of techniques involved, surgeons should consider delayed reconstruction in cases of questionable margin status, aggressive histologic variables (such as perineural invasion or bone involvement), or if postoperative radiation is planned. Importantly, delayed repair can allow the patient an opportunity to see the defect and participate in the decision-making process. Wound contracture during the delay can result in a more favorable defect. In addition, granulation tissue that develops in the bed during the delay often results in better acceptance of skin grafts. Properly maintained, cutaneous wounds can be maintained with a moist dressing for weeks without an increased risk of infection. Escobar and Zide[123] reviewed 280 patients managed with delayed repair techniques following excision of skin lesions. Some patient repairs were delayed up to 35 days with minimal complications. Delayed repair may also be indicated to take advantage of the ability of skin to expand when placed under tension (skin creep). Skin creep occurs by two mechanisms: mechanical, which is a more acute phenomenon, and biologic, which is a more long-term response of skin to load. For example, skin expanders can be used intraoperatively to expand flaps, taking advantage of mechanical creep. They can also be buried and activated over weeks to allow expansion through growth of new tissue (biologic creep).[124] Some patients, however, will not accept delayed repair, and others may not be candidates for delayed repair for a variety of reasons; in these cases, repair at the time of excision may be warranted.

Surgical repair of all wounds is not always necessary, and healing by secondary intention is a viable alternative in some cases. Certain areas of the face are more amenable to healing by secondary intention and may not require repair (see Figure 31-7). Concave surfaces of the nose, ears, eyes, and temple are associated with more acceptable scarring following healing by secondary intention, whereas convex

surfaces of these same areas typically heal poorly by secondary intention (see previous discussion under biopsy). Wounds located at the junction of facial aesthetic subunits typically are well hidden.[125] Patient characteristics, such as age, should be taken into account. Although aged skin tends to heal with less scarring, these individuals may be unable to care for the wound without assistance.

In recent years, negative pressure applied to wounds by use of a vacuum-assisted closure (VAC) device has gained popularity. This device accelerates and improves wound contracture. Vacuum-assisted closure increases blood flow and granulation tissue formation and aids in the removal of fluid and surface contaminants.[126] Aside from aiding in the management of open wounds, it serves as an excellent bolster for skin grafting, leading to increased survival.[127] It may also be used in preparation for delayed skin grafting, as it typically results in an excellent granulation bed. It is not recommended in cases in which there is concern for residual tumor in the wound bed.

Full- or split-thickness skin grafting allows repair of large wounds that are not amenable to healing by secondary intention and in which flap repair is not indicated or necessary. Unlike flaps, grafts are dependent on nutrition from the recipient bed (plasmatic circulation or imbibition) for 48 to 72 hours until capillary ingrowth and inosculation occurs. During the early wound healing phase, absolute stability of the graft provides the best opportunity to prevent shearing and graft loss. Full-thickness grafts include the epidermis and dermis and usually provide a more aesthetic result with less late wound contracture if there is satisfactory acceptance of the graft. The supraclavicular and postauricular areas provide good-quality skin for full-thickness grafting with good color match for most facial sites. Skin harvested from the upper eyelids provides an excellent thin full-thickness graft. Disadvantages of full-thickness grafting include need for closure of the donor site and increased risk for either partial or complete graft failure. Split-thickness grafts include epidermis and a portion of the dermis. Healing of the donor site depends on epithelial migration from skin appendages and lateral edges. Split-thickness grafts are less aesthetic in most cases and are susceptible to more contracture. Advantages include the ability to cover larger areas and greater success with graft take.

Composite grafts contain skin and additional tissue, such as cartilage. Although sometimes used for reconstruction of small alar defects, healing of composite skin/cartilage grafts from the helix is unpredictable.

Flaps

Wounds that are not amenable to grafting require flap coverage. Flaps import their own blood supply, which may be random or axial. Most facial skin defects resulting from cancer extirpation can be managed with random, local flaps, including advancement, rotation, and transposition flaps. Use of flaps creates a second wound, which must be repaired, and the design of the flap should keep this in mind. Advancement and rotation flaps usually create excess tissue at one or both ends of the incision. Although they can occasionally be removed with Burow excision or some modification, this "dog ear" or "standing cone" frequently should be left in place, as it will resolve with time and allow maximal preservation of tissue. Axial pattern flaps are based on larger caliber vessels and can be designed with a narrow base carrying a large territory of tissue. They may be regional or distant in the form of free tissue transfer. Regional flaps commonly employed for larger facial wounds include cervicofacial and cervicopectoral flaps.[128] Free tissue transfer is indicated when local and regional tissues are not adequate and are usually required when composite defects have been created.

Regardless of technique, secondary procedures, such as dermabrasion or scar revision, are frequently necessary for an acceptable result. Patient education plays a critical role in managing expectations, because some patients have unrealistic goals, and surgeons can be drawn into an endless series of efforts to create an "invisible" wound with diminishing returns.

Medical Management

Systemic and Topical Medications

Basic sun protection is the starting point for all skin cancer prevention protocols. Targeted approaches to higher-risk patients are used on an as-needed basis. Chemoprevention involves administering a drug in the hopes of reversing or preventing malignant transformation. It has been applied successfully, using tamoxifen, to patients at increased risk for breast cancer. Chemoprevention is an appealing approach to patients who are at high risk for development of cancers. Field cancerization, as presented by Slaughter in 1953,[129] is a concept that is well known to oral cancer surgeons who have dealt with multiple recurrences following seemingly margin-free resections. Slaughter described histologic abnormalities in tissue not contiguous with the primary tumor, and proposed that this may result in multiple recurrences following treatment. Later work demonstrated that seemingly clear histologic margins harbored precancerous genetic abnormalities.[130] Similarly, some patients with NMSC suffer from multiple recurrences, leading to multiple surgical interventions, and certain populations are known to be at higher risk. These include patients with xeroderma pigmentosum, a rare, autosomal recessive disorder characterized by an impaired ability to repair UV radiation induced damage to DNA, with a resultant increase in skin cancer. These patients develop skin cancers early in life (as early as 2 years old) and with a frequency 1000 times that of the general population.[131] Also, patients with basal cell nevus syndrome—a rare autosomal dominant disorder characterized by multiple odontogenic keratocysts, multiple basal cell carcinomas, hypertelorism, frontal bossing, palmar or plantar pitting, calcified falx cerebri, bifid ribs, and medulloblastomas—are at risk and have been shown to benefit from chemoprevention with retinoids in some cases.[132] As discussed previously, non-melanoma skin cancers have been a vexing problem for transplant surgeons ever since chronic

immunosuppression, which leads to a marked increase in susceptibility to NMSC, made solid organ transplants feasible.

Retinoids are vitamin A derivatives and have been widely studied as chemopreventive agents in skin, oral, breast, and cervical cancers. The relationship between hypovitaminosis A and development of certain cancers led to the study of retinoids for chemoprevention when they were synthesized in the 1970s. By binding to two families, retinoid acid receptors and retinoid X receptors, retinoids affect keratinocytes by modifying their maturation, growth, cell surface, and immune modulation. Retinoids, both systemic and topical, have been the most widely studied medication for chemoprevention. Currently, two retinoids are available: isotretinoin and acitretin, which has a longer half-life. De Graaf and colleagues reviewed topical and systemic retinoids in transplant patients and found that acitretin was particularly effective for prevention of NMSC development in these patients, but the effect was present only while the patient was receiving therapy. Topical retinoids had some effect on actinic keratosis only. Unfortunately, side effects, such as elevation of triglyceride and cholesterol levels and negative liver function tests, limit their long-term use in many patients.[133] Campbell[134] also reviewed the use of the systemic retinoids isotretinoin, etretinate, and acitretin for skin cancer chemoprevention in high-risk patients, such as patients with basal cell nevus syndrome, transplant patients receiving immunosuppression therapy, and patients with multiple recurrent skin cancers. He also recommended starting with low doses and employing appropriate laboratory and radiographic screening to determine toxicity and side effects. Although systemic retinoids do not inhibit healing of surgical wounds, they can predispose to excessive granulation tissue. In addition, the dryness associated with retinoids can increase bacterial colonization, leading to increased risk of infection following surgery. Additionally, side effects of systemic retinoids, including dryness of nasal mucosa, cheilitis, xerosis, blepharitis, and conjunctivitis, often decrease patient compliance. Early treatment of these mucocutaneous effects with appropriate emollients and wetting agents can improve patient acceptance. Laboratory monitoring is required for hyperlipidemia and increased liver enzymes. Despite known risks of birth defects, there are still pregnancies in patients undergoing therapy with systemic retinoids. This has prompted a program, iPledge, which requires physicians, pharmacists, and patients to register through a central office and verify pregnancy-free status before filling prescriptions.[134] In an attempt to overcome the side effects of systemic medication, there has been a continuous search for effective topical medication for chemoprevention of cutaneous malignancies.

Topical Medications

Because patients at risk for development of skin cancers typically have large areas of photodamaged skin, investigators have sought methods to deal with this field effect in an attempt to prevent the development of skin cancers (chemoprevention) and improve the health and appearance of damaged skin while avoiding the side effects of systemic therapy. Common topical treatments for the prevention of NMSC include topical retinoids, topical 5-fluorouracil, diclofenac sodium, and topical imiquimod cream. Although some clinicians use some of these agents for the treatment of superficial cancers, the high relapse rate once therapy is stopped limits their utility in this regard, and most do not recommend their use for invasive cancer. Patients receiving topical therapy must be followed closely for side effects and compliance, and a structured follow-up regimen is recommended to monitor for the development of invasive lesions requiring surgical intervention. Here an overview of topical treatments is presented; more detailed reviews are available.[135,136]

Topical retinoids attempt to avoid the systemic side effects that limit the use of systemic formulations (see earlier discussion). Similar to the systemic formulations, topical retinoids, such as tretinoin, function to inhibit the growth of abnormal cell lines and induce normal maturation into dysregulated growth. Topical therapy with retinoids consists of application of topical tretinoin cream to affected areas. Although it has been used in the treatment of BCC, high relapse rates limit its use to noninvasive skin conditions. Side effects, including irritation and burning sensation, can limit patient compliance, and a variety of formulations and application schedules have been developed in an attempt to counter these side effects.[135]

Antimetabolites, such as 5-fluorouracil (5-FU), block development of certain metabolites critical for cell metabolism. 5-Fluorouracil is a fluoridated pyrimidine analogue that inhibits thymidylate synthetase, blocking the generation of thymidine, which is necessary for DNA synthesis. 5-Fluorouracil is available as a topical formulation, Efudex 5% (Valient Pharmaceuticals, Costa Mesa, CA). It is approved for the treatment of actinic keratosis, and clearance rates of 83% have been published. It has also been used for superficial BCC and SCC in situ. It is not indicated for invasive SCC. Application is associated with a brisk inflammatory response, which can limit patient compliance. Unfortunately, patients with the most intense inflammatory response often have the best result once healing has occurred. A more recent formulation of 0.5% fluorouracil has shown decreased side effects, and may be more tolerable, but is only indicated for the treatment of AK. Treatment with 5-FU is contraindicated in patients with dehydropyrimidine dehydrogenase deficiency (DPD).[135]

The use of nonsteroidal anti-inflammatory drugs has been investigated as a potential chemopreventive agent in a variety of neoplastic conditions, including squamous cell cancers and colon polyps. Cyclooxygenase (COX), specifically COX-2, has been demonstrated to be upregulated in areas of tumor growth. COX-2 inhibitors have been shown to alter the development of neoplasms, although the exact mechanism by which they produce antineoplastic effects is

unknown. Topical diclofenac sodium gel (Solaraze gel 3%, Bioglan Pharmaceuticals, Malvern, PA) is FDA approved for the treatment of actinic keratosis and is better tolerated than topical 5-fluorouracil treatment. Minor skin irritation can still be a concern, and contact allergic dermatitis develops in some patients. Treatment times are longer (up to 3 months), limiting patient compliance, and response rates of 47% on facial lesions are lower than that of topical 5-FU. It is an alternative, however, in patients who will not tolerate the side effects of Efudex.[135]

Imiquimod (Aldara, 3M Pharmaceuticals, St. Paul, MN), is an immunomodulator applied topically. The exact mechanism by which it exerts its effects on actinic keratosis is unknown, but it stimulates T-cell response, leading to upregulation of antitumor effects, such as production of tumor necrosis factor, and this effect can be long-term through the establishment of immunologic memory. Although initially approved for the treatment of genital warts, dermatologists began to use it "off label" in their clinical practices for a variety of neoplastic and non-neoplastic skin conditions, and it was recently approved by the Food and Drug Administration for the treatment of actinic keratosis.[137]

Imiquimod has been shown to be a well-tolerated and effective treatment for actinic keratosis.[83,138] When administered over a 12-week course, 92% of patients demonstrated some response, with 84% showing complete resolution and only 10% showing recurrence 1 year after treatment. Early work has demonstrated some effect on superficial BCC and SCC in situ, but at this time it is approved for treatment of AK only. As with Efudex, a brisk inflammatory response can limit its use in some patients.

Photodynamic Therapy

Given the high rates of multiple lesions in patients with NMSC and their propensity to recur, photodynamic therapy (PDT) is gaining popularity as a potential method for dealing with multiple, diffuse lesions. Photodynamic therapy relies on a complex interaction of a photosensitizing agent that is preferentially concentrated in abnormal tissue with light of various wavelengths, depending on the photosensitizer, to create necrosis through a non-thermal reaction. Tissue necrosis is mediated through the creation of singlet oxygen, a highly reactive species that induces cellular damage through several mechanisms. Advantages of PDT include minimal damage to surrounding tissues and no cumulative damage, which theoretically allows unlimited treatments. Given the propensity for many cutaneous malignancy patients to develop multiple lesions, this is an important advantage over excision or ablation using traditional methods. Minor discomfort, erythema, and itching are common side effects of treatment. Areas treated undergo healing through secondary intention with minimal or no scarring. Disadvantages include marked photosensitivity with systemic PDT, especially with regard to sun exposure, for variable lengths of time after the administration of the agent. Although a complete review of PDT is beyond the scope of this chapter, excellent reviews are available.[135,139]

Photodynamic therapy has been used with success in the treatment of actinic keratosis using systemic 5-aminolevulinic acid PDT, but photosensitivity not relieved with sunscreen can last up to 3 months. In response, investigators began using topical PDT with 5-aminolevulinic acid (ALA), a protoporphyrin precursor. It is absorbed by keratinocytes and converted into an endogenous photosensitizing agent. Effective management of actinic keratosis is possible while minimizing systemic side effects. Clearance rates for actinic keratosis are excellent and range from 70% to 90% at 3 years. Early response of superficial SCC and BCC led some investigators to recommend PDT, but disappointing results at longer term follow-up led most to not recommend PDT for invasive lesions.[140,141]

Radiation

Because of its efficiency and effectiveness, surgery is the treatment of choice for the vast majority of skin cancers. Radiation therapy, however, is indicated for some patients who are not surgical candidates (e.g., large lesions in anatomic locations not amenable to surgical excision without undue morbidity) and in a salvage role for multiply recurrent or multicentric lesions. It can also serve as an adjunct to surgery in lesions with poor prognostic factors, such as perineural extension, positive margins, or nodal involvement.[54] Older orthovoltage radiation machines were ideal for treatment of skin cancers because of the superficial absorption of these lower-energy beams. Indeed, skin damage from radiation treatment was one of the impetuses leading to the introduction of newer high-energy megavoltage linear accelerators. These higher energy machines can also be used to generate low-energy electrons that are better suited for treating skin cancers. Higher energy beams can be used for more deeply seated tumors. Although typically administered over multiple fractions, some investigators have demonstrated good control rates with single-fraction treatment.[142-144]

When used as a single modality, control rates for BCC and SCC are high (95% to 97% and 90%, respectively), but lesions that recur following radiation treatment tend to behave aggressively.[144] Whether this is an effect of the radiation or shows that failure to respond completely to radiation is an indicator of biologic aggressiveness is unknown, but the latter is probably more likely. In addition to its role as primary treatment, radiation therapy can play an important role in recurrent lesions as an adjunct to surgery.[144] With special shielding techniques, radiation can also be an effective tool for management of eyelid and canthal lesions, avoiding the morbidity associated with large resections of this complex area.[144] Radiation therapy generally leads to good cosmetic results following healing, but studies directly comparing radiation to surgery or other treatment modalities are lacking. In addition to its role at the primary site, radiation therapy is recommended as adjuvant therapy in cases of known nodal disease. It has been shown to improve locoregional control and survival.[115]

In contrast to other NMSCs, adjuvant radiation therapy has become standard in the treatment of Merkel cell

carcinoma. Veness et al[129] found that adjuvant locoregional radiation following surgery results in a longer median disease-free interval in Merkel cell carcinoma (23 versus 6 months) and decreased nodal relapse. This is in agreement with other studies that have demonstrated that adjuvant radiation should be considered standard therapy.[129]

Regardless of primary treatment modality, patients with skin cancer require structured follow-up for evaluation of recurrence, as well as new primary lesions.

Special Considerations

Lip Cancer

that of typical oral squamous mucosal cancers. The behavior of lip cancers typically lies somewhere between that of oral squamous cancers and cutaneous squamous cancers. For staging purposes, the lips are defined anteriorly by the skin-vermilion junction and include the mucosal portion that comes in contact with the opposing lip. Upper and lower lips join at the commissures. The lip consists of an inner mucosal lining (more properly known as buccal mucosa), vermilion (that which touches the opposing lip), and the skin on the outer surface. Cancers involving the lip may arise from any of these areas, and determining the epicenter or point of origin is often difficult.

Most commonly the lower lip vermilion is the origin, and squamous cell cancers account for the majority of malignancies affecting the lip. Most lesions arise in an area of actinic keratosis (Figure 31-9), which can be treated with a vermilionectomy. Often it is difficult to discern the epicenter of the tumor and stage it accurately. Some cancers are so large that it is difficult to decide if they arose from the skin of the lip, the vermilion, or the buccal mucosa.

A summary of the current staging follows:

Primary Tumor

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor less than 2 cm in greatest dimension
- T2: Tumor more than 2 cm but less than 4 cm in greatest dimension
- T3: Tumor more than 4 cm in greatest dimension
- T4a: Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, that is, chin or nose
- plates,

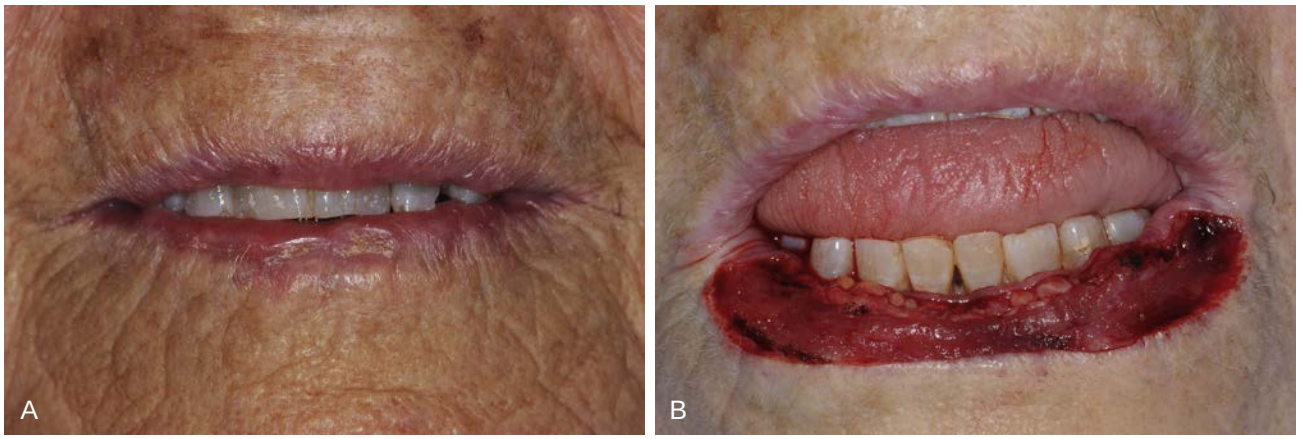
Regional Lymph Nodes

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastases
- N1: Metastases in a single ipsilateral lymph node, 3 cm or less in greatest dimension
- N2: Metastases in a single, ipsilateral lymph node, more than 3 cm but less than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral nodes, none greater than 6 cm
- N2a: Metastases in a single, ipsilateral lymph node more than 3 cm but less than 6 cm
- N2b: Metastases in multiple, ipsilateral lymph nodes, none more than 6 cm in greatest dimension
- N2c: Metastases in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
- N3: Metastases in a lymph node more than 6 cm in greatest dimension

Distant Metastases

- MX: Distant metastases cannot be assessed
- M0: No distant metastases
- M1: Distant metastases

- Stage 0: TisN0M0
- Stage I: T1N0M0
- Stage II: T2N0M0
- Stage III: T3N0M0
  - T1N1M0
  - T2N1M0
  - T3N1M0



• **Figure 31-9** **A,** Actinic keratosis. **B,** Vermilionectomy defect, which is easily closed by mucosal advancement.

- Stage IVa: T4aN0M0
  - T4aN1M0
  - T1N2M0
  - T2N2M0
  - T3N2M0
  - T4aN2M0
- Stage IVb: AnyTN3M0
  - T4bAnyNM0
- Stage IVc: AnyTAnyNM1

The primary etiologic agent for lip cancer (sun exposure) is different than for oral cancers, and the highly visible location of lip carcinomas usually leads to earlier discovery. The behavior of squamous cell cancers of the vermilion border is usually intermediate between that of SCC of the skin and that of the mucosa. The vast majority arise on the lower lip, where sun exposure plays an important etiologic role. Most lip cancers are treated surgically with resection using 0.5- to 1.0-cm margins confirmed with frozen section. Excisions typically take the form of wedge excisions, which may be combined with a lip shave procedure removing vermilion that has suffered extensive actinic damage or contains carcinoma in situ. Mohs micrographic surgery is an alternative to traditional surgical excision. There is potential for perineural invasion and/or mandibular involvement with larger lesions, which can require extensive resections and reconstructive efforts (Figure 31-10).

Certain factors are associated with more aggressive behavior in lip cancer with increased recurrence and metastatic rates. Size greater than 2 cm is associated with local recurrence and metastases more frequently than those less than 2 cm.[145] Histologic grade also influences local recurrence and metastatic rates. Well-differentiated tumors are associated with lower local recurrence rates and metastases compared to poorly differentiated tumors.[83] Perineural involvement is also associated with higher local recurrence and distant metastases, with up to 34% of patients developing distant spread.[84] Finally, age less than 40 years has been associated with increased risk of local recurrence and distant metastases.[145]

As with the cutaneous sites, there is a significant amount of controversy surrounding the need for elective neck dissection of at-risk nodal basins in lip cancer. Early investigators believed that the risk of metastasis was low, at around 0.5%,



• **Figure 31-10** **A,** 3-cm lip carcinoma with perineural invasion, extensive induration and subcutaneous spread, and palpable lymph nodes. **B,** Defect after excision. **C,** Specimen with at least 1-cm margin around palpable tumor. **D,** Reconstruction with radial forearm free flap.

but more recent investigators reported significantly higher rates of metastasis (up to 16%) with longer follow-up.[84]

Although some authors recommend elective neck dissection only in cases of clinical evidence of lymph node involvement by exam or imaging, others recommend consideration of elective treatment of at-risk nodal basins in cases with poor prognostic indicators. For clinical N0 necks, factors that should prompt consideration of elective neck dissection include T3 or T4 tumors, commissure involvement, recurrence, and perineural spread.[146] Although these guidelines exist, at this time elective treatment of the N0 neck in lip cancers is controversial.[71,73] Investigators continue to search for biologic markers and improved predictors of aggressive behavior that will better select patients requiring more intensive therapy.[72,74] Elective nodal dissection for lower lip cancers should include level I bilaterally at a minimum, although some recommend bilateral supraomohyoid dissection. Supraomohyoid (levels I to III) or modified neck dissection of levels I to V is indicated in cases of therapeutic neck dissection.[147] It should be noted that upper lip cancers account for only 10% of lip cancers and have unique characteristics. The upper lip and the commissure may metastasize to the periparotid lymph nodes, and superficial parotidectomy may be required if there are clinically enlarged nodes.[148]

Again, sentinel-node biopsy may play a role in the elective management of lip cancers when there is a question of metastatic potential.

In an effort to preserve cosmesis and function, radiation therapy, both external and brachytherapy, may be used as primary treatment in larger lesions.[149] Radiation therapy may also be indicated as an adjunct to surgery in cases of positive margins or nodal disease.

Summary

Although it makes up only 10% of the surface area of the body, the skin of the head and neck is the site for development of the majority of cutaneous malignancies because of its exposure to harmful ultraviolet radiation. Its increasing incidence associated with the significant costs of treatment will require practitioners to be well-versed in the effective and efficient management of these malignancies to limit their morbidity and costs. Oral and maxillofacial surgeons may be called upon to treat skin cancers primarily, or to reconstruct complex defects following tumor extirpation by other surgeons.

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32

The Use of Radiation Therapy in Treatment of Head and Neck Cancer

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Almost since Wilhelm Roentgen discovered the x-ray in 1896, there has been interest in the use of radiation as treatment for malignant disease, including cancers of the head and neck. The ability of radiotherapy to reduce and sometimes eradicate cancer was appreciated in the early years of experimentation with the new modality. The use of radiation therapy for treatment of cancer of the head and neck was of particular interest because of the frequent morbidity of surgical resection of head and neck cancer with the frequent deleterious effects on speech and swallowing function as well as cosmesis associated with surgical resection. After many years of improving radiotherapy delivery methods and dose schedules, the approach remains attractive today and is frequently preferred, allowing for preservation of speech and swallowing function with eradication of disease in many cases. The modality has evolved through the years with the development of high-energy radiation machines capable of sparing superficial normal tissues; the development of effective radioisotopes for interstitial and intracavitary applications; the appreciation of biologic differences between normal tissues and tumors relative to response to radiation, allowing more optimal radiation dose schedules; the integration of systemic therapies with radiation; and the complex delivery of radiotherapy from multiple orientations and dose modifications to enhance tumor response with protection of normal tissue. The past 100 years have been extremely exciting in the evolution of radiotherapy as definitive treatment and as adjuvant therapy for patients with carcinomas of the head and neck, and the field is currently improving rapidly with continued improvements in technology.

Overview

Histologies

Squamous cell carcinoma is the most common cancer—over 90%—of the head and neck. It has been associated with chronic tobacco and/or alcohol exposure. Prognosis varies with the extent of disease present at the time of treatment, subsites involved, and technical aspects of the treatment delivery. Biologic aspects of the tumor, largely undefined to date, also affect the natural history of the disease and prognosis.

Other cancers include Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), sarcomas of soft tissue and bone, thyroid cancers, salivary gland malignancies, and skin cancers. Mucosal melanomas are uncommon, as are carcinoids and small cell carcinomas.

Lymphomas are considered sensitive to both radiation and chemotherapy, and these modalities are used in treatment strategies for either HL or NHL. Surgery is generally not a part of the therapy regimen for these diseases. Hodgkin disease is most often managed by radiation therapy, chemotherapy, or a combination of those treatments, depending on the extent of the disease and the patient's age, gender, and comorbidities. Radiotherapy is typically delivered as once-per-day treatment with five treatments per week, with total doses typically totaling between 3000 and 4000 cGy, which is associated with high efficacy for disease eradication.[1] NHLs of the head and neck can be managed by observation, chemotherapy, and/or radiation therapy, depending on the histologic grade, extent of disease, patient age, and patient comorbidities. Most NHLs are sensitive to radiation, with doses between 3000 and 4500 cGy most often used.

Sarcomas of the head and neck are most often managed by a combination of surgical resection and radiation therapy given preoperatively or postoperatively. Typical preoperative radiation doses include 4500 cGy in 25 treatments at 180 cGy per day, and postoperative doses are typically on the order of 5940 cGy in 33 treatments with 180 cGy per day. Interstitial radiation when used alone typically entails approximately 4500 cGy delivered over 4 to 5 days, commonly with continuous iridium. When interstitial radiation

is used as a boost following preoperative radiation or before planned postoperative external radiation, the interstitial boost is typically approximately 2000 cGy over 2 days, most often with iridium.[2]

Thyroid cancers can be grossly divided into differentiated carcinomas that concentrate iodine (papillary and follicular) and poorly differentiated carcinomas that typically do not concentrate iodine, including medullary and anaplastic histologies. Papillary or follicular carcinomas of the thyroid are most often managed with surgical resection and frequently adjuvant iodine-131 (^{131}I) treatment. Indications for external radiation therapy include extracapsular extension of disease at the primary site, persistent known or suspected residual disease following ^{131}I therapy on the basis of grossly apparent disease clinically and/or radiographically, or a persistently elevated thyroglobulin level. When adjuvant radiation therapy is delivered, the radiotherapy is typically 5000 to 6000 cGy, typically 180 to 200 cGy per day with five treatments per.[3-5] Similar doses are frequently delivered postoperatively after resection of medullary carcinoma of the thyroid.[6] Anaplastic carcinoma of the thyroid has an extremely poor prognosis and is managed sometimes with surgical resection with adjuvant radiation therapy, sometimes radiation alone, and sometimes radiation with systemic therapy. Radiation doses are typically in the 6000 to 7000 cGy range at 200 cGy per day.

Mucosal melanomas are uncommon. When treated with radiation therapy definitively or as adjuvant therapy, larger fractions of typically 250 cGy or more daily are used to a total dose of 5000 cGy.[7] Cutaneous and mucosal melanomas are thought to require higher doses per treatment than squamous cell carcinomas of the head and neck because of an inherent biologic radioresistance.

Head and Neck Sites of Disease

Oral Cavity

Squamous cell carcinomas of the oral cavity most frequently involve the oral tongue and/or floor of mouth, but other potential primary sites include the lips, buccal mucosa, hard palate, gingiva, and retromolar trigone. Surgical resection is generally the first consideration if the disease is thought amenable to resection with preservation of speech and swallowing function. In the situation of technically unresectable disease or the anticipation that resection would be particularly deleterious to speech and/or swallowing function, radiotherapy as definitive treatment, with or without systemic therapy, is frequently a consideration. Adjuvant radiation delivered preoperatively or postoperatively is frequently considered in the setting of locoregionally advanced disease.

Definitive radiotherapy frequently entails external radiation directed to the primary sites and regional lymph nodes in the neck to a dose on the order of 5000 cGy in 25 treatments with subsequent localized boost radiation to the primary site and any gross adenopathy. Palpable lymph nodes typically receive an additional 2000 cGy in 10 treatments, whereas the primary disease in the oral cavity can be further treated with an electron cone on the order of 2400 cGy in eight treatments or with an interstitial implant, often with iridium delivering 2500 cGy to the tumor over 2 to 3 days. Local tumor control rates by stage of disease are listed in Table 32-1. In the absence of obvious nodal disease, the neck is generally prophylactically treated for the possibility of occult nodal disease. If the decision is made to observe the neck, the primary site can be treated with an interstitial implant alone on the order of 6000 cGy over 6 days with iridium. An oral tongue interstitial implant is pictured clinically and radiographically in Figure 32-1.

Oropharynx

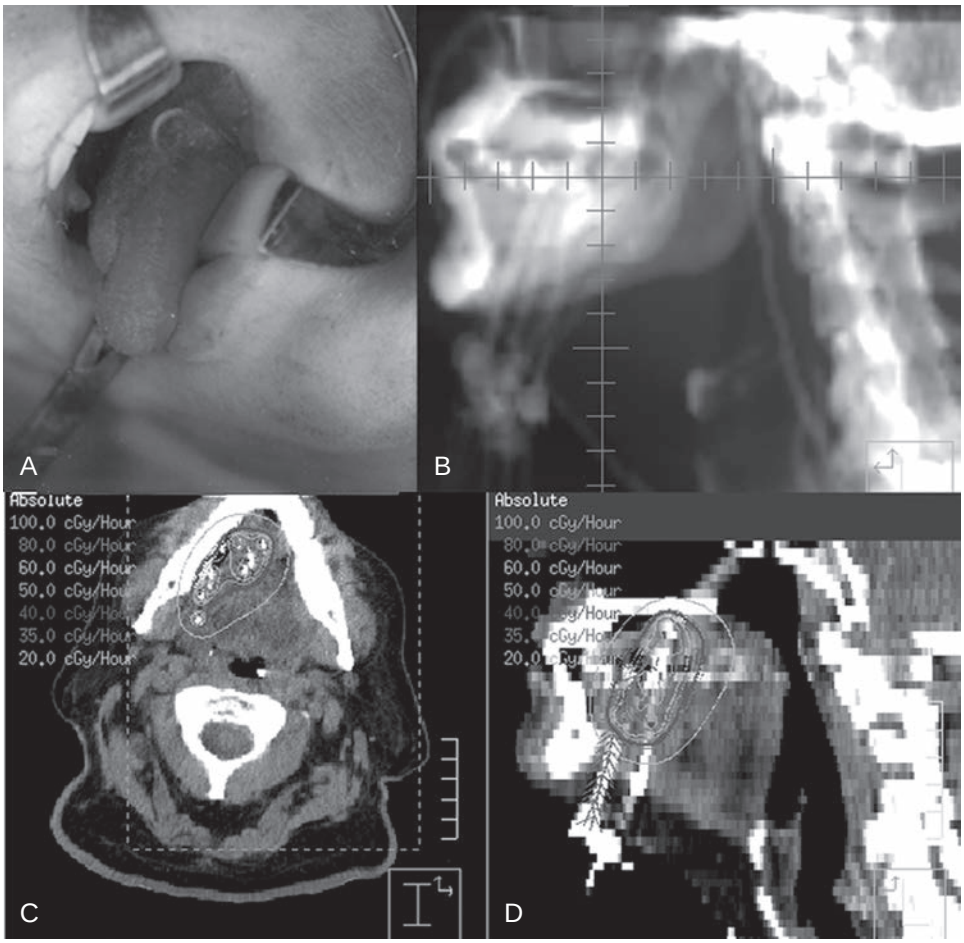
Subsites of the oropharynx include the base of tongue, palatine tonsils, soft palate, and pharyngeal wall. Radiotherapy is frequently used as part or all of the treatment for patients with squamous cell carcinomas in these sites. If disease is considered technically unresectable or if resection is thought to be associated with significant morbidity, radiation therapy alone or with systemic therapy is frequently used. For advanced resectable disease, radiation is frequently delivered preoperatively or postoperatively as an adjuvant treatment. Definitive radiation therapy for tonsil, soft palate, and pharyngeal wall squamous cell carcinomas is typically external radiation throughout. Figure 32-2 demonstrates a patient treated with definitive radiotherapy for a tonsillar cancer. Base-of-tongue cancers are sometimes treated with a combination of external radiation therapy and interstitial implant with doses similar to those used for oral cavity squamous cell carcinomas. Treatment results are listed in Table 32-2.

Larynx

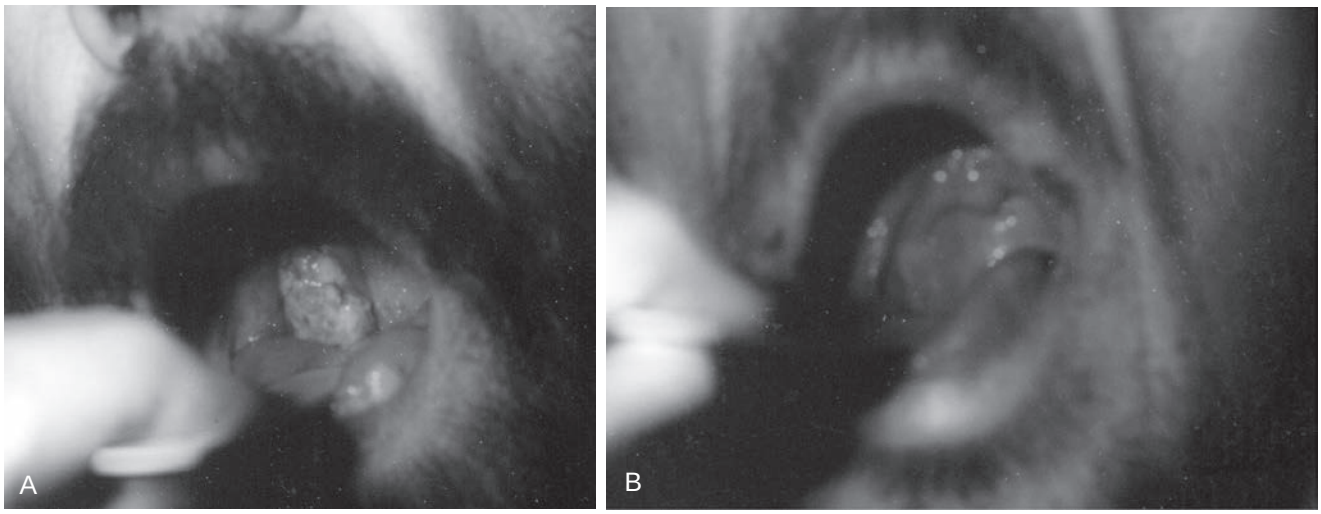
The larynx is typically divided into the glottis, including the true vocal cords and anterior commissure; the subglottis, just below the glottis; and the supraglottic larynx, including the epiglottis, arytenoids, aryepiglottic folds, false vocal cords, and ventricles. Squamous cell carcinomas of the larynx are frequently treated with definitive radiation therapy with or without systemic therapy in an attempt to preserve speech function. Cancers clinically confined to the glottis are thought to have low metastatic lymph node potential and are typically treated with relatively small external radiation therapy fields, as depicted in Figure 32-3. More advanced glottic cancers and supraglottic cancers are considered at risk of lymph node metastases, and lymph nodes are typically treated. A typical 3D conformal field used to

TABLE 32-1 Local Control Rates of Oral Cavity Tumors Treated with Radiation Alone by Stage of Disease

Disease Stage	5-Year Local Control Rate[59,60]
T1	88-100
T2	85-93
T3	50-70
T4	30-60



• **Figure 32-1** **A,** Oral tongue interstitial brachytherapy implant with catheters placed through the tongue. **B,** Digitally reconstructed radiograph of interstitial catheters placed in the tongue. **C,** Dosimetric calculations for iridium-192 tongue implant in transverse and, **D,** sagittal computed tomographic reconstructions. Note the sharp dose falloff with distance from the iridium sources.



• **Figure 32-2** Clinical appearance of a squamous cell carcinoma of the tonsillar fossa **(A)** before and **(B)** after treatment with definitive radiotherapy.

treat an advanced laryngeal cancer is shown in Figure 32-4. Patients who present with hoarseness frequently experience improvement in voice function in the first 2 to 3 weeks of the radiation course with subsequent decline in voice function as a result of mucositis and laryngeal edema, which are typically transient with typical improvement in voice function by several weeks after radiation therapy. Treatment results are shown in Table 32-3. Neoadjuvant chemotherapy prior to radiation therapy has been shown to be no worse than up-front laryngectomy and postoperative radiation therapy for locally advanced laryngeal cancer in a randomized trial,[8] but neoadjuvant chemotherapy followed by radiation therapy has been shown to be no more effective than radiation therapy alone in another randomized trial.[9] That trial did show an advantage to the addition of concurrent cisplatin with radiation for locally advanced laryngeal cancer.

TABLE 32-2 Local Control Rates at 5 years of Oropharyngeal Carcinoma by Site and Stage of Disease Treated with External Beam with or without Interstitial Radiation Therapy

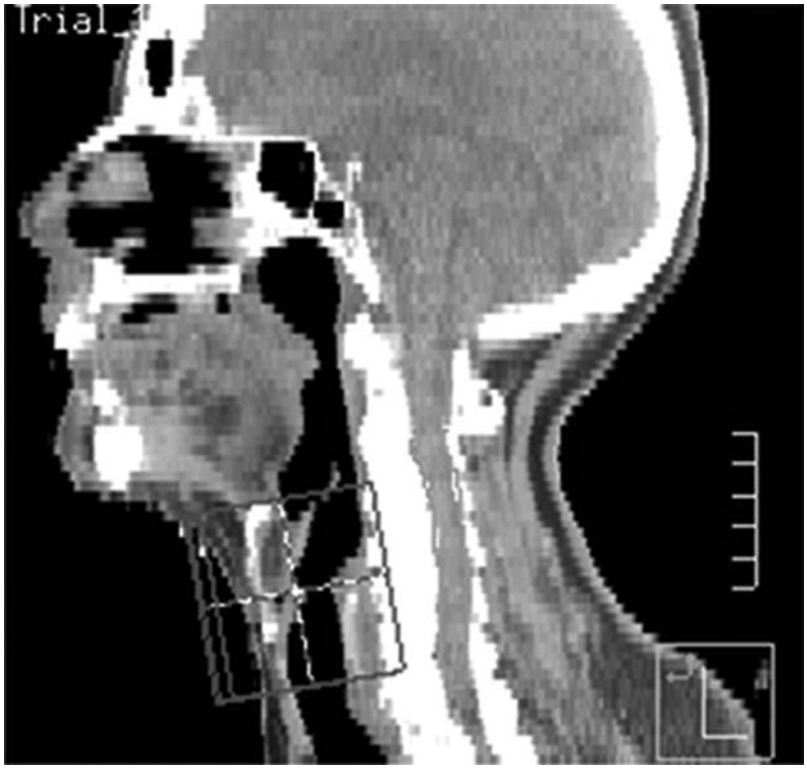
Disease Site	T1	T2	T3	T4
Base of tongue[18-21]	87%-96%	74%-93%	59%-82%	28%-52%
Tonsil[22-25]	83%-95%	79%-88%	58%-74%	40%-60%
Soft palate[26-28]	90%-100%	65%-95%	50%-77%	24%-37%
Pharyngeal wall[29-31]	91%	73%-93%	82%-61%	37%

Hypopharynx

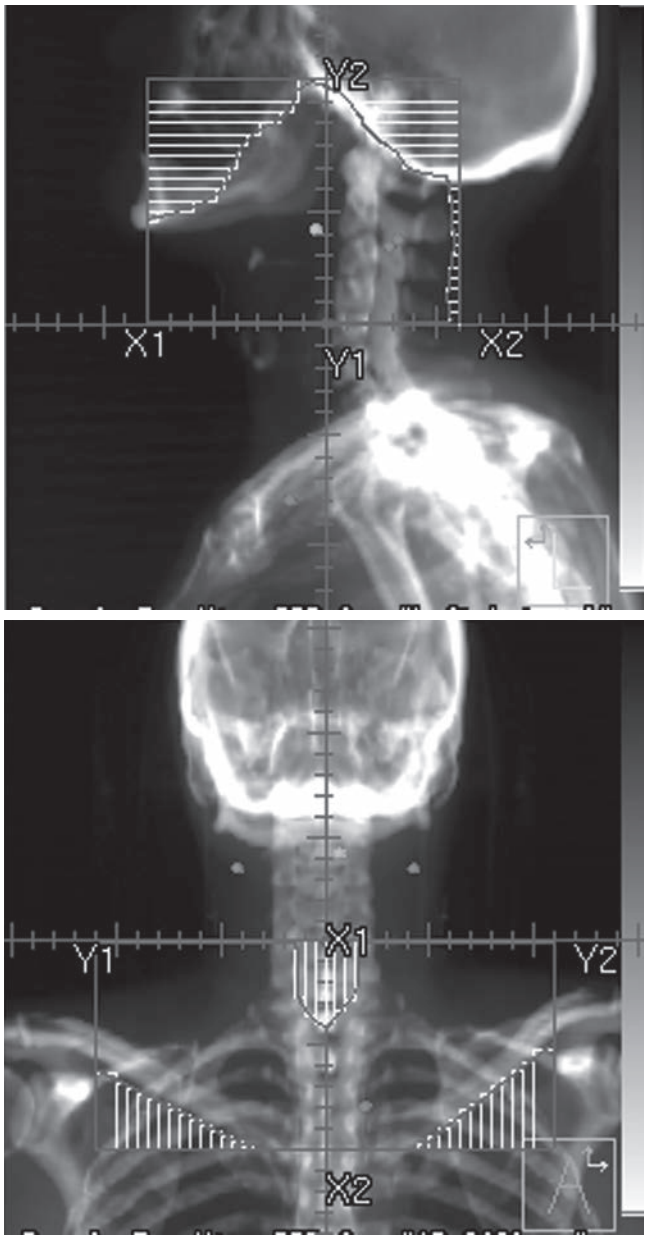
Subsites of the hypopharynx include the pyriform sinuses, post-cricoid region, and posterior pharyngeal wall. Squamous cell carcinomas of the hypopharynx are managed sometimes with surgical resection, often with preoperative or postoperative external radiation therapy, sometimes with definitive radiation therapy, and sometimes with radiation therapy with concurrent systemic therapy. Surgical resection is typically morbid relative to speech and swallowing function where larger tumors require laryngopharyngoesophagectomies. Radiation doses are similar to those discussed for cancers of the oral cavity and oropharynx. Results for treatment of cancers of the hypopharynx are shown in Table 32-4.

Nasopharynx

Cancers of the nasopharynx typically come in two general varieties. Squamous cell carcinomas of the nasopharynx behave in similar fashion to squamous cell carcinomas of other head and neck sites, typically with sequential growth at the primary site and subsequent development of lymph node metastasis and possible later hematologic metastases. The other form of nasopharyngeal cancer, sometimes referred to as lymphoepithelioma or undifferentiated carcinoma of the nasopharynx, (1) is associated with Epstein-Barr virus, (2) is much more common in the Far East than



• **Figure 32-3** Typical small-field radiation treatment portal for an early-stage laryngeal cancer confined to the glottis.



• **Figure 32-4** Typical 3D conformal radiation treatment portals used in the treatment of advanced head and neck cancers. Cervical lymph node levels 1 through 5 are typically treated.

TABLE 32-3 Local Control Results for Laryngeal Cancer Treated with Radiation at 5 Years (by T Stage)

Disease Site	T1	T2	T3	T4
Glottis[32-40]	84%-100%	61%-90%	40%-75%	38%-49%*
Supraglottis[41-45]	80%-93%*	66%-77%*	50%-65%	36%-67%

*Ultimate control rates after surgical salvage 65%-95%.

in the Western world, (3) typically presents with large adenopathy, (4) is particularly sensitive to radiotherapy, and (5) has a high propensity for distant metastases. Radiation therapy with concurrent cisplatin and adjuvant post-radiotherapy, 5-fluorouracil (5-FU), and cisplatin has been shown to be superior to radiotherapy alone for advanced cancers of the nasopharynx.[10] Radiotherapy is typically external radiation therapy alone on the order of 7000 cGy to the primary site and gross adenopathy with 5000 cGy delivered to areas thought to be at risk for microscopic lymph node disease. Results of treatment are shown in Table 32-5.

Unknown Primary

Squamous cell carcinoma involving lymph nodes in the neck without an apparent primary lesion is an uncommon but not rare presentation. The most common management includes a careful clinical and radiographic assessment to rule out an apparent primary tumor, which typically frequently CT of the chest and positron emission tomography (PET) scan. If no primary tumor is apparent, the most common management includes neck dissection followed by radiation therapy to both necks and the most likely sites of an occult primary, including the nasopharynx, palatine tonsils, base of tongue, and pyriform sinuses. Results of treatment are shown in Table 32-6.

Treatment

Definitive Radiotherapy

Many cancers of the head and neck are amenable to definitive radiotherapy as the primary mode of treatment as a curative attempt, frequently with the preservation of function and cosmesis. Adjuvant surgery is sometimes used in a setting of advanced neck disease where neck dissection is performed before or more commonly after definitive radiation. Systemic therapy is sometimes used with definitive radiation therapy in an attempt to sensitize tumor cells to radiation and eradicate tumor cells that may not have been otherwise killed by the radiation. Definitive radiotherapy can be with external radiation therapy alone, sometimes interstitial radiation alone, or sometimes the combination of external and interstitial radiation. Definitive radiotherapy is typically used in the setting of technically unresectable disease or disease in which resection would be anticipated to cause significant morbidity, particularly relative to the patient's speech and/or swallowing function.

Preoperative and Postoperative Radiotherapy

Adjuvant or neoadjuvant preoperative radiation therapy is frequently a consideration for locoregionally advanced cancers of the head and neck. Preoperative radiation may increase

TABLE 32-4 Local Control Rates at 5 years for Hypopharyngeal Carcinomas by Site and Stage of Disease

Pyriform Sinus Cancer[30,46-50]

	T1	T2	T3	T4
Radiotherapy (RT)	74%-90%	59%-94%	33%-49%	33%-49%
Resection and postoperative RT	68%-89%	68%-89%	51%-89%	51%-89%

Pharyngeal Wall Cancer (Including Pyriform Sinus)[30,51-53]

	T1	T2	T3	T4
Radiotherapy	74%-90%	59%-94%	31%-61%	31%-44%
Resection and postoperative RT	66%-100%	66%-100%	51%-89%	51%-89%

TABLE 32-5 Local Control and Disease-Free Survival at 5 Years for Nasopharyngeal Carcinoma Treated with Radiation Therapy with or without Concurrent Chemotherapy

Trial	Stage	Treatment	LC	DFS
	III-IV	Radiation alone	59%	24%
		Concurrent chemoradiation	86%	69%
AOCOA[54]	III-IV	Radiation alone	69%	46%
		Concurrent chemoradiation	75%	58%
INSG[55]	IV	Radiation alone	77%	31%
		Concurrent chemoradiation	85%	47%

TABLE 32-6 Treatment Results for Head and Neck Nodal Carcinomas of Unknown Primary

	Treatment	Failure Rate in the Head and Neck Mucosa	Neck Control Rate	5-yr CSS	5-yr OS
Erkal et al[56]	RT alone	13%	78%	67%	47%
Colletier et al[57]	ND + RT	6%			60%
Reddy et al[58]	ND alone	44%			47%
	ND + RT	8%			53%

CSS, Cancer-specific survival; *ND,* neck dissection; *OS,* overall survival; *RT,* radiotherapy.

resectability of disease, and tumor cells are thought more sensitive to radiation in the preoperative setting compared with the postoperative setting because oxygenation is better before the potential surgical disruption of vascular supply. Typically, lower doses are used in the preoperative setting (i.e., 5000 cGy at 200 cGy/day) compared with the postoperative setting (i.e., 6000 cGy at 200 cGy/day) because of this difference in oxygenation and associated tumor radiosensitivity. The potential disadvantages of preoperative radiation are the possibilities of increased wound complications, delay of the definitive surgical resection during which time the tumor could potentially grow or metastasize, and the lack of detailed pathologic information regarding the extent of the disease, ally advanced squamous cell carcinoma of the head and neck compared with preoperative treatment.[11]

Altered Fractionation

The most commonly used fractionation scheme for squamous cell carcinoma of the head and neck as definitive treatment has been 7000 cGy in 35 treatments over 7 weeks with typically 200-cGy fractions delivered Monday through Friday. Altered radiation fractionation schemes have been studied in

TABLE 32-7 Randomized Phase III Trials of Radiation Therapy versus Concurrent Chemoradiation

Study	Subsites Included	Treatment	3 yr LC	3 yr OS
Bonner et al[14]	Stage III/IV OP, HP, L	RT alone (70 Gy)	34%	45%
		RT (70 Gy) + concurrent cetuximab	47%	55%
	Stage III/IV OP, HP, L, OC	RT alone (70 Gy)	NR	23%
		RT (70 Gy) + concurrent cisplatin	NR	37%
		Split course RT (60-70 Gy) + concurrent cisplatin/5-FU	NR	27%
RTOG 91-11[9]	Stage III/IV L only	RT alone (70 Gy)	56%*	56%†
		RT (70 Gy) + concurrent cisplatin	71%*	54%†
		Induction cisplatin/5-FU, then RT (70 Gy)	68%*	55%†

5-FU, 5-Fluorouracil; *HP*, hypopharynx, *L*, larynx; *NR*, not recorded; *OC*, oral cavity; *OP*, oropharynx; *OS,* overall survival; *RT*, radiation therapy.
*2-year locoregional control.
†5-year overall survival.

an attempt to manipulate biologic differences between tumor and normal tissue to improve prognosis without increasing morbidity. The RTOG studied four fractionation schemes for locoregionally advanced squamous cell carcinoma of the head and neck: standard 7000 cGy in 7 weeks with five daily treatments per week; 120 cGy twice a day, 5 days per week to 7500 cGy (hyperfractionation); 3.5 weeks of once-a-day treatment followed by 2.5 weeks of twice-per-day treatment (concomitant boost); and 160 cGy twice a day for 3.5 weeks with a 2-week break, followed by an additional 2 weeks of the same treatment (hyperfractionated split course radiation). The altered fractionation schemes showed increased acute toxicity with a small improvement in efficacy compared with conventional fractionation.[12]

Radiation with Systemic Therapy

Efforts have been made for many years to optimize treatment of head and neck cancer with a combination of radiation and chemotherapy. For locoregionally advanced squamous cell carcinoma of the head and neck, several studies have suggested benefit to radiation and concurrent chemotherapy, most often cisplatin.[13] 5-FU alone and with cisplatin has been used concurrently with radiation as well, but because severe mucositis is typical with the combination of 5-FU and radiation, this is not often used. Results of randomized trials comparing radiation therapy alone to concurrent chemoradiation are noted in Table 32-7.

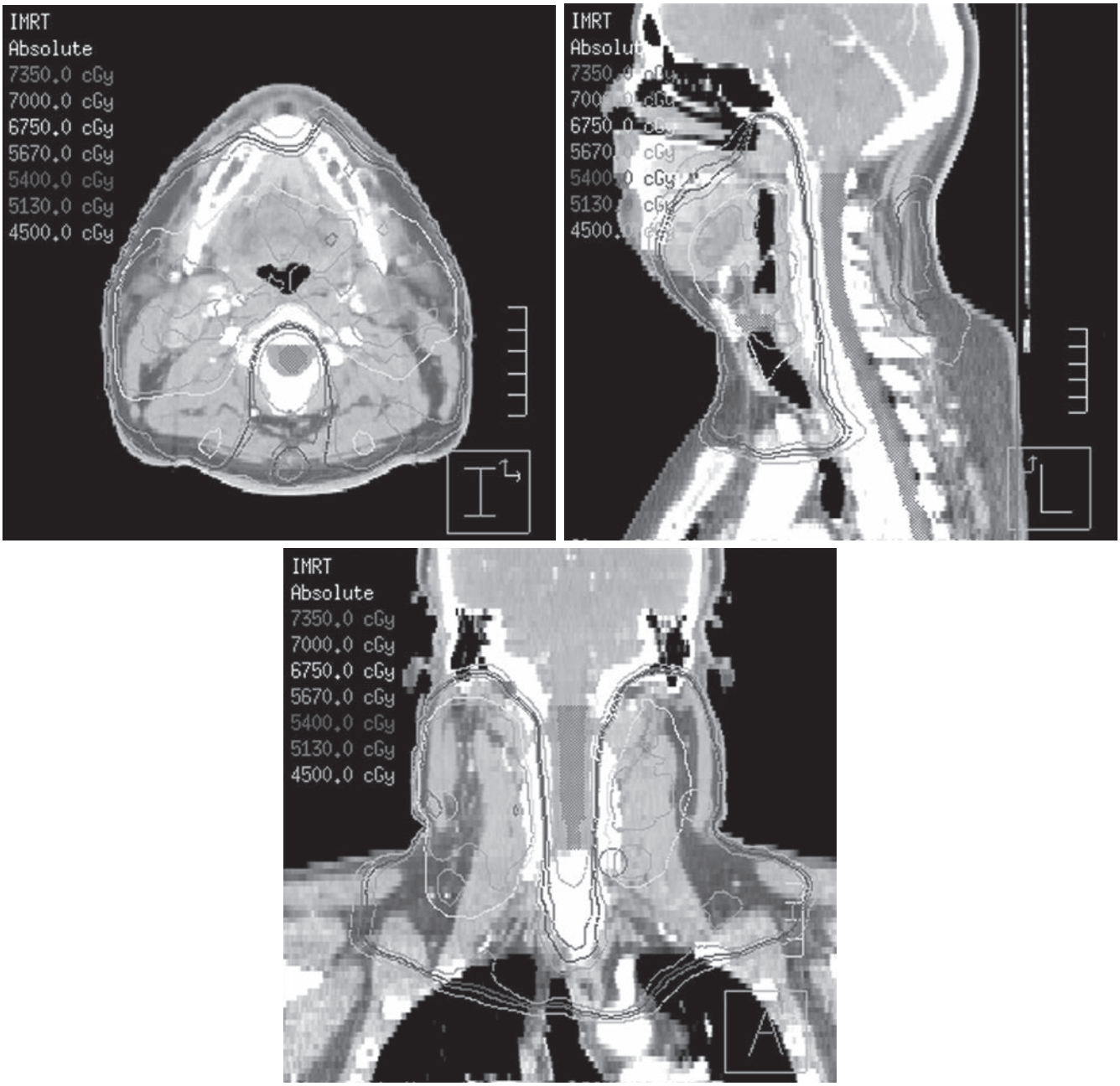
Cetuximab is a newer systemic therapy that is not chemotherapy per se and avoids many of the systemic side effects of chemotherapy. It is a monoclonal antibody to the extracellular domain of the epidermal growth factor receptor (EGFR) of cancer cells. Blocking of this receptor causes impaired cell growth. A prospective randomized trial has shown cetuximab delivered concurrently with radiation to be superior to radiation alone for locally advanced squamous cell carcinoma of the head and neck.[14] Neoadjuvant chemotherapy before definitive radiation therapy is frequently associated with dramatic tumor responses, but generally not with improved outcome in prospective randomized trials relative to radiation alone.[9,15]

Radiotherapy Techniques

Radiotherapy for head and neck cancers can be via teletherapy (external radiation) or brachytherapy (interstitial or intracavitary use of radioactive seeds). Teletherapy is the predominant form of therapeutic radiation and most commonly entails the production of high-energy photons or electrons by a linear accelerator. The radiation is typically aimed at the tumor, often from multiple orientations and with the shaping of radiation fields from each orientation to limit the volume of tissue receiving the full radiation dose. Photons have their maximal effect at a tissue depth depending on their energy, which can be varied depending on the desired depth of treatment. Whereas photons continue to pass through tissue and deposit decreasing amounts of radiation with further penetration, electrons stop more abruptly and are used to treat more superficial tumors with avoidance of more deeply seated normal tissues. Two-dimensional radiation treatment planning refers typically to radiation being directed from anterior, posterior, right lateral, or left lateral orientations where bony structures can be well recognized on x-rays taken from those orientations and the target tissue can be correlated relative to those bony structures. Three-dimensional conformal radiation refers to the use of CT scans and computers to better target tumors relative to normal tissues (see Figure 32-4). The technique involves obtaining a CT scan and putting the CT information into the computer to allow for contouring on the computer work station the target tissue to be treated and the normal tissues to be

avoided. With the help of the computer, orientations and shapes of radiation fields can be devised to better accomplish this. Intensity-modulated radiation therapy (IMRT) adds the ability to vary the amount of radiation coming through each part of each field of radiation to further conform the radiation dose to the target tissues relative to the normal tissues to be spared. Isodose patterns for the treatment of an advanced base-of-tongue cancer with IMRT are shown in Figure 32-5.

Brachytherapy can entail the permanent or temporary placement of radiation seeds directly into (interstitial) tumor-containing tissue or within an orifice adjacent to tumor (intracavitary radiation). Temporary brachytherapy is more commonly used in the treatment of head and neck cancers. Brachytherapy may have the advantage of exposing tumor cells to substantially higher doses of radiation compared with normal tissues distant from the radiation sources, thereby decreasing side effects. Temporary brachytherapy applications can be low-dose-rate radiation in which radioactive sources are typically placed for a matter of a few days, or high-dose-rate radiation in which higher-activity (strength) sources are placed for a matter of minutes. Both forms of brachytherapy are physically advantageous in placing the radiation dose at the location of the disease. The biologic differences in tumor response and normal tissue effects between continuous



• **Figure 32-5** Isodose distributions for an intensity-modulated radiation therapy (IMRT) plan used to treat an advanced base-of-tongue cancer.

low-dose-rate radiation and fractionated high-dose-rate radiation continue to be studied.

Complications of Treatment

Effects of radiation on normal tissues include acute and late effects. Acute effects occur during and immediately after a course of radiotherapy, are typically progressive in nature, and generally resolve 3 to 4 weeks after therapy. These include mucositis, hair loss, skin irritation, loss of taste, dry mouth, bone marrow suppression, and hoarseness from effects of radiation on rapidly proliferating normal tissues. In a 7-week course of daily Monday-through-Friday radiation therapy for cancers of the head and neck, acute side effects are typically noticeable beginning in the second or third week of treatment. Progression of those effects is variable and is typically counterbalanced to some extent by accelerated repopulation of normal cells in response to radiation damage. The acute side effects sometimes increase through the course of treatment as the cumulative radiation dose increases and at times plateaus because of the accelerated repopulation of normal cells. Mucositis and skin changes are typically largely resolved by 3 weeks following completion of radiation therapy. Taste typically takes a matter of months to recover, and xerostomia is frequently long lasting. The addition of concurrent chemotherapy to radiation typically augments all of the normal tissue effects and delays recovery.

Amifostine is an organic thiophosphate drug found to have normal tissue cytoprotective effects on multiple organ systems during chemotherapy or radiation therapy. It has been shown in a randomized trial to reduce acute and chronic xerostomia in patients receiving head and neck radiation therapy and to objectively increase salivary flow over placebo.[16] Unfortunately, this increase in objective salivary flow has not translated into subjective xerostomia improvements in other trials. Furthermore, amifostine is typically given as a subcutaneous injection daily during radiation therapy, and its use has been limited by toxicities including hypotension, nausea, vomiting, and allergic reaction.

Late effects of radiation on normal tissues are ischemic, in which the blood supply to normal tissues is compromised by endothelial fibrosis of small blood vessels induced by radiation. These side effects typically manifest between 6 and 24 months after radiation. Late side effects of head and neck radiation include soft tissue fibrosis of the head and neck, trismus, osteoradionecrosis of the jaw, xerostomia, and esophageal strictures. Chronic laryngeal edema and laryngeal chondronecrosis can occur as well. Osteoradionecrosis of the mandible is a potentially serious late complication of radiation therapy; however, radionecrosis of bones other than the mandible is uncommon. The complication is uncommon but is related to the volume of mandible radiated, the radiation dose delivered, radiation treatment fraction size, and dentition. Edentulous patients rarely develop osteonecrosis, and patients with poor dentition are at higher risk. It has been generally recommended that patients with poor dentition have tooth extractions before, rather than after, radiation to decrease the likelihood of developing osteoradionecrosis. With the frequent urgency to commence radiation, there may be a window for safe extractions between approximately 2 and 4 months after radiation. When teeth are extracted following radiation therapy, prophylactic hyperbaric oxygen treatment is frequently recommended, with 20 treatments before tooth extractions and 10 treatments afterward. Whether this practice is in fact necessary on a routine basis has been questioned.[17]

Second malignancies occur rarely after radiation therapy, with an average latency of 10 years. The risk increases with time after completion of radiotherapy. Criteria for second malignancy include a solid tumor within the previously treated radiation portal, tumor of a different histology than previously treated, and tumor occurring in the correct latency period.

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Principles of Medical Oncology in the Management of Head and Neck Cancer

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Introduction

Medical oncology is an important aspect of treatment in head and neck malignancies. Specific medical therapy in head and neck malignancy is tailored to specific cell types. More than 95% of primary head and neck tumors are squamous cell carcinomas, with adenocarcinoma representing less than 5%. This chapter focuses on squamous cell carcinoma of the head and neck (SCCHN) and on salivary gland adenocarcinomas.

Epidemiology

According to the American Cancer Society's *Cancer Facts & Figures,* approximately 45,780 new cases of cancer of the oral cavity and pharynx would be diagnosed in the United States in 2014. The incidence of head and neck cancer in men is more than twice the incidence in women. Men older than 50 years are at increased risk of developing head and neck cancer. The American Cancer Society estimated that 8,650 people would die of cancer of the oral cavity and pharynx in 2015.[1]

The trend in 5-year survival rates is improving, but a disparity still exists between Caucasian and African American individuals. Five-year survival for Caucasians was 69% in the years 2004 to 2010 compared with 57% in 1987 to 2089; 5-year survival for African Americans was 62% in 2004 to 2010, although this represented an improvement from 43% in 1987 to 1989. Survival rates for head and neck cancer also differ widely depending on the extent of disease, as would be expected. Five-year survival for localized disease is 83%, compared with 51.3% for regional involvement, and only 27.6% for distant metastases.[1] This underlines the importance of early detection, particularly in the population at high risk for development of head and neck malignancy. Screening should be performed by an individual's dentist or primary care provider during regular checkups.[1]

Risk factors for the development of squamous cell carcinoma of the head and neck are known to include tobacco use via smoking (cigarette, pipe, and cigar) and the use of smokeless (chewing) tobacco. This risk is further compounded by excessive alcohol consumption.[1]

Data suggest that passive smoking also increases the risk of development of squamous cell carcinoma of the head and neck.[2] Human papillomavirus (HPV) infection has now been identified as a risk factor for the development of oropharyngeal squamous cell carcinoma, particularly in never smokers.[3]

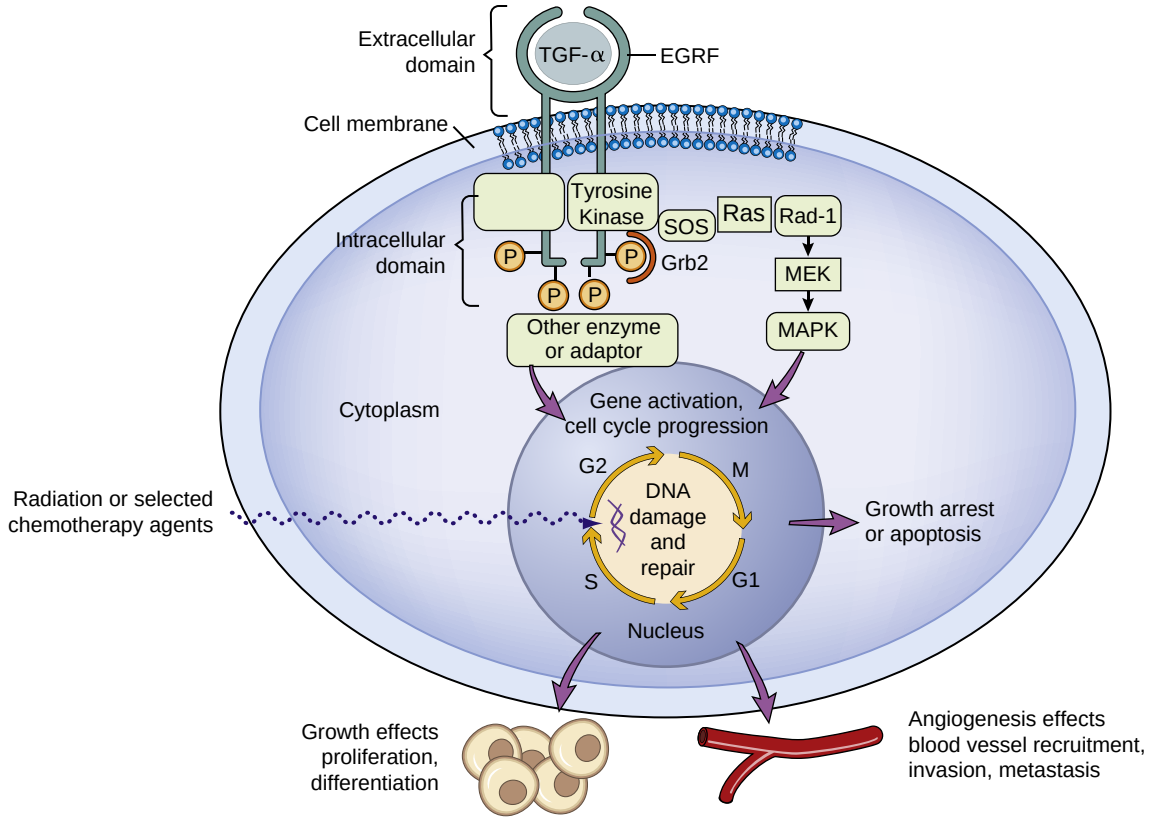
Background

The process of carcinogenesis requires multiple genetic alterations that occur over time, producing a cumulative effect on cell division and differentiation.[4] Proto-oncogenes are responsible for cell growth. When mutated, proto-oncogenes become oncogenes, which are perpetually activated to promote uncontrolled growth of the cell (Figure 33-1).

Historically, the main treatment regimen for head and neck cancer had been surgery. But with recent advances, radiation is an option in both the definitive and adjuvant treatment setting. Traditionally chemotherapy was restricted to treatment of patients with advanced-stage disease. Results from randomized trials have shown that chemotherapy in combination with radiation is effective in the definitive treatment of locally advanced SCCHN and also as adjuvant therapy after surgical resection in selected patients. Also, some randomized trials have examined the role of adding induction chemotherapy prior to chemo-radiotherapy as a treatment option for patients with locally advanced SCCHN. Recent advances in our understanding of novel molecular alterations in cancer have opened new avenues of treatment with targeted agents.

Treatment of Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Patients with TNM stage III and IV SCCHN without distant metastasis are categorized as having locally advanced disease. It is associated with a high rate of disease recurrence,



• **Figure 33-1** Oncogenes implicated in head and neck cancer include cyclin D1, or the epidermal growth factor receptor (EGFR) family.

requiring a multidisciplinary treatment approach, with the site of primary tumor playing a key role in choosing treatment options. Treatment could involve surgical resection followed by adjuvant radiotherapy or chemo-radiotherapy; organ-sparing approaches with chemo-radiotherapy (CRT) alone may be an option as well. Choosing among these different treatment options will depend on various factors such as treatment availability, skill and experience of the treating physician, and the site of primary tumor.

Adjuvant Chemo-radiotherapy

Historically, surgery has been the mainstay of treatment for SCCHN. Even now for most locally advanced oral SCC, surgical resection is the preferred option. After surgical resection, patients should be evaluated for the need for adjuvant therapy. With surgery alone, locoregional control rates and 5-year survival rates have ranged between 10% and 40%.[5] Therefore efforts have been ongoing to improve local control and overall survival after surgical resection. Since the 1970s, adjuvant chemotherapy has been tested both sequentially and concomitantly with radiation treatment. The rationale for inclusion of chemotherapy in the therapeutic management of locally advanced tumors is based on three primary observations:

1. Even though 70% to 75% of patients remain free of disease at 2 years, the long-term prognosis remains poor. Five-year survival rates rarely exceed 30% to 35%.
2. Although a fairly large number of deaths are linked to intercurrent disease, metastasis can occur at a rate from 15% to 20%.
3. A variety of cytotoxic agents have demonstrated efficacy against epithelial cell cancers.[6]

The use of chemotherapy alone has proved disappointing. However, compliance has not been optimal, especially after surgery and radiation treatment. Evidence of a biologic effect was seen, in that the pattern of failure was associated with a decrease in distant metastases in selected studies; no convincing improvement in overall survival was apparent.[7,8]

To improve the prognosis for patients with stage III to

out three cycles of cisplatin/5-fluorouracil (5-FU) to patients with completely resected SCCHN. This study reported no

therapy/radiation therapy (CRT) arm versus the radiation

P

extracapsular extension, and/or positive surgical margins)

Starting in the early 1990s, analyses of clinical trials undertaken to compare CRT versus RT showed that CRT significantly increased locoregional control and survival rates.[9-11]

Platinum compounds and 5-FU have been used most often in prospective clinical trials.[12-15] Various studies have tested the effects of CRT and reported associated benefits.[16-18] However, considerable variability in schedule, dose, and chemotherapeutic agents used was seen in these studies. Because of this, two randomized trials conducted by the

cisplatin (100 mg/m^2) on days 1, 22, and 43, given concurrently with radiation, versus radiation alone in patients with resected, poor-risk SCCHN of the upper aerodigestive tract (high-risk patients were more broadly defined).[19,20]

The EORTC study demonstrated a significant (P = 0.04) (P = 0.02) and locoregional control (P = 0.07) also significantly improved.[20] The RTOG study showed significant benefit for disease control with CRT over RT.

Disease-free survival and locoregional control rates at 2 years favored the CRT arm (P = 0.04 and P = 0.01, respectively). Also, a trend toward higher OS rates was seen with CRT (P = 0.19). No impact on distant control was noted. Both studies yielded positive results with regard to favorable impact of CRT on disease control. The magnitude of impact of chemotherapy on outcomes was greater in the EORTC than in the RTOG trial, but this may reflect variations in patient selection.

Data from a combined analysis of the EORTC and RTOG data indicated that CRT's benefit was primarily seen in tumors with extracapsular nodal spread (ECS) and/or microscopically involved surgical margins.[21] A trend favorable toward CRT was seen in patients with stage III to IV disease, perineural infiltrates, vascular embolism, and/or clinically enlarged lymph nodes at level IV or V associated with tumors in the oral cavity or the oral pharynx. Patients with two or more histologically involved lymph nodes who did not exhibit ECS or positive margins as additional risk factors did not appear to benefit from the addition of chemotherapy in this analysis.

Functional Organ-Preservation Approaches

In many patients with locoregional disease, even though surgical resection maybe feasible, a nonsurgical approach with concurrent CRT can be considered for functional organ preservation. In general concurrent CRT is the preferred option in this setting.

Oropharyngeal Squamous Cell Carcinoma

Several trials have examined the benefit of CRT over RT in the treatment of locally advanced oropharyngeal SCC. The most definitive evidence is provided by the Meta-analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) study.[22] This analysis included studies on CRT and RT alone as well as induction chemotherapy. With 5872 patients with oropharyngeal SCC, the study concluded that regimens with chemotherapy and RT were superior to RT alone (hazard ratio [HR] 0.88; 95% confidence interval [CI] 0.82-0.93).[23] The study also reported that CRT was associated with an improvement in overall survival (HR 0.81, 95% CI 0.78-0.86) but not with induction chemotherapy followed by RT (HR 0.96; 95% CI 0.90-1.02), though it did not include the more modern trials evaluating induction with docetaxel, cisplatin, and 5-FU (TPF) followed by RT. The study also compared different chemotherapy regimens and concluded that platinum-based regimens were superior to non-platinum regimens.

Laryngeal Squamous Cell Carcinoma

Functional organ preservation for laryngeal SCC was first adjuvant RT or induction chemotherapy with three cycles of cisplatin and 5-FU followed by RT. Patients who failed induction chemotherapy underwent surgery followed by RT. The 3-year survival was similar for both treatment arms (56% vs. 53%), and the larynx was successfully preserved in 64% of patients on the induction arm.

Results from the 2011 MACH-NC analysis showed that adding chemotherapy to RT versus RT alone for the treatment of laryngeal SCC (n = 3216) improved overall survival (HR 0.87; 95% CI 0.80-0.96).[23] This improvement in survival was restricted to CRT and not seen with induction or adjuvant chemotherapy. Like the MACH-NC analysis published in 2009, this study did not include the induction studies with the TPF regimen. The addition of chemotherapy to radiation was seen to improve survival in patients with hypopharyngeal SCC as well (HR 0.88; 95% CI 0.80-0.96), though the timing of chemotherapy administration, whether concurrent, induction, or adjuvant, did not appear to affect survival. Based on these data for patients with laryngeal and hypopharyngeal SCC, our experience has been to administer cisplatin 100 mg/m^2 on days 1, 22, and 43 concurrent with radiotherapy.

Induction Chemotherapy in Squamous Cell Carcinoma of the Head and Neck

The role for induction chemotherapy prior to locoregional therapy for locally advanced SCCHN has generated a lot

of discussion and controversy. The potential benefits from the induction approach are to decrease the risk of developing distant metastasis, reduce disease volume, and improve organ function, thereby allowing a more tolerable and effective locoregional therapy. Induction chemotherapy can also increase the risk of toxicity.

In locally advanced oral SCC, induction chemotherapy has been evaluated in the preoperative setting. Induction with three cycles of cisplatin and 5-FU followed by surgery versus immediate surgery was evaluated in a randomized trial.[25] Induction chemotherapy did not improve survival, but it did reduce the rate of mandibulectomy (31% vs. 52%). Also, the rate of postoperative radiation was lower in patients receiving induction chemotherapy (33% vs. 46%). More recent long-term follow-up from this trial confirmed absence of difference in overall survival between the two arms, and there was no difference in locoregional control and rates of distant metastasis. In a subsequent trial, induction with TPF prior to surgery and postoperative RT did not improve overall survival (HR 0.98; 95% CI 0.63-1.51) or disease-free survival (HR 0.97; 95% CI 0.65-1.45) when compared to surgery and RT.[26] Induction chemotherapy prior to surgery does not improve survival for locally advanced oral SCC.

The MACH-NC meta-analysis 2009 update included 31 trials with 5311 patients comparing induction chemotherapy to RT alone or surgery with or without RT and did not identify any significant difference in overall survival between these different treatment modalities (HR 0.96; 95% CI 0.90-1.02).[22] Induction chemotherapy and CRT were compared in six trials, and they showed no significant difference in overall survival between these two treatment modalities (HR 0.90; $P = 0.15$).

More recently there has been an effort to combine induction chemotherapy with CRT to maximize benefits. In the TAX 324 trial, 531 patients were randomized to receive TPF or PF (platinum and 5 FU) followed by CRT with weekly carboplatin.[27] The addition of docetaxel to platinum and 5FU was associated with an improvement in 5-year survival (52% vs. 42%; HR 0.74; 95% CI 0.58-0.94). The addition of docetaxel was also associated with increased incidence of both hematologic and nonhematologic toxicities. Subsequent trials have compared induction TPF followed by CRT to CRT alone. In the Spanish Head and Neck Cancer Cooperative phase III trial, 439 patients were randomized to receive CRT with cisplatin on days 1, 22, and 43, or two different induction regimens with TPF or PF followed by CRT with cisplatin.[28] There was no significant difference in overall survival, progression-free survival, or time to progression between the three treatment arms. Sub-analysis identified improved progression-free survival for patients receiving TPF induction who were also able to receive at least one cycle of CRT when compared to CRT alone: 20.4 months versus 13.3 months (HR 0.72, $P = 0.03$). PARADIGM and DeCIDE were randomized phase III trials that examined TPF induction followed by CRT to CRT alone.[29,30] Both studies were limited by poor accrual, and they did not show any significant survival benefit to adding TPF induction to CRT. Both studies also showed an increased incidence of adverse effects in the induction arms. The DeCIDE trial did identify a trend toward improved overall survival for patients with N2c and N3 disease, but the with locally advanced SCCHN. There may still be a role for induction chemotherapy with locally advanced laryngeal cancer with tumor stage less than T4a for functional organ preservation purposes.

Chemotherapy of Patients with Recurrent or Metastatic Head and Neck Carcinoma

More than 50% of patients given a new diagnosis of SCCHN will experience a recurrence after receiving primary treatment. Patients with SCCHN have a poor prognosis once primary treatment has been unsuccessful and recurrent disease has occurred. Outcomes are poor and have not changed significantly over the past 30 years.[31,32] Several treatment options are available for patients with recurrent disease. Palliative chemotherapy has shown survival benefit over best supportive care alone in one study.[33] Multivariate analysis of data from palliative chemotherapy clinical trials has shown that time to progression and overall survival are greatly influenced by factors other than the chemotherapy agents that are used; poor performance status, prior treatments, and advanced stage of disease all are associated with poor outcomes despite chemotherapy.[34,35] Because treatment is palliative and may be associated with significant adverse effects, clinicians must be careful in selecting patients for chemotherapy treatment. The benefits must be weighed against the side effects and complications of treatment before a patient can be committed to palliative chemotherapy. Salvage surgical intervention for local recurrence has resulted in 15% to 30% long-term disease control. However, if the recurrent disease is inoperable, or if it is metastatic in nature, systemic chemotherapy and/or local radiotherapy should be considered for palliative purposes.

In the 1980s, several clinical trials compared different chemotherapeutic combinations. The outcomes of these trials are presented in Table 33-1.

Multiagent chemotherapy in general was associated with a higher response rate but also had a higher degree of toxicity. Platinum-based combination chemotherapy yielded the highest response rates, approaching 50%.[36-39] The combination of cisplatin (CDDP) plus 5-FU emerged as the most effective treatment for SCCHN in the 1980s and 1990s. In a three-arm study conducted by Clavel and colleagues, 5-FU and CDDP combinations were compared with carboplatin, methotrexate, bleomycin, and vincristine and with CDDP alone. Results with the CDDP plus 5-FU and carboplatin arms were superior to

TABLE 33-1 Clinical Trial Comparisons

Trial	No. of Patients	Response Rate% (CR %)	Median Survival(months)	Year of Publication	High-Grade Toxicity*
CDDP ± cetuximab	117†	26 *v* 10	9.2 *v* 8.0	2005	173 *v* 93
CDDP + FU *v* CDDP + Tax	218†	27 *v* 26	8.7 *v* 8.1; OS at 1 year, 41% *v* 32%	2005	334 *v* 198
MTX *v* docetaxel (weekly)	57	15 (5) *v* 27 (3)	3.7 *v* 3.9	2004	6 *v* 21
CDDP + high-dose Tax *v* CDDP + conventional Tax	210†	35 *v* 36	7.6 *v* 6.8	2001	321 *v* 320
Raltitrexed + CDDP + FU/LV *v* MTX + CDDP + FU/LV	72	81 (28) *v* 42 (8)		2002	67 *v* 32
Edatrexate *v* MTX	264†	21 *v* 16		1995	90 *v* 45
CABO *v* CDDP + FU *v* CDP	382†	34 (9.5) *v* 31 (1.7) *v* 15 (2.5)	7.3 (TTP, 4.8 *v* 4.3 *v* 3)	1994	34 *v* 35 *v* 20
MTX ± lonidamine	89	26 (10.5) *v* 18 (0)		1994	78 *v* 41
CDDP 100 mg/m^2 + FU 4 g/m^2 q21d *v* CBDCA 300 mg/m^2 + FU 4 g/m^2 q21d *v* MTX 40 mg/m^2 wkly	277†	32 *v* 21 *v* 10	6.6 *v* 5.0 *v* 5.6	1992	66 *v* 47 *v* 35
CDDP 100 mg/m^2 + FU 4 g/m^2 *v* CDDP 100 mg/m^2 *v* FU 4 g/m^2; all q21d	249†	32 *v* 17 *v* 13		1992	77 *v* 34 *v* 32
CBDCA + MTX *v* MTX	40†	25 *v* 25	3 *v* 2	1989	
CABO *v* CDDP	209†	30 *v* 15	9 (TTP, 4.5)	1988	57 *v* 11
CABO *v* vincristine + MTX + bleomycin	185†	50 (16) *v* 28 (5)	9 (TTP, 4.5 *v* 3.5)	1987	35 *v* 41
CDDP + bleomycin + vincristine *v* MTX	191	24 *v* 16	7.2 *v* 7.8	1986	43 *v* 57
Control *v* bleomycin *v* CDDP + bleomycin *v* CDDP	117	NA *v* 14 *v* 24 (5) *v* 13 (3)	NS except CDDP arms *v* others 4.3 *v* 1.8	1985	NA *v* 4 *v* 25 *v* 24
MTX + bleomycin + CDDP *v* MTX	163†	48 (16) *v* 35 (8)	(TTP, 3.5)	1985	
CDDP *v* MTX	100†	8 *v* 16	4.5 *v* 5	1985	260 *v* 174
High-dose (1.5 g/m^2) MTX + LV *v* conventional (40 mg/m^2) MTX	47†	32 *v* 22		1984	30 *v* 10

CABO, CDDP + MTX + bleomycin + vincristine; *CBDCA*, carboplatin; *CDDP*, cisplatin; *CR*, complete response; *FU*, fluorouracil; *LV*, leucovorin; *MTX*, methotrexate; *OS*, overall survival; *NA*, not assessable; *NS*, not significant; *q21d*, every 21 days; *Tax*, paclitaxel; *TTP*, time to progression.
*Wherever toxicity was quantified by grade, relative number or percentage of grade 3 to 5 toxicities are reported. This is a sum of the worst event per patient for each toxicity type based on either absolute values or percentages reported in the publication.
†Majority of patients on this trial had prior therapy (excluding chemotherapy).

those with CDDP alone, with a median survival of 73 months. However, greater toxicity was encountered in all CDDP arms.[41]

Numerous single agents have been found to be effective against SCCHN (Table 33-2).[25] When taxanes became available in the 1990s, clinical trials were undertaken to evaluate these drugs. A single taxane agent, either paclitaxel or docetaxel, produced a response rate of 30% to 40%.[41-43] Because of the high rate of single-agent activity and the non-overlapping side effects seen with other agents, taxanes were used in clinical trials in combination with CDDP or carboplatin (Table 33-3).[44-49] These studies showed a response rate of 27% to 53%, with median survival of 5 to 12 months. When double-chemotherapy regimens were found to be successful, triple-chemotherapy combinations were given in an attempt to enhance response rates. Indeed, an increased response rate up to 60% and a complete response rate of 15% were attained with the combination of ifosfamide, paclitaxel, and CDDP or carboplatin.[50,51] The improvement in response rate has been consistent across other three- or four-drug combinations; unfortunately these treatment regimens resulted in significant toxicity and did not improve survival when compared to single or doublet regimens.

TABLE 33-2 Single Agents

Agent	No. of Patients Assessable	Response Rate (%)	Median Survival (months)	Year of Publication
Methotrexate		8-77 (average 31)		1984
Bleomycin		6-45 (average 21)		1977-1984
Cisplatin		14-41 (average 28)		1983-1994
Carboplatin		25		1986
Oxaliplatin		10		1996
Cyclophosphamide		36		1980
Doxorubicin		24		1980
Hydroxyurea	18	39		1980
Vinblastine		29		1980
Vinorelbine		6		1994
Fluorouracil		15		1984
Gemcitabine	61	13		1994
Capecitabine	14	8		2003
Orzel	42	21		2001
Irinotecan		0-14		2005
Paclitaxel 24-hour infusion	34	40 (4 CRs)	9.2	1998
Paclitaxel 96-hour infusion	Chemotherapy naïve/paclitaxel naïve/paclitaxel exposed	13/0/0	5.5	2004
Docetaxel		21-42		1994-2005
Pemetrexed	35	26	6.4	2001
Ifosfamide		26		2003
Cetuximab	103	13		2005
Erlotinib	115	4		2004
Gefitinib	47	11	8.1	2003
Sorafenib (BAY 43-9006)	10	6 SD (60%); 4 SCCHN + 2NPC; range, 3-6 cycles		2005

CR, Complete response; *NPC,* nasopharyngeal carcinoma; *SCCHN,* squamous cell carcinoma of the head and neck; *SD,* Stable disease.

Epidermal Growth Factor Receptor Inhibitors in the Treatment of Squamous Cell Carcinoma of the Head and Neck

The epidermal growth factor receptor (EGFR) is highly expressed in SCCHN; both gefitinib and erlotinib have shown activity against EGFR.[52] Gefitinib has been shown to inhibit other proteins in malignant cells, and this fact could have affected study outcomes.[53,54] However, with SCCHN, it seems that these agents mainly inhibit EGFR and downstream effectors; this appears to be the primary mechanism of action.

Multiple EGFR blockade agents have been used in various clinical trials (Table 33-4).[55] Gefitinib has been studied as a single-agent treatment in SCCHN that yielded an overall response rate of 10.6%, including one patient who exhibited complete response with 1-year survival.[56] Gefitinib seems to be more active when used as first-line treatment than when administered to previously treated patients. However, this difference is not statistically significant.[57]

Erlotinib has been investigated in SCCHN.[58] A 4% partial response was reported, with 1-year survival of 20%. EGFR expression did not correlate with response to or severity of skin rash. The combination of gefitinib and erlotinib with systemic chemotherapy was investigated.

TABLE 33-3 Clinical Trials in Metastatic and Recurrent SCCHN

Agent	No. of Patients Assessable	Response Rate (%)	Survival (months)	Year of Publication
Cisplatin + fluorouracil				
Locally recurrent post-XRT	19	89	8	1984
Metastatic	11	36	6	
Overall	30	70 (27% CR)		
Cisplatin + fluorouracil				
No prior treatment	31	84 (23% CR)		1985
Recurrent post-XRT	30	50 (1% CR)	9	
Docetaxel + fluorouracil	17	24		2000
Prior chemotherapy	20	25		2004
No prior chemotherapy	43	19		
Paclitaxel + cisplatin				
3-hour IV	36	41 (6 CR)	11	2004
No prior chemotherapy; 3-hour IV	50	32 (10% CR)	10	2002
Paclitaxel + carboplatin				
Paclitaxel 3-hour IV	37	27 (3% CR)	4.9	2001
Paclitaxel 1-hour IV weekly	31	52 (3 CR)	12.8	2003
Docetaxel + cisplatin	40	53 (18% CR)	11	2002
No prior chemotherapy	34	53 (17% CR)		2002
Cisplatin + vinorelbine	42	33 (10% CR)	6	2002
TIP				
Paclitaxel 3-hour IV	53	58 (17% CR)	8.8	1998
TIC				
Paclitaxel 3-hour IV	56	59 (17% CR)	9.1	2001
TPF				
Chemotherapy naïve	19	44 (12.5% CR)	11	2000
Docetaxel + irinotecan				
Chemotherapy naïve	17	18	9.8	2005
Prior chemotherapy	34	3	4.9	
Cetuximab + cisplatin				
Prior PD to cisplatin	96	10	6.5	2005
Gefitinib, docetaxel, and cisplatin	24	50 (30% CR)		2005
Cetuximab + cisplatin or carboplatin				
No response to prior platinum	132	13	6.5	2005
Erlotinib + bevacizumab	48	15	6.8	2005
Gefitinib + celecoxib				
Prior chemotherapy	19	22		2005

CR, Complete response; *PD,* Progressive disease; *TIC,* paclitaxel, ifosfamide, carboplatin; *TIP,* paclitaxel, ifosfamide, cisplatin; *TPF,* docetaxel, cisplatin, FFU; *XRT,* radiation therapy.

TABLE 33-4 EGFR Agents

Agent	Dose/Schedule	Prior Therapy	No. of Patients	RR (%)	PFS (months)	OS (months)
Gefitinib[17]	250 mg daily	No limit	70	1	1.8	5.5
Gefitinib[13]	500 mg daily	≤1 prior	47	11	3.4	8.1
Gefitinib[14]	500 mg daily	Cohort A, none	20	15	3	6
Gefitinib[14]	500 mg daily	Cohort B, ≤1 prior	12	0	NA	NA
Erlotinib[18]	150 mg daily	≤1 prior	115	4	3.8	NA
Cetuximab[35]	400 mg/m^2 loading, 250 mg/m^2 weekly	1 prior platinum-containing regimen	103	13	2.3	5.9
Cetuximab*[36]	400 mg/m^2 loading, 250 mg/m^2 weekly	1 prior platinum-containing doublet	96	10	2.2	5.2
Cetuximab*[37]	400 mg/m^2 loading, 250 mg/m^2 weekly	1 prior platinum-containing doublet	766	10	2.8	6.1

Note: Prior therapy represents the eligibility restrictions on patients enrolled on the trials.
EGFR, Epidermal growth factor receptor; *NA*, not available; *OS*, median overall survival; *PFS*, median progression-free survival; *RR*, overall response rate.
*After failure of a platinum-containing regimen, patients on these studies received cetuximab in combination with a platinum.

Docetaxel, cisplatin, and gefitinib showed a 50% overall response rate, with seven patients achieving complete remission.[59] Another study that studied the use of erlotinib with docetaxel and cisplatin showed an overall response of 78%, with complete response reported in 27 patients.[60]

A phase I/II study investigated the combination of erlotinib and bevacizumab-monoclonal antibodies against vascular endothelial growth factor (VEGF) in patients with recurrent and metastatic SCCHN. An overall response rate of 15% and a median survival of 6.8 months were reported.[61] The combination was well tolerated, but skin toxicity with skin rash occurred. For those patients who had not received prior treatment, objective response rate, median PFS, and median OS were 17%, 4.8 months, and 7.5 months, respectively.

Cetuximab is a human murine chimeric immunoglobulin G (IgG) monoclonal antibody that competitively binds to the extracellular domain of EGFR. This drug has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with advanced SCCHN, on the basis of recent study findings.[62]

In the phase III EXTREME trial, treatment-naïve patients with advanced SCCHN were randomized to receive platinum plus 5-FU with or without cetuximab.[63] The addition of cetuximab was associated with an improvement in overall survival (median overall survival 10.1 months vs. 7.4 months; HR 0.80; 95% CI 0.64-0.99. Treatment with cetuximab was associated with increased risk for grade 3 or 4 skin rash, hypomagnesemia, sepsis, and infusion-related

erse effects were similar

was seen between skin rash and favorable outcomes. Cetuximab is also active in the second-line setting for platinum-refractory patients.[64] On progression during treatment with cetuximab, a platinum agent was added to the treatment and an overall response rate of 13% was reported, with five patients achieving complete response and median survival of 5.9 months. In all, 103 patients who received cetuximab progressed while receiving a platinum-based regimen.

In summary, the combination of a platinum agent plus 5-FU or platinum plus taxane are appropriate first line options for patients with advanced stage SCCHN who are chemotherapy naïve or have a prolonged period of disease control after definitive CRT and have good performance status. Adding cetuximab to this combination is an option as well. For patients who cannot tolerate combination chemotherapy or have rapid progression after definitive CRT, single-agent chemotherapy maybe a better option.

Salivary Gland Cancers

Salivary gland cancers (SGCs) make up a broader class

are intercalated or secretory. Further classification has been distinguished by the frequency of disease site location, that is, major (parotid, submandibular) or minor (mucosal) gland. Most cases of SGC are benign and occur in the major gland. Malignancies such as adenoid cystic carcinoma (ACC), mucoepidermoid carcinoma (MEC), and salivary duct carcinoma (SDC) arise in the minor gland. Regardless of type, the therapeutic approach continues to consist of surgical intervention and radiotherapy, followed by chemotherapy in the palliative metastatic setting. Recent discoveries of targeted therapies have been advanced by

[65]

(WHO). The three predominant subtypes (ACC, MEC, and SDC) are discussed here.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) is a relatively rare, slow-growing, malignant epithelial tumor of the salivary glands. Age of onset generally ranges from 40 to 60 years.[66,67] By all accounts, ACC occurs in less than 3% of malignancies. The recommended treatment regimen includes surgical intervention and postoperative radiotherapy. However, despite these modalities, ACC has a high rate of local recurrence, with an unfortunate outcome of 10-year survival of 29% to 40%, with demise often within 2 years.[65,68] Distant metastatic (DM) events, histologically speaking, occur in solid tumor more often than tubular and cribriform subtypes. Unfortunately, metastases of this nature are due to its hematogenous disposition, which primarily involves the lungs. Chemotherapy is reserved for patients with local recurrence and for systemic disease.

Some authors have suggested that trial agents used independently, such as mitoxantrone, vinorelbine, and epirubicin, may be promising, although paclitaxel has produced no response.[65] A series of trials have investigated agents in combination, such as cisplatin-doxorubicin-cyclophosphamide (CAP) with or without the addition of fluorouracil; these have shown inconsistent outcomes. Despite immunotherapy, a combination of surgery and radiotherapy offers these patients the best chance for disease control. Analysis via immunohistochemistry (IHC) has revealed an overexpression of the proteins ErbB2[69], epidermal growth factor (EGF), and vascular endothelial growth factor receptor 2 (VEGFR-2) in the salivary glands involved by ACC. As is the case with ErbB2, trastuzumab (Herceptin) has shown widely varying results, in the range of 0% to 100%. Regimens of AEE788, a multiple-receptor tyrosine kinase inhibitor (inhibition of phosphorylation of tyrosine kinase of EGFR, VEGF2, and ERbB2), induce tumor apoptosis.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC), similar to ACC, has high rates of metastasis and locoregional tumor growth. It is the most common of the salivary gland carcinomas and, unfortunately, it exhibits a low response to therapy. In contrast to ACC, however, MEC has shown response to paclitaxel.[65] Overexpression of Her-2 displayed by IHC, EGFR, and gene amplification equates to a poor prognosis for this tumor. A phase II trial of trastuzumab objectively reported a partial response lasting 2 years. Additional studies are needed to examine tumor regression and the roles of paclitaxel, vinorelbine, and CAP in treatment.

Salivary Duct Carcinoma

Salivary duct carcinoma (SDC), the most invasive of the three malignancies, arises from the parotid gland. Its direct path of metastasis involves lymph nodes. Few data are available on the responsiveness of this tumor to chemotherapy, but in select patients, it is reasonable to use the same agents that are used for other salivary adenocarcinomas, such as CAP with or without 5-FU. Treatment regimens, as studied in phase II trials, consist mainly of palliative chemotherapy in the form of gefitinib or trastuzumab; these have resulted in stabilization of the disease for 26 to 46 weeks.[65] Other studies are ongoing with the goal of developing response of this unfortunate malignancy to multiple agents.

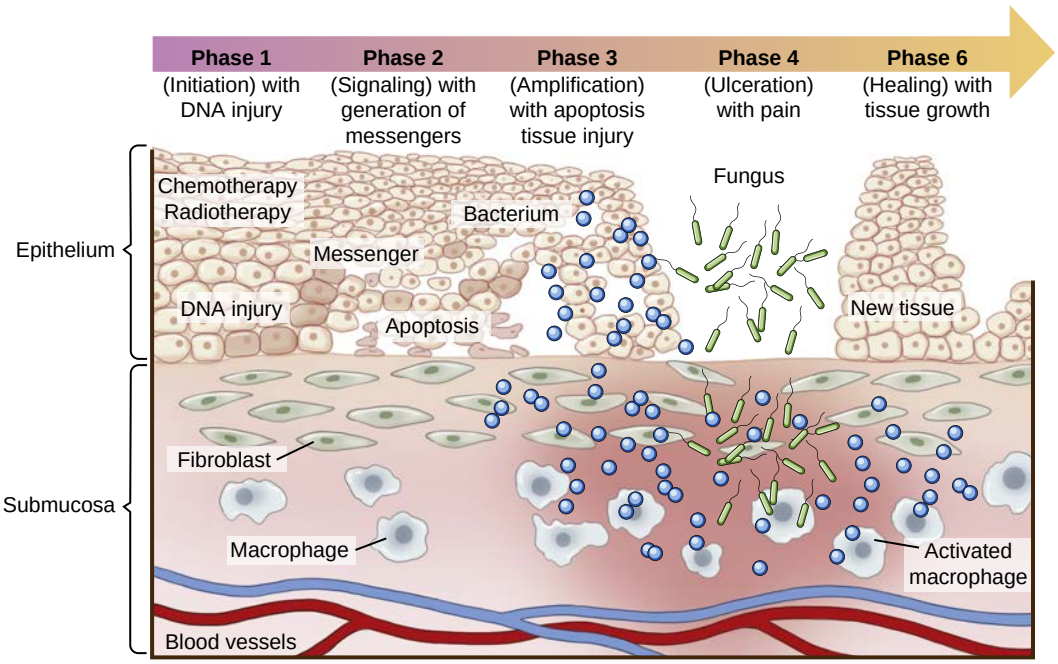
Histologically, salivary gland carcinomas must be clinically staged for identification of appropriate treatment regimens. Therapeutically, salivary gland carcinomas have a dismal prognosis; however, surgical resection and aggressive radiotherapy may provide benefit. Yet, palliative chemotherapy resides as the standard of care.

Phases of Oral Mucositis

Adoption of characterizing traits has been used to further classify mucositis into four distinct pathophysiologic phases. During the initial phase, called the inflammatory or vascular phase, tissue injury induces release of free radicals, inflammatory cytokines such as interleukin (IL)-2, prostaglandins, and tumor necrosis factor-alpha (TNF-α) via the epithelial, endothelial, and connective tissue of the oral canal. Induction of these components causes increased vascular permeability and accumulation of cytotoxic drugs.[70] The epithelial phase occurs 5 days to 1 week after treatment is initiated, or when cytotoxicity affects the dividing cells. Epithelial tissue erosion leads to fibrous exudates and forms a pseudomembrane or ulcerative tissue.[71,72] During this phase, denaturing of the epithelial mucosal lining results in the first symptoms of pain, which results from factors such as inflammation and infection attributed to microbial invasion. Epithelial destruction leads to the ulcerative phase, which can occur within 1 week after treatment is begun. The start of the pseudomembrane is seen during the epithelial phase. It becomes more prominent, leading to further destruction of the lining and ulceration. Further microbial colonization may be exacerbated by concomitant neutropenia.[73] Last, the healing phase commences on days 12 to 16. Tissue proliferation and differentiation and migration of epithelial cells restore the integrity of the mucosa (Figure 33-2).

Treatment

Investigational approaches have been used to attempt to treat or prevent mucositis.[74] It has been suggested that alpha-tocopherol, a component of vitamin E (VE), may act as an antioxidant. In clinical trials, VE has been shown to be potentially advantageous for mucosal preservation. A



• **Figure 33-2** Phases of mucositis.

double-blind randomized trial examined 54 patients with cancer of the oral cavity and oropharynx. Patients rinsed the oral cavity with an oil solution that included VE or a placebo before radiotherapy (RT) and again 8 to 12 hours later. Results indicated that VE reduced the risk of oral mucositis by 36%.[72]

Amifostine is an antioxidant cytoprotective agent that is used in cancer chemotherapy involving DNA-binding chemotherapeutic agents; it acts as a tissue-protective agent. Amifostine serves as a free radical scavenger and radioprotectant. Studies have shown that the benefit of amifostine for episodic events of mucositis is seen in patients with head and neck cancer who are undergoing usual treatment protocols. Additional studies evaluating amifostine during radiotherapy have reported a reduction in the incidence and severity of oral mucositis, but findings have been inconsistent, especially considering the tolerability of the drug and side effects such as nausea, vomiting, and hypertension. Antimicrobial agents are frequently an important adjunctive treatment for mucositis. Because the mucosa usually is colonized by a variety of microorganisms, secondary infection occurs whenever the integrity of the mucosa has been disturbed, particularly because these patients exhibit changes in the saliva and neutropenia, which cause an immunocompromised state.

Antifungal agents constitute important adjunctive treatment. Although fungal infection is not primarily involved in the development of mucositis, these agents are the most frequent causes of infection of the damaged mucosa in the immune compromised host. Prophylactic and therapeutic uses of antifungal agents, either topical (e.g., nystatin) or systemic (e.g., fluconazole), are very important in the treatment of patients with mucositis.

Second only to fungi, viruses, particularly herpes simplex virus (HSV) and varicella zoster virus (VZV), represent the most aggravating mucositis in the immunocompromised host, because of the pain and lack of response to general supportive care that they cause; these viruses respond well to antiviral agents such as acyclovir (Zovirax) or famciclovir (Famvir). Because of the severe pain that is involved, oral solutions with local anesthetics such as diphenhydramine, viscous xylocaine, lidocaine, or dicyclomine hydrochloride frequently serve as the palliative and supportive treatment required for the management of painful and damaged mucosa.

Evaluating therapeutic interventions remains difficult because of the variability of treatment regimens, the heterogeneity of patient populations, and the small number of double-blind and placebo-controlled clinical trials that have been completed.[73]

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34 History of Temporomandibular Surgery

GREGORY M. NESS

Despite a vast body of supportive scientific literature reaching back into the 19th century, surgical treatment of patients with temporomandibular joint disease remains controversial in the early 21st century, perhaps in part because relatively few surgeons (or patient advocates) have examined the rich history of these operations. Certainly, reading about the history of temporomandibular joint surgery enhances our understanding of the principles behind contemporary surgical therapy. Yet, as we read the unfamiliar and dated language of individuals whose names may sometimes be known but whose faces have faded from human memory, the mists of time lift slightly and we catch glimpses of what it meant to be a surgeon 50, 80, or 100 years ago. Although this chapter can only briefly summarize the accomplishments (and failures) whose legacy is our contemporary knowledge and practice, it will fulfill its purpose if the reader is inspired to visit some of the pioneering articles themselves, seeing them in their original context among papers describing advances in general, orthopedic, or plastic surgery, and (in more recent decades) encased by advertisements for the latest and best materials, pharmaceuticals, and instruments, most of which are now long forgotten.

In fact, it is often difficult for the contemporary reader to examine outdated techniques and concepts without an anachronistic and even arrogant sense of omniscience. To understand the significance of our surgical forefathers' accomplishments, we must abandon our comparatively vast understanding of human physiology, inflammation, pain, and healing, not to mention our sophisticated technology, instrumentation, imaging capabilities, and pharmaceutical armamentarium. Imagine instead devising an approach to a temporomandibular joint that you have not imaged and whose normal structure and function are largely matters of speculation. Then, perform your operation on a patient anesthetized with an open cloth soaked in ether or chloroform. The latest textbooks discuss the comparative risks and benefits of these two anesthetic gases; both are known to have major safety and efficacy risks to patient and surgical team alike. Finally, hope that any infection afterward does not prove to be fatal, and that the operation leaves the patient better off, not worse.

Pioneers

Numerous advances notwithstanding, most fundamental surgical procedures employed in the treatment of temporomandibular joint (TMJ) disease have been known, practiced, and described in the surgical literature for a century or longer.

Thomas Annandale[1] generally is credited with the first published description of temporomandibular joint disc repair in 1887 (Figure 34-1). He describes successfully treating two patients with locking or painfully clicking TMJs using surgical disc repositioning, having correctly hypothesized that the problems lie with the "inter-articular" cartilage of the TMJ displaced "either from a sudden tearing of their connections or from a gradual stretching of them." The contemporary wisdom of the time was represented by a textbook that he quoted, which describes the disorder as "an affection occurring principally in delicate women . . . thought to depend upon relaxation of the ligaments of the joint permitting too free a movement . . . and possibly a slipping of the inter-articular cartilage."[2] This opinion may sound eerily familiar to the contemporary reader, but other 19th-century concepts are now unthinkable: Annandale's second patient was kept in hospital 10 days before her surgery and 13 days after.

Treating the temporomandibular joint was by no means a standard operation in the 19th and early 20th centuries. Annandale used a small incision comparable with a modern conservative preauricular approach. In contrast, the 1895 edition of Stimson's *Manual of Operative Surgery* describes excision of the mandibular condyle through a T-shaped incision with its horizontal arm along the inferior aspect of the zygoma about 1¼ inches in length and the vertical arm, through skin only, about 1 inch long. The "parotid, nerves and vessels" were retracted inferiorly to prevent injury.[3] In 1914, John Murphy of Chicago produced a detailed report

ON

DISPLACEMENT OF THE INTER-ARTICULAR CARTILAGE OF THE LOWER JAW, AND ITS TREATMENT BY OPERATION.

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THAT the proper movements of the temporo-maxillary joint may be interfered with by conditions inside the articulation is a fact recognised by all surgical authorities. That a displacement of the inter-articular cartilage—the "subluxation" of Sir Astley Cooper—may be one of these conditions is also recognised. But most modern works on surgery describe this affection as being generally due either to relaxation of the ligaments of the joint allowing a too free movement, or to inflammatory changes of a simple, gouty, or rheumatic nature. Heath[1] writes upon the subject thus: "It is an affection occurring principally in delicate women, and has been thought to depend upon relaxation of the ligaments of the joint permitting a too free movement of the bone, and possibly (though this is conjecture) a slipping of the inter-articular cartilage." Believing with Mr. Heath and other authors that inflammatory results may cause interference with the movements of this joint, I feel further convinced that, as in the case of the semilunar cartilages of the knee, the inter-articular cartilages of the temporo-maxillary joint may become displaced either from a sudden tearing of their connexions or from a gradual stretching of them.

But the chief object of this short paper is to advocate a new method of treating by operation cases of this condition which resist counter-irritation and the other means usually advised, and in which there are symptoms of a too free movement of one or both of these cartilages. The operation is upon the same principle as that which I have described and successfully carried out in connexion with the displacement of the semilunar cartilages of the knee-joint. The method is as follows:—An incision slightly curved, about three-quarters of an inch in length, is made over the posterior margin of the external lateral ligament of this joint, and is carried down to its capsule. Any small bleeding vessels having been secured, the capsule is divided, and the inter-articular cartilage is seized, drawn into position, and secured to the periosteum and other tissues at the outer margin of the articulation by a catgut suture. The following two cases illustrate the condition, and also the good result obtained by the operation suggested.

CASE 1.—Mary M'C——, aged thirty-eight, was admitted into my wards on March 2nd, 1886. Nine years before her admission she injured her temporo-maxillary joints during an attack of vomiting. The joints remained "locked" for a few minutes, but after a little manipulation she herself put the condition right. Ever since this time she has suffered great discomfort in the joint upon the left side, for whenever any extra movement of the jaws was made this joint became fixed, and remained so until she had practised some manipulations, when movement returned. Frequently also, when she tried to open her mouth, she found that she could only do so to a limited extent, but by using the manipulations the proper separation of the jaws was completed. On March 12th an incision was made over the left temporo-maxillary joint, and, its capsule having been divided, the inter-articular cartilage was found to be loosened from its attachments, and much more movable than usual. The cartilage, having been seized with artery forceps, was drawn into position, and a catgut suture passed through it and the periosteum and other tissues at the outer margin of the joint. The wound healed rapidly, and she left the infirmary on March 25th. At this time the movements of the joint were natural, and she could close and separate the jaws perfectly, without any locking or catch.

CASE 2.—Ann M——, aged eighteen, admitted on Jan. 20th, 1885. Two years before admission, the patient when yawning found her jaws fixed. After a little manipulation she was able to close the jaws, but with a "click" on the right side. Since then she has suffered from pain and stiffness upon the left side, and the movements of the joint were constantly interfered with by something "slipping" in it. She had been treated by blistering and other remedies without obtaining any relief. On July 23rd the usual operation was performed, and the left inter-articular cartilage, being found loosened, was stitched in position with a catgut suture, as in the former case. The wound was healed at the end of a week, and she left the infirmary on July 31st, with perfect and proper movement of the jaws.

[1] Injuries and Diseases of the Jaws, third edition, p. 415.

PHOSPHATIC DIABETES.[1]

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AMONG the numerous investigations that have engaged the attention of physiologists during the last fifteen years, few yield in interest and importance to the study of the part played by the inorganic constituents of the body in histogenesis, and their influence in producing the daily and hourly variations which occur in the chemical composition of the secretions. Although this branch of animal physiology is only partially developed, yet our knowledge in this direction is steadily and constantly advancing, and the advance will be more rapid when it becomes clearly perceived how greatly minute variations of the inorganic constituents conveyed by the blood plasma to the cells influence for good or evil the processes of nutrition going on in the tissues. I can here only glance at some of the more important facts that have been established in this direction, and touch only on those points which are most closely related to the subject matter of the present paper.

Twenty years ago it was stated in most text-books that inorganic substances passed unaltered through the body, and that the same weight of saline constituents was recoverable from the urine and fæces as was introduced during the same period with the food and drink. The first advance on this simple view was made when it was discovered that chloride of sodium was retained in the body, and consequently disappeared from the urine, in certain diseases attended with increased cell-formation; and that even under normal conditions only four-fifths of the common salt ingested left the body as such, the remaining fifth being decomposed and altered in constitution within the system. Further researches led to the important discovery that whilst inorganic salts pass with immense and usually uniform rapidity into the circulation, and thence to the tissues, their discharge is by no means so regular, and they are detained for very unequal periods, which apparently depends on the need of the tissue to which they are supplied. Thus both Hoffmann and Lascar have shown that, however great the tendency of the alkaline bases is to combine with acids and acid salts, these cannot be withdrawn from the alkaline blood, but are powerfully withheld to maintain its alkalinity. And this fact is illustrated by what occurs in scurvy, for, as I pointed out in 1877,[2] and it has since been corroborated by Zuelzer,[3] as soon as the alkaline carbonates cease to be supplied by means of vegetables, the alkaline phosphates begin at once to disappear from the urine, evidently to maintain the alkalescence of the blood diminished by the withdrawal of the alkaline carbonates. In connexion with this it is interesting to notice that Dr. Gee[4] has likewise called attention to the remarkable fact that in ague, on the days of the paroxysms, the phosphates almost entirely disappear from the urine; and although Dr. Gee has not attempted an explanation of the phenomenon, still it is not unlikely that this is again an instance of a salt being withheld to supply a special requirement, whilst another is being discharged in excess; for it is important to notice in connexion with this withdrawal of phosphoric acid during the ague fit that the chlorides are at that time eliminated in considerable excess. It would be easy to multiply examples, but enough has been said to emphasise the importance of the *rôle* played by the inorganic substances in the economy.

Of all inorganic constituents phosphorus has always been regarded as holding the prominent position. When first separated from the urine by Brandt (1669) it was at once hailed by the physiologists of the day as the "blood of

[1] Read before the Medical Society of London, Jan. 10th, 1887.
[2] General Pathology of Scurvy (Lewis. London, 1877).
[3] Untersuchungen über die Semiologie des Harns; Berlin, 1884.
[4] St. Bartholomew's Hospital Reports, vol. viii.

• **Figure 34-1** Thomas Annandale's landmark article in *The Lancet* is just over a single column in length, has no illustrations, and includes only a single formal reference citation. (From Annandale T: Displacement of the inter-articular cartilage of the lower jaw, and its treatment by operation, *Lancet* 8:411, 1887.)

on nine cases of TMJ ankylosis treated by arthroplasty with rotation of an interpositional flap of temporal fat and temporalis fascia.[4] His incision was L-shaped, with its base along the superior aspect of the zygomatic arch and a vertical arm at the posterior end, extending upward 1½ inches. Murphy claimed that keeping the horizontal incision above the zygomatic arch avoided branches of the facial nerve.

Behan published a detailed and well-illustrated description of TMJ arthrotomy in 1918, returning to the vertical preauricular approach.[5] In the same year, John Blake in Boston noted the difficulties of approaching the TMJ: "It is hard to reach for the purpose of careful detailed attack, as it lies deep below the surface, and is surrounded by good-sized arteries and nerves; a clear dry field is hard to obtain, and accurate work on the joint is consequently far from easy."[6] Even so, others pressed on: In Philadelphia, Ashhurst called Blake's concerns "undue emphasis" and reached the joint through an inverted L-shaped incision, following the zygomatic arch horizontally for 2 cm, then turning inferiorly from the posterior end for 3 cm.[7]

These early TMJ surgeons and several others in the United States, Great Britain, and Europe were pioneers in devising approaches to the TMJ and procedures to restore the joint to better function. According to contemporary standards, their incision designs range from unsophisticated to dangerous and disfiguring, but these men were hardly unsophisticated themselves. All were exceptional anatomists and broadly trained surgeons who critically reassessed the little TMJ pathophysiology known to them, brought fresh thinking to their patients' problems, and applied principles gained from experience in other operations and diseases to the TMJ in novel and perceptive ways. They were certainly aware of one another's work: Most cited one another, and nearly all referenced Annandale's article from a quarter-century before, as well as still earlier compilations of jaw dysfunction cases[8] that offered insight into the TMJ symptoms they faced, although they were of little use regarding surgical therapy.

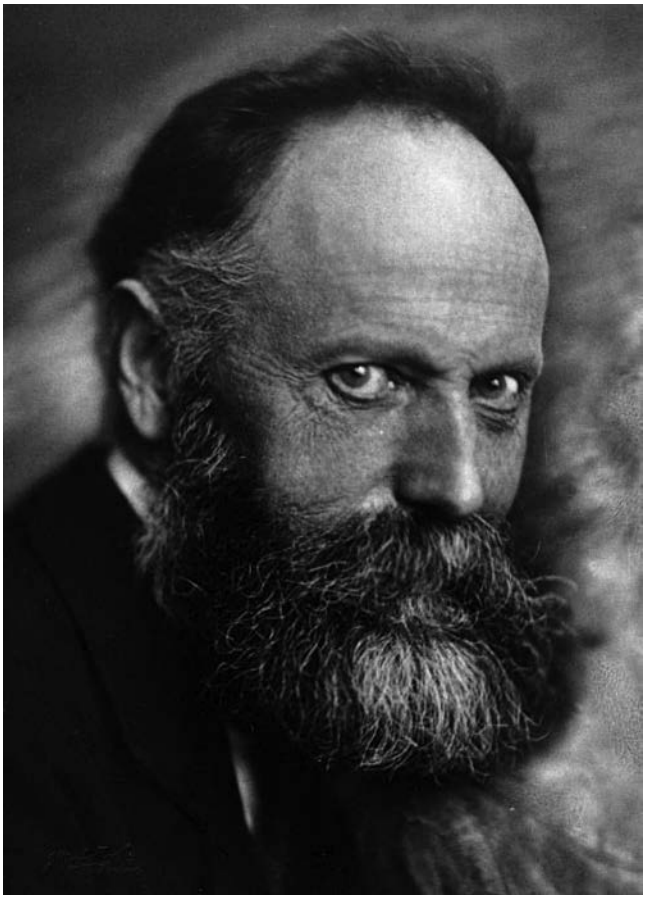
Early Arthroplasty

The Snapping Jaw

By the 1920s, a reasonable body of literature and clinical experience had accumulated regarding TMJ anatomy and function, and several distinct joint pathologies now possessed documented surgical remedies. Annandale had treated painful locking and clicking joints with disc repositioning 30 years earlier, but for many years, little more was published on surgery for this particular condition. In 1918, Behan[5] described finding either anterior or posterior disc attachments torn and he repaired them to reposition the disc. That same year, Pringle[9] hypothesized that the lateral pterygoid muscle could displace the articular disc anteriorly and medially, and treated the condition with what he believed to be the first excision of the disc. Ashhurst duplicated this operation successfully in 1921 on a 16-year-old female patient.[7] Unknown to both of them, the Swiss surgeon Otto Lanz (Figure 34-2), professor of surgery in Amsterdam, had published two cases of TMJ discectomy on an 18-year-old and a 24-year-old woman that he had performed in 1906 and 1908.[10] Lanz, who also invented the mesh skin graft during this time,[11] had reported his surgeries a decade earlier in the German-language journal *Zentralblatt für Chirurgie*.

It was Ashhurst, however, who resurrected a term first painful popping or snapping jaw that might intermittently become stuck open, closed, or something in between.

In fact, confusion reigned regarding the actual location and movement of the articular disc in normal function, not to mention its role in the intermittently locking, subluxing, dislocating, and/or snapping joint. Early on, Cooper had compared the subluxing TMJ to injured knees and hypothesized that capsular ligamentous laxity allowed subluxation, although he also believed that the disc could become displaced behind the mandibular condyle and thus prevent full mandibular closure.[8] The debate on whether capsular laxity or disc displacement was responsible for the



• **Figure 34-2** Otto Lanz, the surgeon who first treated painful locking temporomandibular joints in 1906 by removing the intra-articular disc. (Reproduced in Haeseker B: Historical notes on 50 years of plastic surgery in the Netherlands, *Eur J Plast Surg* 23:164, 2000.)

observed symptoms continued for a century and longer. Despite multiple reports of encountering the disc displaced anteriorly at surgery and repositioning it posteriorly, some authors persisted in blaming a posteriorly displaced disc or a loose lateral capsule for the pain and snapping noises in the TMJ. Some confusion may stem from inconsistent use of terminology: Many case reports were unclear on precisely what jaw mobility dysfunction was present, and the term *subluxation* seems to have been applied sometimes to the disc and sometimes to the mandible (without specifying whether the disc was thought to be malpositioned anteriorly or posteriorly). Contemporary understanding of anterior disc displacement and reduction is relatively recent, and perhaps the early confusion is understandable. If one considers the broadly diverse treatments available today for chronic subluxation/dislocation, it can be seen that we may have not progressed all that far in our understanding of this condition.

Although Lanz, Ashhurst, and Pringle directed surgery at the disc, others attempted to control "subluxation" through extracapsular procedures. Blake[6] successfully prevented recurrent dislocation in an adult male patient by wiring the coronoid process to the zygomatic arch to restrict mandibular opening. And in Germany, Nieden[12] improved on safe access to the TMJ and devised a new procedure to restrict condylar movement. He elevated an inferiorly based flap of temporalis fascia, rotated it inferiorly, and secured the free end to the lateral joint capsule to tighten it and restrict condylar movement. Several years later, this surgery was declared to be "based upon the soundest surgical principles" for treating hypermobility,[13] and the loose lateral capsule was believed to be the main point of origin for several more decades.

The story of Professor Doctor Nieden illustrates another aspect of reviewing history: Our admiration of an important figure's achievement should not automatically extend to his character. Nieden's story would not be complete without taking note of a darker side. A highly decorated military surgeon during World War I, Nieden chose a less than noble course during the National Socialist years. He joined the Nazi party early, worked with the Gestapo before and during World War II, and served in the SS. Published accounts name him as a surgeon who performed compulsory sterilization on mixed-race children in the 1930s.[14,15]

Ankylosis

Painful snapping was not the only TMJ pathology treated by operation, nor the most common. Ankylosis was perhaps the earliest TMJ condition treated surgically, although most 19th-century surgeons in Europe attempted to solve the problem with osteotomies away from the TMJ itself. In the United States, Murphy reported on nine patients with TMJ ankylosis whom he treated during the years leading up to 1914.[4] His paper is a grim reminder of the fearsome complications caused by infection in the pre-antibiotic era. Table 34-1 lists the ages of onset and causes of ankylosis for his case series.

TABLE 34-1 Age at Onset and Cause of Ankylosis in Murphy's Case Series, 1914

Case #	Onset Age	Cause
1	6 mo	Otitis media, mastoiditis
2	6 yr	Kicked in jaw by horse, angle fracture with infection
3	Birth?	Difficult delivery, facial deformity noted early in life
4	9 yr	Fall from third story, chin impact, immediate trismus
5	Birth	Unknown
6	2½ yr	Severe mastoiditis, otitis, recurrent abscesses for over 6 months
7	14	Fall from horse without direct facial injury; progressive hip, spine, and jaw immobility
8	2½ yr	Throat infection, subsequent generalized abscesses
9	17	Sepsis, osteomyelitis

Data from Murphy JB: Arthroplasty for intra-articular bony and fibrous ankylosis of temporomandibular articulation, *JAMA* 62:1783-1794, 1914.

Although some cases appear to represent congenital deformities or sequelae of direct trauma, a significant number of his ankyloses appear to be late effects of local (especially mastoiditis) or widely disseminated infection, leading to septic arthritis of the TMJ, a condition very rarely seen today. His treatment consisted of freeing the ankylosis by removing the bone in the area of the condyle and rotating a fascia and a fat flap from the temple into the gap, then propping the patient's mouth open for 2 weeks with a wedge-shaped wooden block. His purpose for this was to "prevent possible compression necrosis of the interposing flap." He reported good mandibular movement at follow-up periods of 4 to 11 months, with one recurrent ankylosis.

The Role of Dental Occlusion

During the early 20th century, intrinsic pathology of the TMJ was addressed with little apparent consideration for the state of the patient's dental occlusion. Orthopedic principles derived from greater experience in other joints were applied to the TMJ, with results reportedly satisfactory to patient and surgeon alike. By 1930, John Morris was able to present a thorough and insightful review of the state of the art in treating the snapping jaw.[13] He perpetuated the assertion that capsular laxity with consequent excessive condylar movement was responsible for the observed snapping, pain, and hypomobility. However, he recognized that posterior disc displacement was anatomically unlikely and therefore an unacceptable cause. Building on the work of Pringle,[9] he postulated that anterior displacement ultimately led to secondary joint laxity, which, in turn, produced symptoms.

• BOX 34-1 Treatment Options for "Subluxation of the Inferior Maxilla"

I. Nonoperative methods
  A. Dental technical procedures
    1. Outside mouth
      (a) Apparatus, fastened around chin and held in position by cap on head; limits chewing motion and depression of point of jaw
    2. Inside mouth
      (a) Splint, fastened to upper and lower jaw with intervening catch hinge, is adjustable to limit motion of lower jaw (Schroeder)
      (b) Hard rubber plate, fixed to upper jaw and provided with process pointing of edge of masseter muscle or coronoid process, limits excursion of latter (Fritzsche)
  B. Injection of corrosive fluids into joint (to produce shrinkage of capsule and promote adhesions)
    1. Tincture of iodine (0.75 mL tincture of iodine injected into joint posteriorly secured permanent cure in case of girl, aged 20 years, as reported by Perthes)
    2. Alcohol
II. Operative method
  A. Treatment of capsule
    1. Excision of portion of capsule is followed by suture to overcome redundancy (Perthes)
    2. Simple plication of capsule after exploration of joint takes up redundancy and tightens joint
  B. Use of fascial strip (turned down from temporal region to check excursion of head, as described by Nieden)
  C. Treatment of meniscus
    1. Fixation of disc by suture to periosteum of mandibular fossa (Haeber)
    2. Fixation of disc in vertical position in front of condylar process (Konjetzny)
    3. Removal of the articular disc (Ashhurst)

From Morris JH: Chronic recurring temporomaxillary subluxation: surgical consideration of "snapping jaw" with report of a successful operative result, *Surg Gynecol Obstet* 50:483-491, 1930.

More significantly, he summarized the contemporary treatments available for the snapping jaw (Box 34-1) and argued convincingly that joint surgery offered the best solution.

Morris's writings reflect progress made since the time of Annandale nearly half a century earlier, not only with respect to the TMJ but for all of orthopedic surgery. He decries that "standard surgical texts limit operative indications to such conditions as ankylosis, arthritis, irreducible dislocations, and a few unusual fractures. Subluxation of the joint as a surgical consideration is either dismissed as of no importance, or its existence is completely ignored." He responds by asserting that "operative indications, which were formerly limited to the more grave pathological conditions, have been gradually extended to include a variety of derangements the minor character of which did not justify the hazards imposed by the older methods. The acceptance of the minor joint lesions for radical surgical treatment indicates the highest degree of confidence in the safety and efficiency of the methods employed and offers as well the most convincing evidence of the advances made in this field."

However, within a few years, the philosophy undergirding temporomandibular joint care would turn in the opposite direction. Washington University otolaryngologist James Costen studied a large cohort of patients with varying combinations of headache, ear pain, neuralgia, glossodynia, and other less common complaints associated with abnormal jaw movement and malocclusion. He theorized that loss of posterior occlusal support (a common phenomenon of the time) led to excessive pressure on the TMJ with subsequent destruction, dysfunction, and nerve compression. His theory was ultimately published in the *Journal of the American Medical Association*[16] and gained widespread acceptance for nearly two decades; the "snapping jaw" became "Costen's syndrome."

Treatment of patients with this new syndrome, whose symptoms were correctly observed to be much more common than was previously recognized, was dental. The posterior occlusion was gradually opened; this was believed to decompress the nerves and other tissues within the TMJ and to allow healing. Most patients improved; those who did not were sometimes assumed by their treating physicians to have received poor care from their dentists.[16] In fact, Costen even advocated against removing the molar teeth in any pa

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energized an entire school of thought that attributed joint pathology to occlusal disharmonies. In fact, therapy following Costen's principles and the many subsequent dental refinements was reasonably effective, although probably not for the reasons cited. However, as early as 1940, some authors questioned the anatomic basis of Costen's neurologic symptoms. Dingman[17] concludes a thorough review of TMJ therapy by warning, "We must not lose sight of the fact that many of the statements made regarding this subject [Costen's syndrome] are still within the realm of speculation and need further scientific investigation for substantiation. . . . By assuming a critical attitude and proceeding in a cautious manner, the dental profession may avert severe criticism that might arise as a result of misguided therapy." His advice remains wise today.

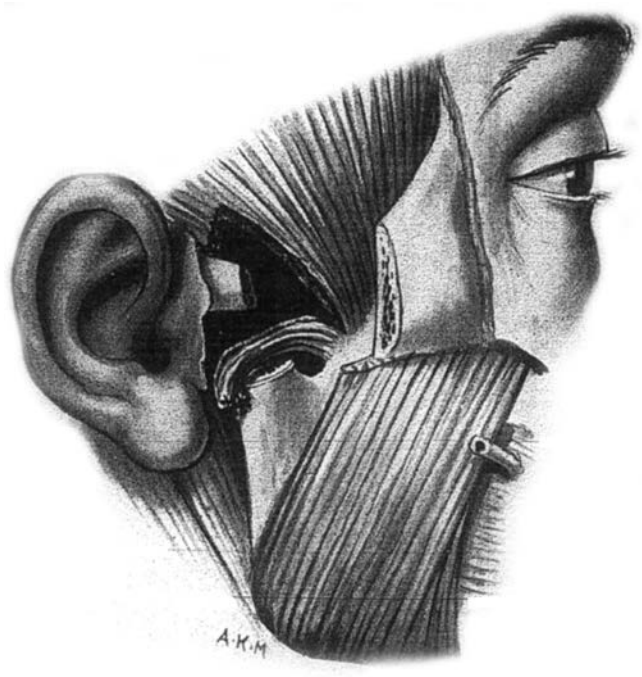
Finally, in 1948, Harry Sicher, the legendary teacher and anatomist at Loyola School of Dentistry, published a definitive anatomic study that refuted the neural compression mechanism underlying Costen's syndrome.[18] His article concludes with a balancing perspective. He notes that "destruction of the disk and degenerative and proliferative changes on the condyle and tubercle" meet "the well-defined picture of deforming arthritis. . . . The symptoms of pain, local and irradiating (referred), cracking of the joint and the restriction of movements of the joint are simply the symptoms of arthritis." Yet he does attribute TMJ arthritis to mandibular overclosure or displacement and concludes by stating, "The beneficial influence of reconstructive dentistry has to be fully recognized." Thus, the two schools of TMJ treatment, surgical and occlusal, remained established and in some tension with one

another, although perhaps forming the beginnings of a stronger scientific foundation.

The Mid-20th Century and the Science of TMJ Therapy

Professor Cecil Wakely of King's College, London, published a new review on surgery of the temporomandibular joint in 1939.[19] In a series of 38 patients (30 male and 8 female) with mandibular dislocation, he found only two whose condition was recurrent and did not operate even on those. He advocated arthroplasty with a gap for treating ankylosis and was the first to use a pedicled temporalis flap, tunneled beneath the zygomatic arch, as an interpositional tissue graft (Figure 34-3). Regarding allografts, he noted presciently, "The human body does not tolerate foreign tissue kindly."

The largest part of Wakely's paper is devoted to the displaced articular disc, a topic that he had explored a decade earlier.[20] He describes this condition as "an uncommon accident, but a much more difficult condition to treat than dislocation of the joint." He believed that synovitis resulting from displacement was in part responsible for the pain, which is perhaps the first recognition of a noninfectious, intracapsular inflammatory process as a contributing cause of the disorder. He also bluntly associated gender-related emotional issues with chronic disc displacement: "The psychologic effect of a snapping joint may be very marked, especially in females. They become introspective and nervous and are afraid to have meals in public."[19] In cases that failed "every other form of treatment" (which he does not describe), he performed discectomy and claimed good outcomes with follow-up of up to 15 years, comparing the procedure to the well-established successful operation of excising torn medial menisci from the knee.



• **Figure 34-3** Professor Wakely's temporalis flap, 1939. (From Wakely CPG: The surgery of the temporomandibular joint, *Surgery* 5:697-706, 1939.)

The following year, Reed Dingman of Washington, DC, also published a broad review of diagnosis and treatment of TMJ disorders.[17] Many of the conditions he identified are curiosities to the modern reader. Suppurative lesions of the TMJ were becoming less frequent but might still result from middle ear infection, gonorrheal ophthalmitis or urethritis (he cites a large series that found TMJ infection in 3% of gonorrheal urethritis cases), measles, scarlet fever, diphtheria, pertussis, typhoid, pneumonia, or influenza. He attributed the reduction in cases to the introduction of vaccination for many of these diseases, the use of sulfanilamide to treat infection, and the instillation of silver nitrate eyedrops to prevent gonorrhea neonatorum. He notes that without incision and drainage, a suppurative TMJ can be expected to drain preferentially into the middle ear or the external auditory canal and much less commonly to the pretragal area. Yet even with proper care, many of these cases ended in ankylosis, which remained a relatively common indication for TMJ surgery. In such cases, Dingman advocated arthroplasty with a pedicled interpositional temporalis flap, although he abandoned Murphy's mouth wedge.

Dingman also wrote at length on arthritis of the TMJ—both atrophic (rheumatoid) and hypertrophic (osteoarthritis). In either case, unless the patient developed an ankylosis or severely symptomatic disc displacement, he advocated nonsurgical care consistent with that given for other afflicted joints. He noted that TMJ arthritis previously had been thought to be rare, but its actual, more common incidence had become widely recognized. With respect to subluxation and dislocation, Dingman, like many before him, appears to have considered cases of disc displacement and condylar subluxation/dislocation as a single broad entity. He describes nonoperative treatment with intermaxillary fixation or sclerosing injections, the latter as "generally ineffectual," although he gives details of the method used by Schultz[21] with good effect. Of published surgeries for internal derangements, he concludes (although without providing evidence) that discectomy "seems to be the best and most logical procedure."[17]

Dingman and Wakely were by no means the only surgeons performing TMJ operations in the 1930s and 1940s. Caroll Silver, an orthopedic surgeon who trained in New York in the late 1930s, participated in several cases as an intern wherein mandibular hypermobility was treated by grafting a block of bone to the articular eminence. Patients were kept in a plaster head cast for 6 weeks and were fed through a straw; they reportedly did not suffer from subluxation or dislocation after healing.[22] Later in his career, Silver performed hundreds of discectomies and contributed some of the largest series of long-term outcomes in the literature.[23] In Stockholm, Karl Bowman published his doctoral dissertation entitled "Temporomandibular Joint Arthrosis

and Its Treatment by Extirpation of the Disk: A Clinical Study."[24] This landmark scientific treatise was arguably its time's most complete, well-documented compilation of knowledge regarding the TMJ and its anatomy, pathophysiology, normal and impaired function, and response to discectomy (including measured outcomes). He summarizes, saying in part the following[24]:

> Examination of a healthy material including 1350 individuals of all ages showed that symptoms of arthrosis, such as snappings, crepitations and disturbances in motion are very common and more frequent in women than in men. At least ⅓ of all grown-up persons have or have had such symptoms. They can occur already at the age of 6-8, but are more common in later ages.
>
> Contrary to information in the literature, there have been no incongruities as regards the frequency of symptoms in individuals with normal bites, straight bites and deep bites, whether the molar-premolar supports have been good or bad. In individuals with incomplete bites, down to total loss of teeth, temporomandibular joint symptoms have not occurred more frequently than in individuals without noteworthy loss of teeth. In persons without teeth, temporomandibular joint symptoms are less frequent than in denture cases. The symptoms of arthrosis are, as a rule, associated with very slight trouble. They can disappear spontaneously without leaving any clinically demonstrable traces. In exceptional cases, however, they can be associated with more severe symptoms which require treatment. . . . There is nothing to indicate a detrimental effect of the extirpation of the disk on the unoperated joint. There is no reason always to perform a bilateral extirpation of the disk, as has been recommended. In cases with bilateral symptoms, the most severely affected joint should be operated. Even the other joint is often improved thereby. There are no disadvantages of a subsequent operation on the other joint, if necessary. . . . The treatment of the temporomandibular joint arthrosis should, first and foremost, be conservative. . . . In cases with severe symptoms (constrictions, luxations, pains, disturbing snappings) which cannot be improved by conservative therapy, an extirpation of the disk is indicated. The operation offers immediate and permanent relief from these symptoms.

Nearly 70 years later, Bowman's assertions remain valid. His conclusions can hardly be better stated today.

These men and the many other surgeons they represented continued the search for better ways to treat TMJ dysfunction, applying the dramatic new medical knowledge and surgical techniques that were revolutionizing all of surgery. Their work provided the foundation for the creative treatment concepts about to emerge.

The Era of Innovation

At the end of World War II, medical and surgical innovation accelerated dramatically, and TMJ surgery received its share of attention from creative, and sometimes bold, surgeons. As Costen's influence faded and that of Wakely, Dingman, Bowman, and others grew, care of the TMJ drew renewed interest. With clearer distinction between diagnostic entities, it became easier for clinicians to choose appropriate therapies for their patients and, in turn, to assess their outcomes. The influence of basic science was felt in the world of patient care as well, not only through an exponential increase in knowledge and the resultant drugs and technologies, but also via application of scientific criteria to clinical research. It would no longer do to perform an operation a few times, declare the patient qualitatively better, describe his or her satisfaction, and publish the operation as an appropriate and successful treatment.

Nonsurgical Therapy

Not all innovations in therapy were surgical. Although occlusal equilibration continued to find acceptance, other nonoperative treatments were devised for specific conditions. Although others had attempted TMJ sclerosis using a variety of agents, Louis Schultz of Chicago had reported an improved method of reducing TMJ hypermobility with sclerosing injections in 1937, and in 1947, he published a report on 10 years' experience.[21] His method was innovative, appealing when compared with other contemporary alternatives (he mentions either surgery or mandibular fixation by head bandage for 1 to 1½ years—to be repeated if necessary), and apparently successful, although he follows the older tradition of providing no outcome data. In 1954, while treating the opposite end of the TMJ disease spectrum, Laszlo Schwartz applied the newly described concepts of myofascial pain, myalgia, and trigger areas to stiff, sore muscles in the masticatory muscle system.[25] Along with these concepts, he introduced the new therapies of local anesthetic injection and vapocoolant "spray and stretch" treatment to the TMJ literature. Of equal significance, he presented tabular data showing outcomes for a series of cases, including patients treated and those observed only. Although not blinded, randomized, placebo controlled, quantitative, or authorized by an institutional review board, his presentation of evidence was nevertheless a great leap forward from the preceding body of literature, perhaps excepting Bowman's scientifically rigorous publication.

Early Implants

Operative treatment remained the only viable alternative for severe fibrous or bony joint ankylosis, and attention was turned toward reducing the common complication of recurrence. Most surgeons used a flap of fascia, fat, or muscle in the hope of preventing bony regrowth, but with unpredictable results. In 1946, Eggers[26] reported the use of an alloplastic material, tantalum foil, to line bony surfaces at the ankylosis resection site in a 4-year-old girl. At 13 months, she had good mandibular opening, but long-term follow-up was not available. His description of the material and its use may make a contemporary surgeon who is familiar with the catastrophic failures of later alloplasts cringe: "It is a bit brittle and cracks, but satisfactory coverage can be secured

and even small pieces can be packed in areas where intervening material is desired."

Gordon,[27] when treating patients with subluxation (clicking joints), reported having 3 years' good experience placing polyethylene caps in the joint space after removing discs. His purpose was to prevent long-term malocclusion from an assumed reduction in vertical dimension at the condyle, although he admitted that in the short term, this was rarely a problem. Again, long-term follow-up was not available on this cohort of patients.

In July 1960, Sir Terence Ward lectured the Royal College of Surgeons on surgery of the mandibular joint.[28] He distilled surgical treatment of the TMJ into three operations. He casually mentioned two advances in anesthesiology used in his cases: endotracheal intubation and controlled hypotension. These techniques were relatively new, although it is now difficult for the modern surgeon to imagine operating without them. He also illustrated the use of a rounded chrome-cobalt cap, which was inserted at surgery on a curved osteotomy into the mandibular ramus above the mandibular foramen. In this way, a new rotational joint was created below the mass of the ankylosis, and the bony surfaces separated and presumably were prevented from fusing by the chrome-cobalt cover. Ward reported "good" function following bilateral implants, without noting the duration of observation.

At the forefront of autogenous grafting, Georgiade at Duke University and colleagues reported a new application of transplanting autogenous dermis into the TMJ in 1957.[29] Tested first on dogs, the procedure was then performed on eight patients with ankylosis, and only one partial re-ankylosis was formed, although at relatively short follow-up. This landmark work gave TMJ surgeons a new biocompatible graft option that offered success at least as good as historical experience with fascia, fat, or muscle flaps.

From our vantage point a half-century later, it would be easy to fault these innovators for risking great complications or spectacular failure. However, at the time, the risks of alloplast failure could hardly seem worse than an all-too-predictable re-ankylosis, which was not only a failure but a terrible challenge to re-treat, or a malocclusion that would condemn the patient to heroic dental reconstruction or orthognathic operations that were in their infancy as well. These surgeons' contributions represented pioneering efforts to improve outcomes, and although we must surmise that these treatments failed, because they were generally abandoned, implanted materials with documented long-term success were only a few years away.

Joint Reconstruction

TMJ implants took a substantial leap forward in 1964, with Christensen's publication of a new arthroplasty technique in which a cast Vitallium glenoid fossa prosthesis was used.[30] He created a set of 20 cast prostheses based on impressions on skulls with varying anatomy, then selected the best-fitting implant for insertion into the patient.

Implants were secured with screws into the zygomatic arch, away from the occlusal surface. They were intended to provide a stable surface against which the mandibular condyle might function, preventing re-ankylosis by serving as a permanent mechanical barrier. In time, some surgeons advocated extending the indications for placement of the Christensen fossa to discectomy patients, to prevent the hypothetical but dreaded "bone-on-bone" contact and its presumed negative consequences.

The Christensen fossa implant soon was joined by a matching condylar prosthesis with a polymethylmethacrylate condylar head, thus forming the first total alloplastic temporomandibular joint prosthesis. Although other total joint replacement systems with advanced materials and engineering principles have been developed more recently, the Christensen implant remains on the market today as the first and longest used TMJ replacement system available.

Nonsurgical Treatment Revisited

Technical advances notwithstanding, surgery on the TMJ remained an imperfect and unpredictable science, facing criticism from those whose philosophy (and case study outcomes) supported nonsurgical treatment of all but tumor and ankylosis cases. During the 1960s, interest grew in the work of Schwartz and others, who believed that TMJ dysfunction was less a result of mechanical failure (either capsular or intracapsular) and more an outcome of masticatory muscle dysfunction. This in turn was attributed in large part to emotional stress and anxiety in patients, most of whom were young and female. In 1969, Daniel Laskin published an articulate paper in the *Journal of the American Dental Association* that proposed a shift of emphasis from joint to muscle pathology.[31] He provided a cogent argument for a strong psychological origin behind the physiologic muscle disorder in many patients and suggested the term *myofascial pain-dysfunction* to describe the condition.

In contrast to Costen's work, which was based to a significant extent on speculation, Laskin provided sound evidence for his theory. The paper became a lightning rod for renewed and sometimes contentious debate over the relative importance of psychological, emotional, occlusal, muscular, and intracapsular factors in patients with pain, popping and clicking joints, and stiff jaws. Unfortunately, despite its reasoned and scientific principles, the writing also reinforced the preconceptions of many clinicians who had always quietly believed TMJ disease to be a weak woman's affliction that was more "supratentorial" than organic in origin.

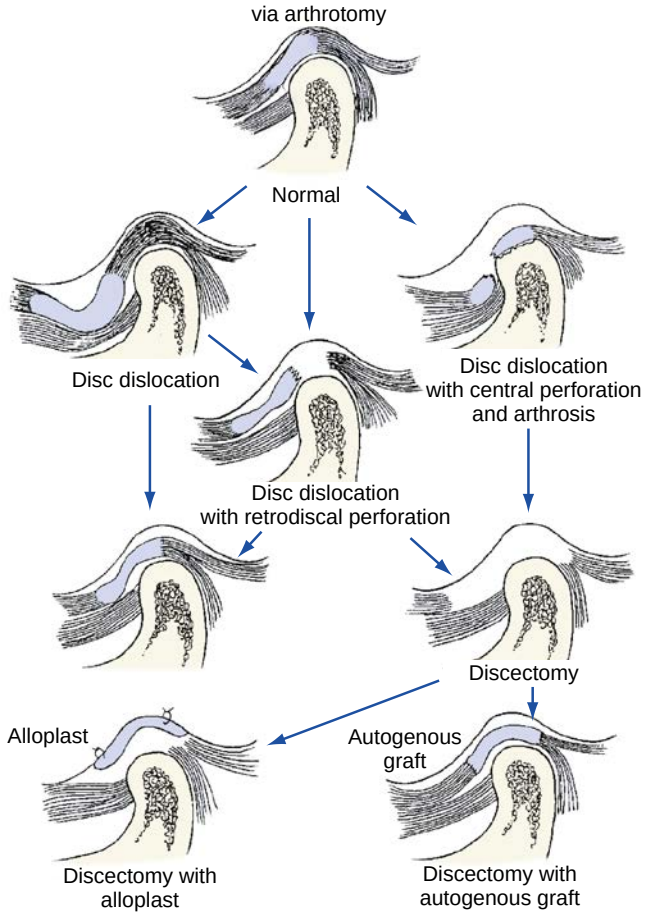
For a time, TMJ surgery was unpopular. Even so, amid the controversy and renewed interest in occlusal and muscle therapy, a new generation of surgical pioneers prepared the next round of advances.

The Return of the Operation

Open Joint Surgery

In the 1970s and 1980s, Wilkes brought new understanding to TMJ surgery, advancing interpretation of imaging, and Farrar,[34,35] Dolwick and colleagues,[36] and many others promoted a more complete understanding of the normal and abnormal function of the articular disc, leading to a resurgence of interest in disc surgery. Although discectomy continued to be performed, new techniques for disc preservation surgery were widely promoted by these and other authors (Figure 34-4).

The preauricular approach became standard, with modifications in skin incision placement behind the tragus by Kiehn[37] and widely cited improvements based on research by Al-Kayat and Bramley.[38] Indresano and Mobati have written an excellent summary of advances in TMJ surgery, particularly during the late 20th century.[39]



• **Figure 34-4** A schematic of options for temporomandibular joint disc surgery, 1989. (From Braun T, Kent J: Temporomandibular joint surgery, part II: partial and total joint reconstruction and osseous procedures, *Selected Readings Oral Maxillofac Surg* 1:1-24, 1989.)

The wide resurgence of interest in TMJ surgery contributed to a tragic chapter in its history. With disc surgical procedures being performed in great numbers, attention was directed to finding a suitable disc replacement. Autogenous grafts, including Georgiade's dermal graft, were widely used, although evidence for their improving outcomes was minimal. However, many surgeons turned to alloplastic materials for implantation. By the mid 1980s, two commonly used implants—silicone sheeting and a Teflon-Proplast implant specifically developed as an articular disc replacement—proved to be poor choices. The Teflon-Proplast implant in particular was prone to fragmentation and evoked an intense and locally destructive foreign-body giant cell reaction, resulting in catastrophic local destruction and, in many cases, consigning the patient to a lifetime of intractable pain. The manufacturing company withdrew it from the market (Figure 34-5), was subject to extensive litigation, and ultimately went bankrupt. Silicone sheeting was also subject to degeneration and foreign body reaction, but with less intense local destruction.

The TMJ implant debacle brought repercussions well by disastrous and expensive outcomes in their affected clients, simply wrote blanket exclusions for any TMJ-related care into most of their policies. Furthermore, a large cohort of patients with iatrogenically created chronic pain now joined the TMJ surgeons' caseloads, bringing complex long-term medical management issues into practices that were more comfortable providing acute surgical care to a relatively straightforward patient population. As a result of these forces, many surgeons stopped providing TMJ care in their practices, thereby reducing patient access to interested and qualified TMJ surgeons—a situation that persists to the present day.

Total Joint Replacement

The 1980s were a time of new developments in alloplastic total joint reconstruction. Although relatively few patients required total joint replacement, a small number with severe rheumatoid arthritis, traumatic joint destruction, failed reconstruction with autogenous grafts (most commonly costochondral grafts), or ankylosis had few other reasonable alternatives. The Christensen implant system remained the state-of-the-art total joint replacement technique throughout the 1970s, but then advances in materials, biomechanical engineering, and understanding of joint pathophysiology dramatically altered joint reconstruction in general orthopedics. Joint replacement for knees, hips, and other joints had become frequent and predictably successful surgery, and oral and maxillofacial surgeons began working to bring the same contemporary technologies to the TMJ. Kent and others[40,41] developed a joint reconstruction system with a polymeric fossa prosthesis and a metallic condylar head—the opposite of Christensen's design,

VITEK, Inc.
Technology for Life

March 23, 1990

VOLUNTARY SAFETY ALERT

PRODUCT: VITEK TEMPOROMANDIBULAR JOINT (TMJ) INTERPOSITIONAL IMPLANT (IPI) - ALL LOTS

Dear Doctor:

The purpose of this letter is to inform you of the following reported concerns which affect the Vitek TMJ IPI. The corresponding product catalogue numbers are 912.71, 912.72, 912.74, 912.76, 912.77 and 912.78. Vitek's IPI's may fragment, delaminate or otherwise be damaged or punctured. Debris in the joint from alloplastic implants can contribute to progressive bone degenerative changes and to giant cell reaction. All patients, including asymptomatic patients, should be monitored closely to assure proper patient maintenance. This monitoring should include clinical and radiographic examination. The radiographic examination may include transcranial or tomographic x-rays, CAT scans or bone scans.

As you know, the 1984 AAOMS criteria for meniscus surgery recommends continuing postsurgical follow-up. Because it is often difficult to distinguish between normal bone remodeling changes that can occur and long term extensive bone resorption in presently asymptomatic patients who have received alloplastic implants such as the TMJ IPI, it is strongly recommended that these patients be followed indefinitely. Please inform all your patients who have received a Vitek IPI of the importance of follow-up.

The prophylactic removal of Vitek's IPI is not recommended.

Additionally, do not implant any more of these devices if you have any of them in your possession. These implants should be returned for credit. Return these implants to the address below in their original boxes with, if available, a copy of the corresponding shipping memorandum.

For our records, we would appreciate your completion and return of the enclosed postage paid, self-addressed postcard.

If you have any questions, concerning this notification, please call Sue Tellkamp at the telephone numbers given below.

Thank you for your assistance and cooperation.

Enclosure

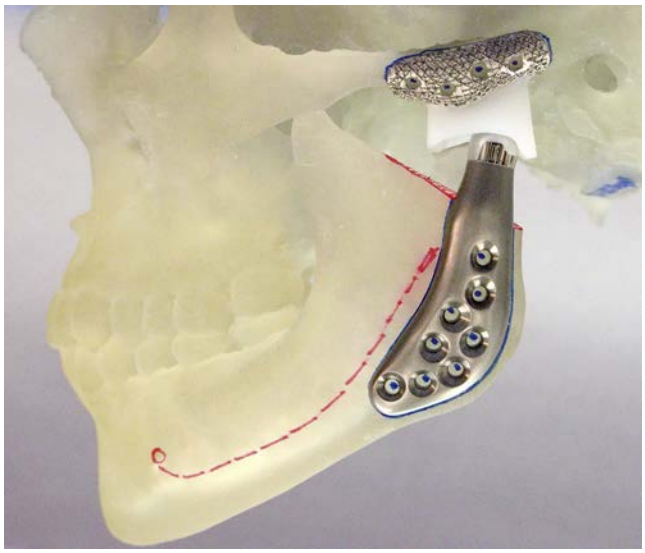
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• **Figure 34-5** The letter distributed to oral and maxillofacial surgeons announcing the recall of the Vitek Teflon-Proplast implant. By the time of its distribution, many surgeons were already well aware of the implant's risks for patient safety.

but consistent with contemporary biomechanical research. This system was used successfully in many cases, but it was manufactured by the ill-fated Vitek Corporation and disappeared from the market with that company's collapse. Several other investigators and large manufacturers developed TMJ implant designs, but in the aftermath of the Teflon-Proplast debacle, a combination of relatively few potential patients (compared with the market for large orthopedic joints) and a particularly—and understandably—harsh regulatory climate brought nearly all to a halt before production or while still in early clinical trials. Ironically, many of the patients most in need of total alloplastic reconstruction were those with severe iatrogenic joint destruction from failed fossa implants.

Ultimately, one TMJ reconstruction system completed rigorous trials and was approved by the FDA for use in limited indications in the mid-1990s. This system uses a computer-aided design/computer-aided manufacturing (CAD-CAM) design with custom-fitted fossa and condylar implant that differed from prior systems, which allowed selection from a set of stock sizes and configurations. Computed tomography (CT)-derived data are used to construct a full-size model of the patient's jaw and skull base, which in turn is used to design and manufacture the implants (Figure 34-6).

Their custom-fitted nature eliminated the need to shim or backfill the implants, particularly the fossa component, with polymethylmethacrylate or other materials, and resulted in a stable prosthesis without micro-movement, even in patients with severely mutilated joints. This system remains on the market today, with numerous reports of good function and stability generated over a decade or longer.[42-44] A second total TMJ replacement system, designed using similar principles and materials, offers standard-sized, as opposed to custom, components. Nevertheless, a well-documented and significant drawback to these and all TMJ reconstruction technologies available to date is their inability to predictably reduce or eliminate pain, even when movement and function are improved.



• **Figure 34-6** The TMJ Concepts Patient-Fitted Implant. The components are shown here on the laser stereolithographic model derived from computed tomography data and used in their fabrication. (Courtesy of TMJ Concepts Inc., Ventura, CA.)

Minimally Invasive Treatment

the TMJ, but Watanabe developed a suitably thin instrument for small joints. Ohnishi and Murakami developed

with lower costs and less morbidity. Early adaptors included Sanders and McCain, both of whom published extensively on the technique,[47-51] including the development of elegant and sophisticated advanced operative techniques.[52] A large

multicenter retrospective study was published in 1992 by several leading authorities to document high success rates for [53]

sur

who would otherwise be candidates for open surgical procedures. However, critical evaluation of the success and outcomes of arthroscopic lysis and lavage led to new theories about the mechanical basis of TMJ disease. In 1990, Nitzan, Dolwick, and Heft published an article in which they questioned the direct primary role of disc displacement in TMJ symptoms, based on strong evidence that arthroscopic surgery was highly successful clinically but failed to reduce discs to the "normal" position in all but a few cases.[54] In 1991 Nitzan, Dolwick, and Martinez described a novel technique for treating patients with acute closed lock of the TMJ, which they called *arthrocentesis*.[55] Moreover, they postulated that anterior disc displacement in the TMJ might better represent an anatomic variant than a true pathology. They offered alternative hypothetical explanations for mandibular hypomobility not dependent on mechanical obstruction of the condyle by an anterior disc.[56] These theories remain somewhat controversial to the present day, but they represent a further evolution in our understanding of the pathophysiologic mechanisms underlying TMJ sy

disease. Scientist clinicians, as represented by Milam[57,58] at the University of Texas in San Antonio, are essential allies of the current generation of surgeons. Today they bring the tools of molecular biology to bear on the diseases Cooper struggled to describe 165 years ago.

Summary

Diseases of the temporomandibular joint have been recognized in the Western medical literature for 200 years or more, and they have been treated with surgery since the latter part of the 19th century. The earliest operations were pioneering efforts by early general surgeons, whose solutions for the most seriously debilitating problems were, in many cases, not dissimilar to contemporary operations. Advances in the early 20th century paralleled those in other arenas of medicine and surgery, including the introduction of minimally invasive surgery near the end of the century.

Surgical management of TMJ disease, particularly internal derangement, has been provided with varying degrees of tension with nonsurgical therapy almost since the beginning. Over the 20th century, expert opinion and clinical practice swung between the two poles, and some confusion and dogma persist on both sides to the present day. As scientific study has improved our knowledge about the treatment, both types of therapy have found their place in the contemporary surgeon's armamentarium.

Perhaps the most critical lesson to be learned by reviewing the history of treatment for temporomandibular joint disease is that we can still learn from the errors of our predecessors. It is remarkable how little is truly new in TMJ arthroplasty, for example, and the surgeon who is considering a clever "innovation" probably should examine the literature from longer ago than he or she might have thought necessary before declaring the idea new. Perhaps the direction most likely to yield truly new knowledge and therapies will be molecular medicine. Even with this, future scientists likely will wish to read the works of contemporary arthroscopists and surgeon-scientists, or they will risk re-invention rather than true innovation.

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35

Structure and Function of the Temporomandibular Joint

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Providing motion is the central function of the craniomandibular or temporomandibular articulation, where mandible and cranium are connected as the temporomandibular joint (TMJ). As part of the stomatognathic system, the TMJ allows simple and complex movements such as free movement during phonation, gesticulation, swallowing, and breathing, as well as different types of load-bearing movements during incision and chewing. Although all other bony segments of the head are fused via synostoses, only the three ossicles within the middle ear also show articulations. Therefore, the description of the phylogenetic development of the TMJ is helpful for an understanding of its structure and function.[1-8]

Developmental Perspective of the Craniomandibular Articulation

In mammals, the articulating bony parts of the TMJ are derived from membrane bone. These are formed directly from intramembranous centers of ossification. These developing bones, the squamous portion of the temporal bone, and the condyles of the mandible become completely surrounded by periosteum, including areas that eventually form the articular surfaces of the TMJ and build the "secondary" TMJ there.[9,10] In contradistinction to that is the development of the "primary" TMJ of nonmammalians, deriving from cartilage. In bony fish, reptiles, and birds, the proximal parts of the mandible constitute the TMJ, which is actually the primary TMJ. In mammals, the primary or primitive TMJ is subjected to complex changes, also ultimately forming the joints for three ossicles within the middle ear. The secondary TMJ in humans starts to develop by the 10th week of gestation from mesenchymal condensations of two separate blastemas for the mandibular condyle and the temporal bone.[5,10-12] The condylar and temporal mesenchymal cells differentiate into osteoblasts, which lay down membrane bone. The periosteum that lines these articular surfaces gradually is transformed during its early development into the dense fibrous articular tissues of the TMJ.[6] In the center of the condyle, cartilage develops and becomes the growth center, with subchondral bone formation by an enchondral mechanism.[13] Superior to the condylar blastema, a band of mesenchymal cells develops that differentiates into the disc, which is considered as deriving from an extension of lateral pterygoid muscle.[5,9,14,15] The configuration and shape of the TMJ are also related to the development of dentition. During infancy, the articular fossa is a flat furrow with almost no eminence. Eruption of the primary dentition increases the groove, forming a fossa. The final adult formation of the TMJ is associated with eruption of the permanent dentition. Articular forces acting through the TMJ play an important role in this gradual transformation.[6,16] Depending on the preservation of the dentition, the TMJ may maintain a stable form throughout life. Edentulism of the jaws again causes secondary changes within the TMJ, with flattening of the articular fossa and eminence. The configuration and shape of the TMJ depend on skeletal and dental relationships of the maxilla and mandible. For example, a deep bite is correlated with a steep eminence.[4,9]

Most synovial joints have hyaline cartilage that lines their articulating surfaces, because bones of typical synovial joints are endochondrally formed bones that are initially preformed in hyaline cartilage. In contrast, articulating surfaces of the TMJ are lined by dense, avascular, fibrous connective tissue. Most of this cartilage eventually is calcified and then is replaced by bone, although the cartilage that lines the articular surfaces persists in a modified form. Thus, the lack of hyaline cartilage on the articular surfaces of the TMJ reflects its unique ontogenetic and phylogenetic development; although it is not a hyaline cartridge-covered joint, it is capable of bearing loads. Although a secondary cartilage is present in the condyle of the growing mandible, this



• **Figure 35-1** Lateral view of human cranium and mandible.



• **Figure 35-2** Basal view of human cranium.

cartilage does not form part of the articular surface because the periosteum-derived articular tissues cover it.[17,18]

Surgical Anatomy and Histology

The mandible and cranium make up the craniomandibular articulation, which frequently is referred to as the *temporomandibular articulation.* This articulation of the mandible consists of two synovial joints: left- and right-sided TMJs. The bony components include the mandibular condyles below and the squamous temporal bones above (Figure 35-1). The articular space of each TMJ is divided into upper and lower compartments because of the interposition of the fibrous articular disc between the temporal bone and the mandible. Gliding or translatory movements occur primarily in the upper compartment, while the lower compartment functions primarily as a hinge or rotary joint.[1,4,6,18-23]

Glenoid Fossa—Articular Eminence

The *glenoid* or *mandibular fossa,* is the concavity within the temporal bone that houses the mandibular condyle. Its anterior wall is built by the articular eminence of the squamous temporal bone and its posterior wall by the tympanic plate of the temporal bone, which also forms the anterior wall of the external acoustic meatus. The bony roof of the glenoid fossa is thin and often appears translucent when transilluminated (Figure 35-2).

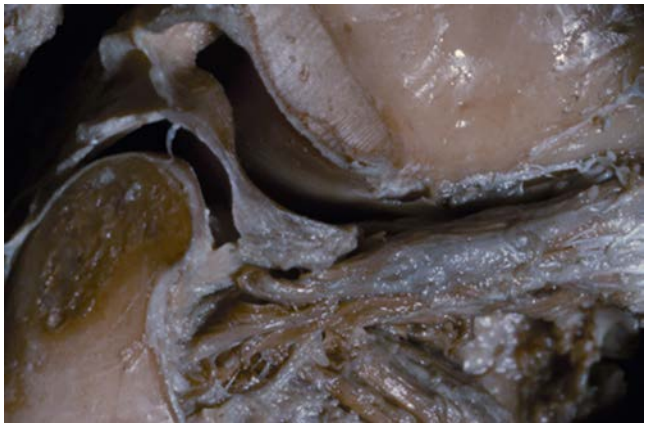
It is important to note that the term *articular fossa* refers to the particular portion of the glenoid fossa that is covered by articular tissues. It is built entirely by the squamous portion of the temporal bone (see Figure 35-1). The posterior part of the articular fossa is elevated to a ridge called the *posterior articular lip.* In most individuals, the posterior articular lip is higher and thicker at its lateral end and thus is visible from the side as a cone-shaped process between the articular fossa and the tympanic plate. This structure is the postglenoid process. The lateral border of the articular fossa sometimes is marked by a narrow, low ridge or crest.

In the posterior and lateral parts of the *glenoid fossa,* a fissure separates the articular and nonarticular portions of the glenoid fossa. This fissure, called the *tympanosquamosal fissure,* also separates the tympanic portion from the squamous portion of the temporal bone. Medial to this fissure, a bony plate of the petrous portion of the temporal bone, the tegmen tympani, protrudes between the tympanic and squamous portions. Therefore, instead of a tympanosquamosal fissure along the medial aspect of the glenoid fossa, an anterior petrosquamosal fissure and a posterior petrotympanic fissure occur. The petrotympanic fissure is slightly widened laterally to permit passage of the chorda tympani nerve and the anterior tympanic blood vessels. These neurovascular structures are located within the glenoid fossa, but not within the articular fossa (see Figure 35-2).

The *articular eminence* is the transverse bar of dense bone that forms the posterior root of the zygomatic arch and the anterior wall of the articular fossa. It has a large articular surface. It is strongly convex on a side view and moderately concave when viewed from the front or back. The degree of this convexity and concavity is highly variable. Fine bony ridges often outline the medial and lateral borders of the articular eminence. Although a thin layer of fibrous tissue covers the roof of the articular fossa, the fibrous tissue that covers the articular eminence is thick and quite firm. Moreover, different from the roof, the articular eminence is made up of a fairly thick layer of dense bone. Lateral to the articular eminence, a small bony projection, the *articular tubercle,* is located. The articular tubercle is not an articular surface. Instead, it serves as the attachment area for portions of the temporomandibular ligament (TML).[24-26]

Articular Disc—Disc Ligaments

The *articular disc* is a firm, oval, fibrous plate that is positioned between the mandibular condyle and the articular fossa and eminence (Figure 35-3). Its central part, the



• **Figure 35-3** Parasagittal section of temporomandibular joint disc area and lateral pterygoid muscle.



• **Figure 35-4** Parasagittal section of temporomandibular joint disc area.

intermediate zone, is considerably thinner than its periphery—the anterior and posterior bands. Anteriorly, the disc continues as the anterior attachment and is fused to the capsule of the TMJ. Posteriorly, the disc continues as the posterior attachment or bilaminar zone—a thick double layer of vascularized connective tissue. The bilaminar zone splits into two parts: (1) an upper fibroelastic layer that attaches to the postglenoid process, posterior articular lip, and tympanosquamosal fissure; and (2) a lower fibrous layer that attaches to the posterior portion of the condylar neck immediately below the articular tissues. Posteriorly, these two layers are separated by the intermediate layer, which contains loose connective tissue that attaches to the posterior wall of the joint capsule. The posterior attachment has a profuse supply of nerves and blood vessels.[11,12,27-30]

Unlike its anterior and posterior attachments, the disc is not attached to the capsule laterally or medially. Instead, it is tightly bound directly to the medial and lateral poles of the mandibular condyle. The position of the disc relative to the condyle also is influenced by the pull of the superior head of the lateral pterygoid muscle because a small portion of this muscle often attaches to the disc (Figure 35-4). Because the superior head of the lateral pterygoid also attaches to the mandibular condyle, and the disc is tightly bound to the medial and lateral poles of the condyle, this muscle arguably may have no special influence on movements of the articular disc relative to the condyle.[31,32]

Ontogenetically, the articular disc derives from a mesenchymal block of tissue that also gives rise to the capsule of the TMJ and the lateral pterygoid muscle.[33] This tissue mass is located between the developing squamous temporal bone and mandibular condyle. In adults, the uppermost part (or superior head) of the lateral pterygoid muscle often retains its original connection to the capsule and articular disc of the TMJ.

Blood vessels and nerves are absent in the intermediate zone, that is, the firm central region of the articular disc, as well as in the avascular fibrous layers that cover the mandibular and temporal articular surfaces of the joint. A lack of these neurovascular structures is compatible with the hypothesis that a considerable reaction force occurs along this portion of the joint. It has been suggested that one main function of the articular disc is to reduce stress concentrations between the articular surfaces of the mandibular condyle and the squamous temporal bone—that is, the compliant nature of the disc helps to distribute reaction force more evenly along these joint surfaces.[7,20,34-36]

Condyle

The articular surface of the mandible is the upper and anterior surface of the condyle (Figure 35-5). The adult human condyle is about 15 to 20 mm from side to side and 8 to 10 mm from front to back. Its long axis lies at right angles to the plane of the mandibular ramus. Because of the flare of the ramus, however, the long axes of the left and right condyles cross approximately at the anterior margin of the foramen magnum, forming an obtuse angle varying from 145 to 170 degrees.[37]

The articular surface of the condyle is strongly convex when viewed from the side and less so when viewed from the front. The articular surface faces upward and forward, so that in side view, the condylar neck is bent forward. As seen from the front, the articular convexity often resembles a tentlike configuration that is divided into medial and lateral slopes by a variably prominent crest. The lateral pole of the condyle extends slightly beyond the outer surface of the ramus and is roughened for the attachment of the articular disc and the TML.[19] The medial pole of the condyle protrudes considerably beyond the inner surface of the ramus and also is slightly roughened for the attachment of the articular disc. Variations in the shape of the condyle are frequent. Irregularities of the bony articular surfaces are obscured and smoothed by the thick covering of fibrous tissue that is derived from and directly continuous with the periosteum of the mandible.



• **Figure 35-5** Mandibles with different condylar head shapes and angles.

Synovial Membrane

The synovial membrane, a highly vascularized layer of connective tissue, lines all structures of the articulation that do not experience compressive forces. The largest area of synovial lining covers the upper and lower surfaces of the posterior attachment, including the loose connective tissue that binds the posterior border of the disc to the capsule. Synovial tissue also lines the inner aspect of the fibrous capsule. When the condyle is positioned in the glenoid fossa, the synovial membrane forms rather heavy folds posteriorly (see Figure 35-4). When the condyle is protruded toward the summit of the articular eminence, the folds disappear as the synovial tissues are stretched.[38]



• **Figure 35-6** Lateral view of temporomandibular joint capsule and position of maxillary artery.

Capsule—Extracapsular Ligaments

The articular capsule is quite thin anteromedially, medially, and posteriorly, but it is thick anterolaterally and laterally, where it attaches to the articular tubercle.[39] This reinforced lateral portion of the capsule is the temporomandibular ligament. The capsule attaches to the squamous portion of the temporal bone along the outer limits of the articular surface of the articular eminence, fossa, and preglenoid plane. Posteriorly, the capsule arises from the postglenoid process, the posterior articular lip, and the tympanosquamosal fissure (Figure 35-6).

The anatomy of the capsule and that of the TML show considerable variability.[16,40-43] The TML can be split into two layers: a wide, fan-shaped superficial portion, and a narrow deep portion. The broad origin of the superficial portion along the articular tubercle and its narrower insertion along the condylar neck account for its somewhat fan-shaped morphology. Its anterior fibers run from the articular tubercle obliquely down and back; the posterior fibers have a more vertical orientation. Fibers of the deep portion are oriented horizontally (anteroposteriorly), attaching along the lateral pole of the mandibular condyle and extending to a crest situated along the articular tubercle. This deep horizontal band sometimes is named the *lateral polar ligament.*[19,39]

The fibrous capsule of the TMJ and the TML allows and limits jaw movements. The vertical fibers control distraction movements of the condyle from the articular eminence and fossa, the horizontal fibers (polar ligaments) prevent excessive retrusive movements of the condyle, and the posterior portion of the capsule limits protrusive movements. The anterior part of the capsule and the anterolateral part of the TML may limit condylar rotation during jaw opening, although most of this limitation is imposed by the stretched jaw-closing muscles.[19,39]

Accessory Ligaments

The sphenomandibular and the stylomandibular ligaments are considered accessory ligaments of the temporomandibular articulation (Figure 35-7).



• **Figure 35-7** Posterior view of temporomandibular joint capsule and ligaments.



• **Figure 35-8** Masseter muscle: superficial and deep parts.

Sphenomandibular Ligament

The sphenomandibular ligament arises from the spine of the sphenoid bone and is directed downward and outward, inserting on the mandible at the mandibular lingula, which is located along the upper border of the mandibular foramen. It is derived from Meckel cartilage. In most individuals, the sphenomandibular ligament is a thin layer of connective tissue with indistinct anterior and posterior borders that protects the blood vessels and nerves passing through the mandibular foramen from additional tensile stress during jaw opening and closing.[44] It normally has no influence on mandibular movement.

Stylomandibular Ligament

The stylomandibular ligament is a reinforced sheet of cervical fascia that extends from the styloid process and the stylohyoid ligament to the region of the mandibular angle. Many of its fibers are attached to the back edge of the lower part of the mandibular ramus; others continue onto the deep fascia along the medial surface of the medial pterygoid muscle. The upper border of the stylomandibular ligament normally is a thickened cordlike structure.

This ligament is relatively loose when the jaws are closed and when they are wide open; it is tensed only when the mandible is maximally protruded. Thus, apparently this ligament can limit excessive protrusive movements.

Muscles

erful masticatory muscles (masseter, temporalis, medial pterygoid, and lateral pterygoid), the morphology and function of other important muscles that play a role in mandibular movements are described here.[45,46]

Masseter Muscle

The masseter muscle reaches as a rectangular plate from the zygomatic arch to the lateral surface of the mandibular ramus (Figure 35-8). It is divided into a superficial and a smaller deep portion. The superficial masseter arises from the lower border of the zygomatic arch as strong tendinous fibers. The most anterior fibers may arise from the outer corner of the zygomatic process of the maxilla. Posteriorly, the origin of the superficial portion ends along the zygomaticotemporal suture. The superficial masseter is covered on its outer surface by a strong tendinous layer that extends down from the zygomatic arch over the upper third or half of the muscle.

In a frontal view, these fibers are directed downward and medially. In a side view, the muscle fibers of the superficial masseter are directed downward and backward to insert along the angle of the mandible. The mandibular attachment of the superficial masseter extends along the lower one third of the posterior border of the ramus and along the lower border of the mandible anterior to the third molar; it covers, more or less, the lower half of the lateral surface of the ramus. The field of insertion has ridges into which the tendons insert, as well as grooves between the ridges into which the fleshy fibers insert.

Posteriorly, the fibers of the superficial masseter wrap around the posterior and inferior aspects of the angle of the mandible, joining fibers of the medial pterygoid muscle in a tendinous raphe. This muscular arrangement is called the *pterygomasseteric sling*. The deep and superficial portions of

the masseter fuse anteriorly, but posteriorly, the two can be separated. Fibers of the deep masseter arise from the entire length of the zygomatic arch up to the anterior slope of the articular eminence. Some of its fibers also may arise from the lateral wall of the TMJ capsule.[31,47]

The deep masseter inserts above the superficial masseter along the mandibular ramus as a triangular insertion field. The base of this triangle faces posteriorly, and the apex faces anteriorly. In the side view, the fibers of the deep masseter, which have a near vertical alignment, pass downward at an angle of about 30 to 40 degrees to the fibers of the more obliquely aligned superficial masseter.

The masseter muscle is a powerful elevator of the mandible. A lateral view reveals that the deep masseter exerts primarily a vertical force on the mandible. In contrast, the superficial masseter exerts a vertical and slightly anteriorly directed force on the mandible that is approximately perpendicular to the occlusal plane of the molars. The entire masseter also exerts a lateral component of force on the mandible.[48]

Temporalis Muscle

The temporalis muscle has a fan-shaped origin along the lateral surface of the skull and the dense fascia overlying this muscle (Figure 35-9). The bony attachment field, the temporal fossa, is encircled above by the inferior temporal line. This attachment field includes a narrow strip of the parietal bone, the greater part of the temporal squama, the temporal surface of the frontal bone, and the temporal surface of the greater wing of the sphenoid bone. Muscle fibers and tendons also arise from the postorbital septum, which is the bony partition that separates the temporal fossa from the orbit. Both the zygomatic and frontal bones and the greater wing of the sphenoid contribute to the formation of the postorbital septum. The bony field of origin of the temporalis muscle reaches downward to include the infratemporal crest of the sphenoid.

Many of the temporalis muscle fibers originate from the medial surface of the temporalis fascia. The temporalis fascia attaches to the superior temporal line and the upper border of the zygomatic arch. Passing downward from the superior temporal line, the temporalis fascia thickens considerably and then splits into two layers; the superficial layer continues into the periosteum of the zygomatic arch along its lateral surface, and the deep layer extends into the periosteum of the zygomatic arch along its medial surface.

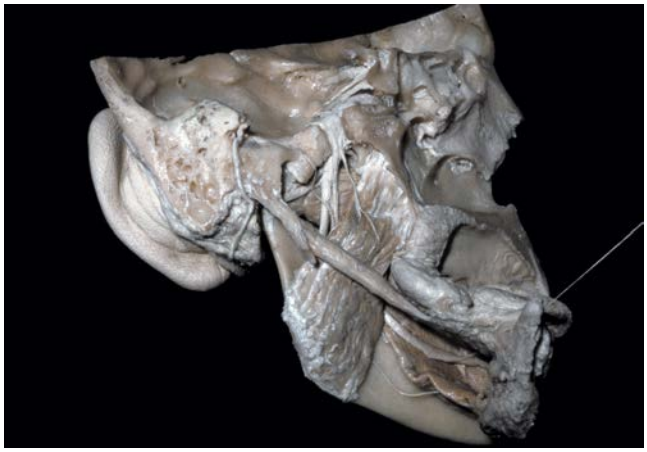
The bundles of the temporalis muscle converge toward the opening located between the zygomatic arch and the lateral surface of the skull (temporal foramen). The tip of the coronoid process projects into this opening. The anterior fibers of the temporalis muscle, which form the major bulk of the muscle, are largely vertical; the fibers in the middle part of the muscle are increasingly oblique. The most posterior fibers run forward almost horizontally, bend around the posterior root of the zygomatic arch in front of the articular eminence, and pass downward vertically to the mandible.

The middle and posterior portions of the temporalis muscle, respectively, are attached along the apex of the coronoid process and along its posterior slope to the deepest point of the mandibular notch. The more superficial fibers of the anterior temporalis muscle insert along the apex of the coronoid process, the anterior surface of the coronoid process, and the mandibular ramus. The deeper fibers of the anterior temporalis attach along the medial anterior surface of the mandibular ramus.



• **Figure 35-9** Temporalis muscle.

Similar to the masseter muscle, the temporalis muscle mainly elevates the mandible. Its fan-shaped morphology indicates that its direction of pull varies considerably, depending on which portions are mechanically active. Superficially, it appears that its most posterior fibers retract the mandible because of their horizontal orientation along the side of the skull; however, as previously noted, when the condyle is situated in the mandibular fossa, the fibers of the posterior temporalis are bent around the posterior root of the zygomatic arch at a sharp angle and thus are oriented vertically. Therefore, this portion of the temporalis muscle exerts primarily an upward force on the mandible during normal



• **Figure 35-10** Medial view of medial pterygoid muscle.



• **Figure 35-11** Medial view of medial and lateral pterygoid muscle.



• **Figure 35-12** Oblique view of lateral pterygoid muscle.

closure. When the condyle is translated anteriorly into a more protruded position, these posterior fibers likely cause the mandible to retrude because, in this instance, the posterior temporalis is aligned more horizontally. Because its most posterior fibers pass very close to the condyle, the posterior temporalis probably also functions as a stabilizer of the TMJ.

The middle and obliquely aligned portion of the temporalis muscle is capable of exerting a vertical and retracting force on the mandible. Most of the anterior portion is capable of a vertical pull on the mandible. That portion of the anterior temporalis that originates from the postorbital septum, however, likely pulls the mandible upward and forward. Finally, the deep fibers of the anterior temporalis that originate along and just above the infratemporal crest pull the mandible upward and somewhat medially. Thus, the morphology of the entire temporalis muscle indicates that its fibers are capable of considerable variability in their direction of pull.

Medial Pterygoid Muscle

The medial pterygoid muscle is situated on the medial side of the mandibular ramus as a powerful rectangular muscle (Figure 35-10). Its main origin is the pterygoid fossa, a depression that is located between the back edges of the medial and lateral pterygoid plates of the sphenoid bone. The deepest fibers arise from strong tendons; others arise directly from the medial surface of the lateral pterygoid plate. A flat tendon covers the medial surface of the muscle at its origin, and it is as wide as the tensor veli palatini, with which it is in contact.

The most anterior fibers of the medial pterygoid arise from the outer and inferior surface of the pyramidal process of the palatine bone and from adjacent parts of the maxillary tuberosity. These fibers, which are referred to as the superficial head of the medial pterygoid, are positioned lateral to the lateral pterygoid muscle. The remaining and largest portion of this muscle, the deep head, is positioned medial or deep to the lateral pterygoid muscle.

The fibers of the medial pterygoid muscle run downward, backward, and laterally and are inserted along the medial surface of the angle of the mandible. The field of insertion is approximately triangular and is located between the mandibular angle and the mylohyoid groove. As noted earlier, the fibers of the medial pterygoid muscle often meet fibers of the masseter in a tendinous raphe behind and below the mandibular angle (the pterygomasseteric sling). Because of the overall fiber orientation of the medial pterygoid muscle, it is primarily an elevator of the mandible (Figure 35-11).

Lateral Pterygoid Muscle

The lateral pterygoid muscle arises from two heads (Figure 35-12). The inferior head is about three times larger than the superior head.[49,50] The superior head (sometimes called the *superior pterygoid*)[51] originates from the infratemporal surface of the greater wing of the sphenoid medial to the infratemporal crest. From its origin, the fibers of the superior head run almost horizontally backward and laterally in close relation to the external surface of the cranial base. The inferior head originates from the outer surface of the lateral pterygoid plate. Although the fibers of the inferior head also run backward and laterally, they pass upward at an angle of about 45 degrees relative to the superior head.

The two heads of the lateral pterygoid muscle are separated at their origins by a wide gap but fuse in front of the TMJ. The fibers of the superior head are attached



• **Figure 35-13** Digastric muscle and mylohyoid muscle.

primarily to a roughened fossa on the anteromedial surface of the condylar neck. This fossa is called the *pterygoid fovea.* In addition, a small portion of the superior head frequently is attached directly to the anteromedial part of the TMJ capsule and extends into the anteromedial part of the articular disc. All fibers of the inferior head insert into or along the periphery of the pterygoid fovea. This description of the lateral pterygoid is based on the work of numerous authors.[16,27,31,32,39,47,49,52-54]

The lateral pterygoid muscle also consists of two functionally distinct parts. The superior head contracts during jaw closing, and the inferior head contracts during protraction, opening, and shifting of the jaw to one side.[55-58] The superior head of the lateral pterygoid stabilizes the mandibular condyle against the articular eminence during biting and mastication.[16,59] Bilateral contraction of the lower head of the lateral pterygoid muscle creates a protruding mandibular movement. Unilateral action of the inferior head shifts the midline of the mandible to the opposite side (lateral excursion). Finally, if either or both heads of the lateral pterygoid muscle are actively recruited during mandibular closure, this muscle must experience an eccentric or lengthening contraction.[14,39] Under these conditions, the lateral pterygoid muscle exhibits considerable stiffness; this also facilitates joint stability by controlling or limiting condylar movements.[6,32,60]

Digastric Muscle

As the name implies, the digastric (two-bellied) muscle consists of an anterior belly and a posterior belly (Figure 35-13). The posterior belly arises from the mastoid notch medial to the mastoid process; the intermediate tendon is held to the body of the hyoid bone by a fascial loop. The anterior belly attaches to the digastric fossa of the mandible. This fossa is located at the lower lingual border of the mandible slightly lateral to the midline. In the side view, the two bellies of the muscle form an obtuse angle. The posterior belly is much longer than the anterior belly and is only slightly flattened in the mediolateral direction.

If the hyoid is fixed by the action of the infrahyoid muscles, contraction of the digastric muscles pulls the front of the mandible back and down and thus facilitates retrusive and opening movements of the mandible.[61,62] If the teeth are held firmly in occlusion (by the jaw-closing muscles), then contraction of the entire digastric elevates the hyoid as long as the infrahyoid muscles are relatively relaxed.

Mylohyoid Muscle

The mylohyoid muscle builds a muscular diaphragm or floor for most of the oral cavity (see Figure 35-13). It is a flat, continuous, pentagonal sheet of muscle located deep to the anterior belly of the digastric. The base of this pentagon attaches to the body of the hyoid bone, and the two adjacent sides of the base have a free edge. The remaining two sides attach to the medial or lingual aspect of the left and right mandible corpora along the mylohyoid line. The apex of this pentagon attaches to the midline lingual surface of the mandible. It also attaches to a midline mylohyoid raphe that connects the body of the hyoid with the lingual midline surface of the mandible. This raphe divides the mylohyoid into left and right sides.

The mylohyoid slightly raises the hyoid (and tongue) and floor of the mouth. Moreover, if the mandible is stabilized, it can also pull the hyoid forward. In the event that the hyoid is stabilized or is being pulled down and/or backward, this muscle also can depress the mandible.

Geniohyoid Muscle

The geniohyoid muscle is a strap-shaped muscle that runs from the ventral surface of the body of the hyoid to the lingual aspect of the mandible immediately lateral to the midline (Figure 35-14). It is located superficial to the mylohyoid. The muscle is made up of nearly parallel muscle fibers that run straight from origin to insertion. The anatomy of the geniohyoid indicates that if the mandible is stabilized in occlusion, these muscles can slightly raise the hyoid (and tongue) during contraction, and it can pull these structures forward. Conversely, in the event that the hyoid is pulled downward and/or backward, the geniohyoids can depress the mandible. The geniohyoid muscles are not branchial arch derivatives. These muscles are the serial homologs of

Innervation and Blood Supply

The sensory nerves of the *capsule* for proprioception and pain are branches of the auriculotemporal, deep temporal,



• **Figure 35-14** Geniohyoid muscle.



• **Figure 35-15** Lateral view of trigeminal nerve when condyle is removed.

and masseteric nerves. The blood supply to the capsule and disc is provided mainly by branches from a maxillary artery. Nerves (Figure 35-15) and blood vessels are numerous in the posterior portions of the articular disc and fibrous capsule.[4,6]

The *masseter muscle* is derived from the first branchial arch and therefore is innervated by the trigeminal nerve (cranial nerve V). More specifically, the masseteric nerve, a small branch of the mandibular or third division of the trigeminal nerve (V_3), innervates the masseter muscle. This nerve passes above the lateral pterygoid muscle and then, after passing through the mandibular notch behind the tendon of the temporalis muscle, enters the medial surface of the deep masseter muscle. The masseteric nerve supplies the deep masseter, perforates it, and then enters the superficial masseter.

The *temporalis* muscle is innervated by the deep temporal branches of the anterior trunk of V_3. Of the three deep temporal nerves ordinarily present, the posterior and middle branches arise as separate filaments from the anterior trunk immediately after the trigeminal nerve emerges through the foramen ovale. The anterior branch initially is united with the buccal nerve; this common trunk, which lies in a sulcus adjacent to the foramen ovale, runs anteriorly and laterally, close to the base of the skull. It is held in place by a ligament that bridges the sulcus. If this ligament ossifies, it contributes to the formation of the temporobuccal foramen.

The anterior temporal nerve usually separates from the buccal nerve after the latter has passed between the two heads of the lateral pterygoid muscle. Its most anterior portion, however, is not positioned nearly as far forward as the anterior portion of the superficial masseter.

The nerve to the *medial pterygoid* arises from V_3 immediately before it divides into its anterior and posterior trunks. The medial pterygoid nerve, which also innervates the tensor tympani and tensor veli palatini muscles, reaches the medial pterygoid muscle at its upper posterior border.

The nerve to the *lateral pterygoid muscle* is usually a branch of the buccal nerve, which is a branch of the anterior trunk of V_3.

The bellies of the *digastric muscle* are derived from the first and second branchial arches and are innervated by the mandibular division of the trigeminal (V_3) and facial nerves (cranial nerve VII), respectively. The mylohyoid nerve, which is a branch of the inferior alveolar nerve, innervates the anterior belly, a first-arch derivative. A branch of the facial nerve supplies the posterior belly, a second-arch derivative.

V_3 innervates the *mylohyoid muscle* via the mylohyoid nerve. Occasionally, the anterior belly of the digastric is fused to the ventral surface of the mylohyoid. This fusion reflects the embryologic origin of these two muscles from a common muscle mass derived from the first branchial arch.

The *geniohyoids* are innervated by ventral rami of the first and second cervical nerves. These nerve fibers connect to the left and right hypoglossal nerves (cranial nerve XII) to reach the floor of the mouth.

TMJ Function

Comprehending TMJ function requires consideration of the relationship of fossa, disc, and condyle during motion. If a finger is placed just in front of the tragus of the ear, the forward and downward sliding of the mandibular condyle can be felt. Soft tissues behind the moving condyle

Elevating Muscles

Temporalis
Masseter
Medial pterygoid

Depressing Muscles

Digastric
Mylohyoid
Geniohyoid

Protracting Muscles

Lateral pterygoid

Retracting Muscles

Digastric

sink in slightly, and a shallow groove often becomes visible during jaw opening. If a finger is introduced into the external acoustic meatus, it is easy to feel the prominence of the lateral pole of the mandibular condyle on the cartilaginous anterior wall of the meatus and the widening of this passage when the mouth is opened. Differences due to active and passive motion-free (or empty) movements of the mandible, which are those that occur without food in the oral cavity, are distinguished from incision and mastication movements, which are associated with biting and chewing of food (Box 35-1).[1-6,64-76]

The muscles of the TMJ combine in various patterns to execute movements of the mandible. A muscle may act synergistically with different muscles at different times. Moreover, antagonistic muscles may act simultaneously

pterygoid muscles; depressors—the digastric, mylohyoid, and geniohyoid muscles; and protractors—the lateral ptery-

muscles. When the stylohyoid and infrahyoid muscles fix the hyoid, the mylohyoid and geniohyoid also may help to retract the protruded mandible. The fibers of the deep portion of the masseter also help in this. Thus, both elevators and depressors can function as retractors of the mandible. The infrahyoid muscles function to control hyoid movements; therefore, their action is important during both jaw opening and jaw closing.

Free Movements of the Mandible

Two basic movements of the mandible can occur: (1) the rotary or hinge movement, which consists of rotation of the mandible around a transverse axis that passes through the centers of the mandibular condyles, and (2) the translatory or sliding movement, which involves bodily movement of the mandible in the anteroposterior and/or mediolateral direction. Whereas rotating movement occurs mainly between the disc and the condyle in the lower joint compartment, anteroposterior and mediolateral translatory movements occur mainly between the articular eminence and the disc (and mandible) in the upper compartment of the temporomandibular articulation. Sometimes, the translation movements are not symmetric between the left and right joints. Generally, translation occurs simultaneously with rotation, so during normal rotary movements, the center of rotation is not located within the mandible or the condyle.[66]

Free movements of the mandible, which combine rotation and translation, include opening and closing, protrusion and retrusion (symmetric forward and backward movements), and lateral shifts of the mandible. The extreme or outer limits of the various combinations of these movements make up what have been called the border movements of the mandible.[67,68]

Opening

Although highly variable, on average, a nearly equal or linear combination of translation and rotation is observable in the opening and closing movements of the mandible.[66] Translation brings the disc and the condyle forward and downward along the posterior slope of the articular eminence. The condyle and disc may even move anterior to the greatest height of the articular eminence onto the preglenoid plane. The opening movement is so extensive that normally the opening between the maxillary and mandibular incisors easily accommodates three fingers (40 to 60 mm).

The opening movement is caused by gravity, relaxation of the elevator muscles, and a combined action of the lateral pterygoid, geniohyoid, mylohyoid, and digastric muscles. If the opening movement occurs without resistance, the depressors act without any great force. If the amount of opening is only slight, relaxation of the elevators and the force of gravity can accomplish this movement. When wide opening occurs, the protracting force of the inferior head of the lateral pterygoid muscles, which act on the condyles and discs, combines with the depressing and retracting forces of the geniohyoid, digastric, and mylohyoid muscles, which act on the chin and body of the mandible.

Closing

The elevators of the mandible execute the closing movement. If the mouth is opened to its maximal extent, timing of the activation and relaxation of different parts of these muscles may be important for proper closure. During maximum opening, each disc and condyle glides anterior to the summit of the articular eminence onto the preglenoid plane. At the beginning of mouth closure, the discs and condyles are moved back from this anterior position. The elevators execute this phase of the closing movement. This action returns the jaw to the rest or occlusal position.

Protrusion

During protrusion, the mandible is pulled forward, with the mandibular teeth slightly separated from or in light contact with the maxillary teeth. The mandibular condyles are pulled forward together with the articular discs at this time. Therefore, movement occurs primarily in the upper compartment of the TMJ, and it is symmetric.[19] Protrusion of the mandible is primarily the result of contraction of the inferior heads of the lateral pterygoid muscles, although slight activity of the masseter and medial pterygoid muscles also is noted at this time. The temporalis muscle usually is not active during this movement, and the depressors are only slightly active. The lateral pterygoid muscles pull the mandibular condyles (and discs) forward and downward along the articular eminences, while the elevators and depressors apparently stabilize the position of the mandible relative to the maxilla. Contraction of the elevators and the depressors in an unresisted forward thrust often is not noticeable on palpation. However, if the mandible is moved to the extreme forward position, contraction of the superficial masseters can be felt. The forward and backward movements of the mandible are mainly, but not exclusively, translatory.

Retrusion

The reversal of the forward movement, retrusion, is also mainly translatory. These forward condylar movements, which can be confirmed easily by palpation, are limited by the posterior portion of the joint capsule.[43] Most people with a relatively normal masticatory apparatus can retrude the mandible 1 to 2 mm from the full occlusal position or centric occlusion. The capsular and polar ligaments of the TMJ limit retrusion from this position. This retruded position beyond centric occlusion (referred to as centric relation) is not reached during normal jaw movements in humans, although by definition, it falls along the border movements of the mandible. When the condyles are situated in the mandibular fossa, the obliquely aligned middle fibers of the temporalis muscle combine forces with the depressors so as to retrude the mandible, while the remaining elevators exhibit varying amounts of activity. From the maximum protruded position, the posterior temporalis assists the middle temporalis during mandibular retrusion.

Lateral Shift

A lateral shift of the mandible (e.g., a shift to the right) results if the condyle and disc on the opposite or left side are pulled forward, downward, and medially along the articular eminence. In this instance, the left side is often called the *balancing side (b-s) condyle,* whereas the right side is called the *working-side (w-s) condyle.* The w-s condyle, sometimes called the *resting condyle,* executes very limited movement at this time. This movement consists primarily of a rotation of the mandible around a nearly vertical axis located within or immediately behind the w-s condyle. This movement also results in a slightly transverse translation of the two condyles toward the working side.

Lateral shift of the mandible results from an asymmetric variation of protrusion, that is, the b-s lateral pterygoid muscle combines forces with the slightly active elevators. The middle portion of the w-s temporalis muscle must assist in this movement by holding the w-s condyle and preventing it from deviating anteriorly to any great extent. Continued rotation of the w-s condyle is prevented as the lateral polar ligament is pulled straight. Under guidance of this ligament, the center of the w-s condyle is forced to move slightly forward and laterally. The lateral component of this movement often is called the *Bennett movement.* As noted, the different movements of the w-s and b-s condyles can be palpated easily.

Masticatory Movements of the Mandible

The two basic mandibular movements, namely, rotation and translation, combine during masticatory jaw movement. Two general types exist: a cutting movement, as occurs when a piece of food is bitten off, and a crushing and grinding movement, which is used to comminute a piece of food. The cutting of food into bite-sized pieces, often referred to as *incision,* is carried out mainly by the incisors. The rhythmic and repetitive crushing and grinding of food, termed *mastication,* is carried out almost exclusively along the premolars and molars. When mechanically resistant foods are eaten, chewing usually occurs unilaterally, that is, chewing takes place on only one side of the dental arch.[75-89]

Incision

Incision consists of three parts, namely, (1) opening, (2) closing, and (3) power strokes.[69,70] (1) Starting from the rest or occlusal position, depression of the mandible opens the mouth, and the extent of opening is primarily dependent on the size of the food object. (2) The mandible is elevated or closed. An upward and forward movement of the mandibular incisors occurs along with an upward and backward movement of the mandibular condyles during jaw closure, and this part of the incision continues until the maxillary and mandibular incisors contact the food object. (3) Following food contact, the jaw continues to close with the simultaneous application of force on the food object. In many instances, the closing stroke does not occur simply, because when the food object is large (e.g., a whole apple), the amount of jaw opening is just enough to accommodate this object between the maxillary and mandibular incisors.[6]

Mastication

Similar to incision, mastication or chewing consists of three basic parts: opening, closing, and power strokes,[71] which combine to make up a single chewing cycle. All chewing cycles associated with the mastication of a single piece of food are referred to as a *chewing sequence.* A chewing cycle begins with opening of the mouth. During the opening stroke, the amount of opening varies from one chewing cycle to the next, and this depends in part on the size and

consistency of the food object. The closing stroke starts from the position of maximum opening. The mandibular incisors then are moved upward, forward, and away from the midline toward the working side. Completion of the closing stroke leads to the power stroke, which is the forceful contact of the food between the occlusal surfaces of the molar and premolar teeth. The w-s teeth posterior to the canine are moved back toward the midline during the power stroke. With the exception of those movements associated with contact between the maxillary and mandibular teeth, mandibular incisor movements during mastication are well within the border movements.

When tough, mechanically resistant foods are chewed, the power stroke of mastication often ends before the maxillary and mandibular teeth make contact. This type of power stroke is called *puncture crushing.* However, a power stroke often does involve direct contact between the maxillary and mandibular teeth; this type of power stroke is called *tooth-tooth contact.*[77-83] When a large food object suddenly breaks during incision, the holding force and stiffness of each lateral pterygoid muscle prevent uncontrolled posterior and upward displacement of the mandibular condyles, as the condyles and discs are situated precariously near the summit or along the posterior slope of the articular eminence.

Summary

Clinicians constantly are challenged to deal more effectively with their patients' TMJ problems when they do arise. Moreover, the very narrow definitions of ideal intraindividual and interindividual TMJ morphology and mandibular function may divert clinicians to regard otherwise normal variability in asymptomatic populations as a pathologic condition that requires treatment. This chapter has provided insights into the structure and function of the craniomandibular articulation. In keeping with the evolutionary history of this articulation, which is reflected in its early ontogeny, unique aspects of the TMJs were highlighted. The articulating surfaces are covered by fibroelastic tissue distinct from hyaline cartilage in other synovial joints. The TMJs as load-bearing joints always must function bilaterally and are influenced by dental occlusion. The articular discs are interposed between articular fossae and condyles, allowing complex rotational and translatory movements, especially during incision and mastication. In conclusion, the craniomandibular articulation within the stomatognathic system has an enormous capacity to function in a wide variety of patterns and displays great ability to adapt to different functional demands.

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36

Assessing Temporomandibular Disorders

GARY M. HEIR

This chapter discusses the assessment of pathology and abnormal function of the temporomandibular joint (TMJ). In order to comprehend pathologic processes resulting in pain and dysfunction of the temporomandibular joints, a clear understanding of normal anatomy and biomechanics is essential. Assessment of the temporomandibular joint, typically performed on a symptomatic patient, requires an understanding of the various clinical conditions that encompass temporomandibular disorders.

Research in the field of temporomandibular disorders is limited in its utility because of a lack of consistency in the standardized nomenclature, in definitions of the various disorders that might affect the masticatory system, and in the quality of research.[1] In an attempt to better define temporomandibular disorders, the International RDC/

A persistent problem appearing in the literature, addressed by the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), is use of "Temporomandibular Disorders (TMD)" as a comprehensive term incorporating all aspects of masticatory pain, regardless of etiology or severity. The DC/TMD addresses this by separating out two categories of painful TMD: myogenous, or muscle-generated pain, and arthrogenous, or joint-generated pain. The DC/TMD fur-

ation[3] (Table 36-1). Non–TMJ-related topics are beyond the scope of this chapter, but familiarity with these diagnostic entities and techniques is encouraged.

Temporomandibular Disorders

Temporomandibular disorders are defined as clinical problems involving the masticatory musculature, the temporomandibular joints and associated structures, or both. Articular disorders of the TMJ often coexist with masticatory muscle pain, and a clear differential diagnosis is necessary, especially when surgery is a possibility. Articular disorders include disc displacement disorders, arthritic or degenerative changes, and neoplasm.[4] Other conditions that may affect the temporomandibular joints include congenital disorders, inflammatory conditions, and systemic disease.

TMDs are considered the most common cause of musculoskeletal orofacial pain. Common features of a TMD include: (1) pain with mandibular function, (2) limitation of mandibular movement, and (3) joint sounds. One, two, or all three conditions, when present, may represent signs of chronic adaptation of the anatomy of the joint that require no treatment interventions, or may reveal symptoms of dysfunction that may affect the activities of daily life due to dysfunction and/or pain.

Although pain in the masticatory system can arise from the muscles of mastication or can be referred to the orofacial region from remote musculoskeletal structures, a discussion of muscle pain is not within the scope of this chapter. However, it is important to consider that myogenous pain occurs more frequently than pain arising from articular disorders.[4]

treatment.[5] For the purpose of classification, temporomandibular disorders will be considered as pain or dysfunction of the musculoskeletal system involving the temporomandibular joints and the masticatory muscles.

With myogenous pain, the patient typically provides a history of regional pain, a sense of muscle weakness, easy fatigability of the masticatory muscles, and a limited passive mandibular range of motion. A palpatory examination of the masticatory muscles often reveals myofascial trigger points and muscle tenderness, which also can produce referral patterns to the region of the temporomandibular joints.

TABLE 36-1 Detailed and Validated Diagnostic Approach to Temporomandibular Disorders as Proposed by the DC/TMD

Disc Displacement with Reduction (ICD-10 M 26.63)

Description	An intracapsular biomechanical disorder involving the condyle-disc complex. In the closed mouth position, the disc is in an anterior position relative to the condylar head and the disc reduces upon opening of the mouth. Medial and lateral displacement of the disc may also be present. Clicking, popping, or snapping noises may occur with disc reduction. A history of prior locking in the closed position coupled with interference in mastication precludes this diagnosis.
History	Positive for at least one of the following: 1. In the last 30 days,* any TMJ noise(s) present with jaw movement or function; OR 2. Patient report of any noise present during the exam.
Exam	Positive for at least one of the following: 1. Clicking, popping, and/or snapping noise during both opening and closing movements, detected with palpation during at least one of three repetitions of jaw opening and closing movements; OR 2a. Clicking, popping, and/or snapping noise detected with palpation during at least one of three repetitions of opening or closing movement(s); AND 2b. Clicking, popping, and/or snapping noise detected with palpation during at least one of three repetitions of right or left lateral, or protrusive movement(s).
Validity	Without imaging: sensitivity 0.34; specificity 0.92. Imaging is the reference standard for this diagnosis.
Imaging	When this diagnosis needs to be confirmed, TMJ MRI criteria are positive for both of the following: 1. In the maximum intercuspal position, the posterior band of the disc is located anterior to the 11:30 position and the intermediate zone of the disc is anterior to the condylar head; AND 2. On full opening, the intermediate zone of the disc is located between the condylar head and the articular eminence.

Disc Displacement with Reduction with Intermittent Locking (ICD 10 M 26.63)

Description	An intracapsular biomechanical disorder involving the condyle-disc complex. In the closed mouth position, the disc is in an anterior position relative to the condylar head, and the disc intermittently reduces with opening of the mouth. When the disc does not reduce with opening of the mouth, intermittent limited mandibular opening occurs. When limited opening occurs, a maneuver may be needed to unlock the TMJ. Medial and lateral displacement of the disc may also be present. Clicking, popping, or snapping noises may occur with disc reduction.
History	Positive for both of the following: 1a. In the last 30 days,* any TMJ noise(s) present with jaw movement or function; OR 1b. Patient report of any noise present during the exam; AND 2. In the last 30 days,* jaw locks with limited mouth opening, even for a moment, and then unlocks.
Exam	Positive for both of the following: 1. Clicking, popping, and/or snapping noise detected during both opening and closing movements, detected with palpation during at least one of three repetitions of jaw opening and closing movements; OR 2a. Clicking, popping, and/or snapping noise detected with palpation during at one of three repetitions of opening or closing movement(s); AND 2b. Clicking, popping, and/or snapping noise detected with palpation during at least one of three repetitions of right or left lateral, or protrusive movement(s).
Validity	Without imaging: sensitivity 0.38; specificity 0.98. Imaging is the reference standard for this diagnosis.
Imaging	When this diagnosis needs to be confirmed, the imaging criteria are the same as for disc displacement with reduction if intermittent locking is not present at the time of imaging. If locking occurs during imaging, an imaging-based diagnosis of disc displacement without reduction will be rendered and clinical confirmation of reversion to intermittent locking is needed.
Note	Although not required, when this disorder is present clinically, examination is positive for inability to open to a normal amount, even momentarily, without the clinician or patient performing a maneuver to reduce the lock.

Disc Displacement without Reduction with Limited Opening (ICD 10 M 26.63)

Description	An intracapsular biomechanical disorder involving the condyle-disc complex. In the closed mouth position, the disc is in an anterior position relative to the condylar head, and the disc does not reduce with opening of the mouth. Medial and lateral displacement of the disc may also be present. This disorder is associated with persistent limited mandibular opening that does not reduce with the clinician or patient performing a manipulative maneuver. This is also referred to as “closed lock.” This disorder is associated with limited mandibular opening.
History	Positive for both of the following: 1. Jaw locked so that the mouth would not open all the way; AND 2. Limitation in jaw opening severe enough to limit jaw opening and interfere with ability to eat.

TABLE 36-1 Detailed and Validated Diagnostic Approach to Temporomandibular Disorders as Proposed by the DC/TMD—cont'd

Exam	Positive for the following: 1. Maximum assisted opening (passive stretch) movement including vertical incisal overlap <40.
Validity	Without imaging: sensitivity 0.80; specificity 0.97. Imaging is the reference standard for this diagnosis.
Imaging	Maximum assisted opening of <40 mm is determined clinically.
Note	Presence of TMJ noise (e.g., click during opening) does not exclude this diagnosis.

Disc Displacement without Reduction without Limited Opening (ICD 10 M 26.63)

Description	An intracapsular biomechanical disorder involving the condyle-disc complex. In the closed mouth position, the disc is in an anterior position relative the condylar head and the disc does not reduce with opening of the mouth. Medial and lateral displacement of the disc may also be present. This disorder is NOT associated with current limited opening.
History	Positive for both of the following in the past: 1. Jaw locked so that the mouth would not open all the way; AND 2. Limitation in jaw opening severe enough to limit jaw opening and interfere with ability to eat.
Exam	Positive for the following: 1. Maximum assisted opening (passive stretch) movement including vertical incisal overlap ≥40 mm.
Validity	Without imaging: sensitivity 0.54; specificity 0.79. Imaging is the reference standard for this diagnosis.
Imaging	When this diagnosis needs to be confirmed, TMJ MRI criteria are the same as for disc displacement without reduction with limited opening. Note: Maximum assisted opening of ≥40 mm is determined clinically.
Note	Presence of TMJ noise (e.g., click during opening) does not exclude this diagnosis.

Degenerative Joint Disease (ICD 10 M 26.69)

Description	A degenerative disorder involving the joint characterized by deterioration of articular tissue with concomitant osseous changes in the condyle and/or articular eminence.
History	Positive for at least one of the following: 1. In the last 30 days,* any TMJ noise(s) present with jaw movement or function; OR 2. Patient report of any noise present during the exam.
Exam	Positive for the following: 1. Crepitus detected with palpation during at least one of the following: opening, closing, right or left lateral, or protrusive movement(s).
Validity	Without imaging: sensitivity 0.55; specificity 0.61. Imaging is the reference standard for this diagnosis.
Imaging	When this diagnosis needs to be confirmed, then TMJ CT criteria are positive for at least one of the following: Subchondral cyst(s), erosion(s), generalized sclerosis, or osteophyte(s). Note: Flattening and/or cortical sclerosis are considered indeterminate findings for degenerative joint disease (DJD) and may represent normal variation, aging, remodeling, or a precursor to frank DJD.

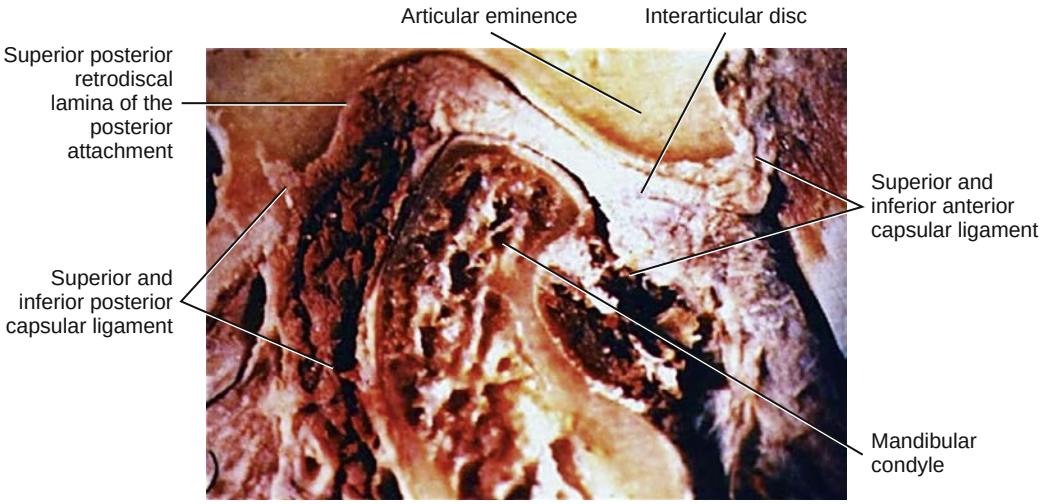
Subluxation (ICD 10 M 26.69)

Description	A hypermobility disorder involving the disc-condyle complex and the articular eminence: In the open mouth position, the disc-condyle complex is positioned anterior to the articular eminence and is unable to return to a normal closed mouth position without a manipulative maneuver. The duration of dislocation may be momentary or prolonged. When the patient can reduce the dislocation himself/herself, this is referred to as subluxation. When the patient needs the assistance of the clinician to reduce the dislocation and normalize jaw movement, this is referred to as luxation. This disorder is also referred to as "open lock." The sensitivity and specificity have been established for only subluxation.
History	Positive for both of the following: 1. In last 30 days,* jaw locking or catching in a wide open mouth position, even for a moment, so could not close from the wide-open position; AND 2. Inability to close the mouth from a wide-open position without a self-maneuver.
Exam	Although no exam findings are required, when this disorder is present clinically, examination is positive for inability to return to a normal closed mouth position without the patient performing a manipulative maneuver.
Validity	Without imaging and based only on history: sensitivity 0.98; specificity 1.00.
Imaging	When this diagnosis needs to be confirmed, imaging criteria are positive for the condyle positioned beyond the height of the articular eminence with the patient unable to close his/her mouth.

*Validity for assessing selected biomechanical intra-articular disorders is in "the last 30 days"' since the stated sensitivity and specificity of these criteria were established using this time frame.

CT, Computed tomography; *DJD,* degenerative joint disease; *ICD-10,* International Classification of Diseases 10th Revision; *MRI,* magnetic resonance imaging; *TMJ,* temporomandibular joint.

Adapted from Schiffman E, Ohrbach R, Truelove E et al: Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for clinical and research applications:



• **Figure 36-1** Cross-sectional anatomy of the temporomandibular joint. (Courtesy Dr. Peter Neff.)

su
result from local trauma or infection. Upon palpation, muscles with myositis may also be tender and feel swollen and warm.

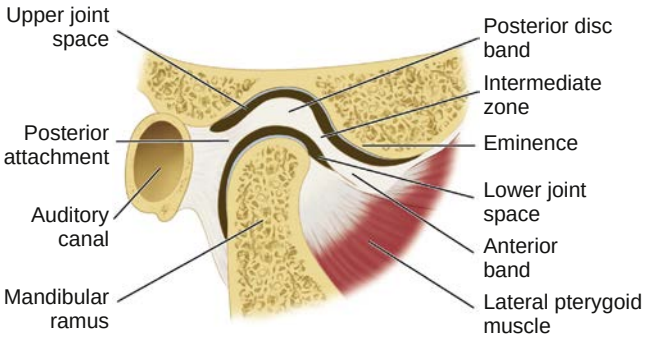
Myospasm is an often-overused diagnostic term that describes an involuntary muscle contraction. The patient with myospasm may present with a restricted mandibular range of motion that must be differentiated from an internal derangement of the joint, because this condition also can restrict mandibular movement. Spastic muscles may be tender to palpation. True myospasm may be secondary to a neuromuscular disorder and can be diagnosed by needle electrode electromyography.

With time, masticatory muscles exhibiting chronic contraction or other local myopathies may develop myofibrotic contracture. This may not be a painful condition, but will also limit the mandibular range of motion. For this reason, a differential diagnosis requires a detailed history and thorough evaluation. Myofibrotic contracture may be characterized by local tenderness and may be differentiated from other forms of muscle disorders via needle electrode electromyography.

Anatomy

The temporomandibular articulation is among the most complex in the body. It is a synovial joint that has two joint compartments and four articular surfaces, contains vascularized tissue within the joint capsule, and has articular surfaces of fibrous rather than chondrocartilage.

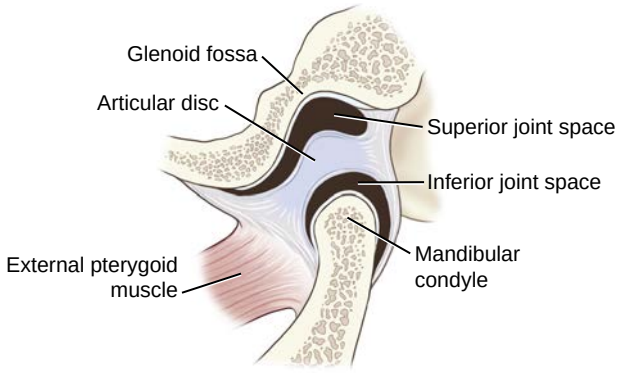
The temporomandibular joint functions within the glenoid or temporomandibular fossa of the skull. The fossa is located in the temporal bone bilaterally, just anterior to the external auditory meatus. The TMJ fossa is not so much a precise socket as a depression in the base of the skull, within which the mandibular condyle functions.



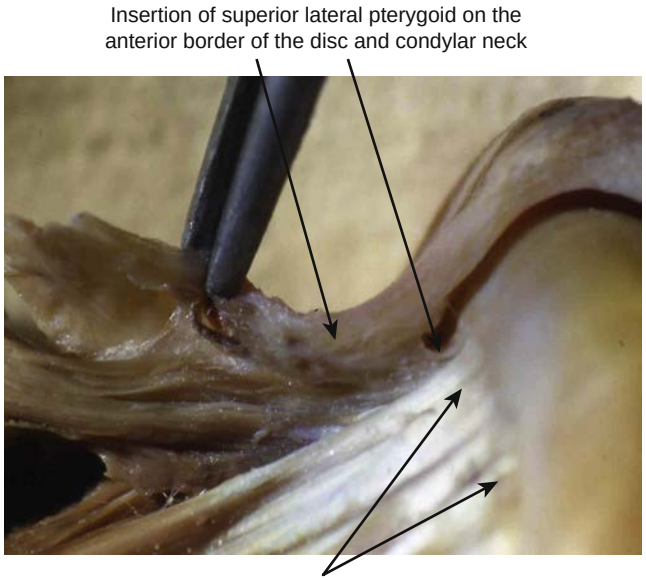
• **Figure 36-2** Articular disc and associated structures. (From Nelson SJ: *Wheeler's dental anatomy, physiology and occlusion*, ed 10, St Louis, 2015, Elsevier.)

The mandibular condyle is a spheroidal structure that is capable of a wide range of anterior, posterior, and lateral movements. The fibrocartilaginous articular surfaces of the condyle and fossa function against the fibrous interarticular disc that is interposed between these two bony structures (Figure 36-1). The disc is attached to the mandibular condyle by lateral and medial collateral ligaments and blends into the capsule anteriorly. Posteriorly, the disc attaches to the complex retrodiscal tissues. Although the disc is avascular and is not innervated, the retrodiscal tissue is highly vascularized and richly innervated (Figure 36-2). Therefore, intracapsular pain may be due to injury or inflammation of the retrodiscal tissue (retrodiscitis).

Like any synovial joint, the temporomandibular joint is encapsulated and stress bearing. The disc and its circumferential attachments separate the joint into upper and lower joint spaces. The disc-condyle complex and the mandibular fossa are enclosed within the capsular ligament, which is lined by synovial tissue with collateral ligaments that blend into the capsule. The TMJ lateral ligament complex arises from the articular eminence and attaches to the posterior aspect of the neck of the condyle (Figure 36-3). The lateral ligament complex functions to limit lateral movement.



• **Figure 36-3** Components of the temporomandibular joint.



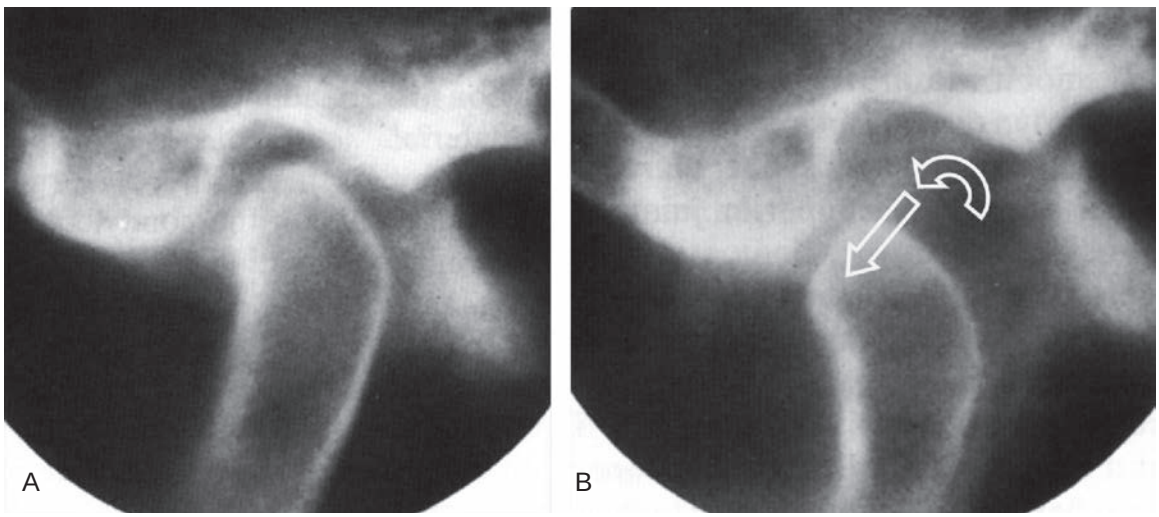
• **Figure 36-4** The superior and inferior lateral pterygoid muscles insert on the condylar neck. The inferior lateral pterygoid protrudes the mandible, whereas the superior lateral pterygoid contracts during mandibular closure. Some fibers of this muscle attach to the anterior border of the disc and contract eccentrically to stabilize the disc against the posterior slope of the articular eminence during closure. (Courtesy Thomas M. Wilkinson, BDS, MSO.)

Normal Biomechanics

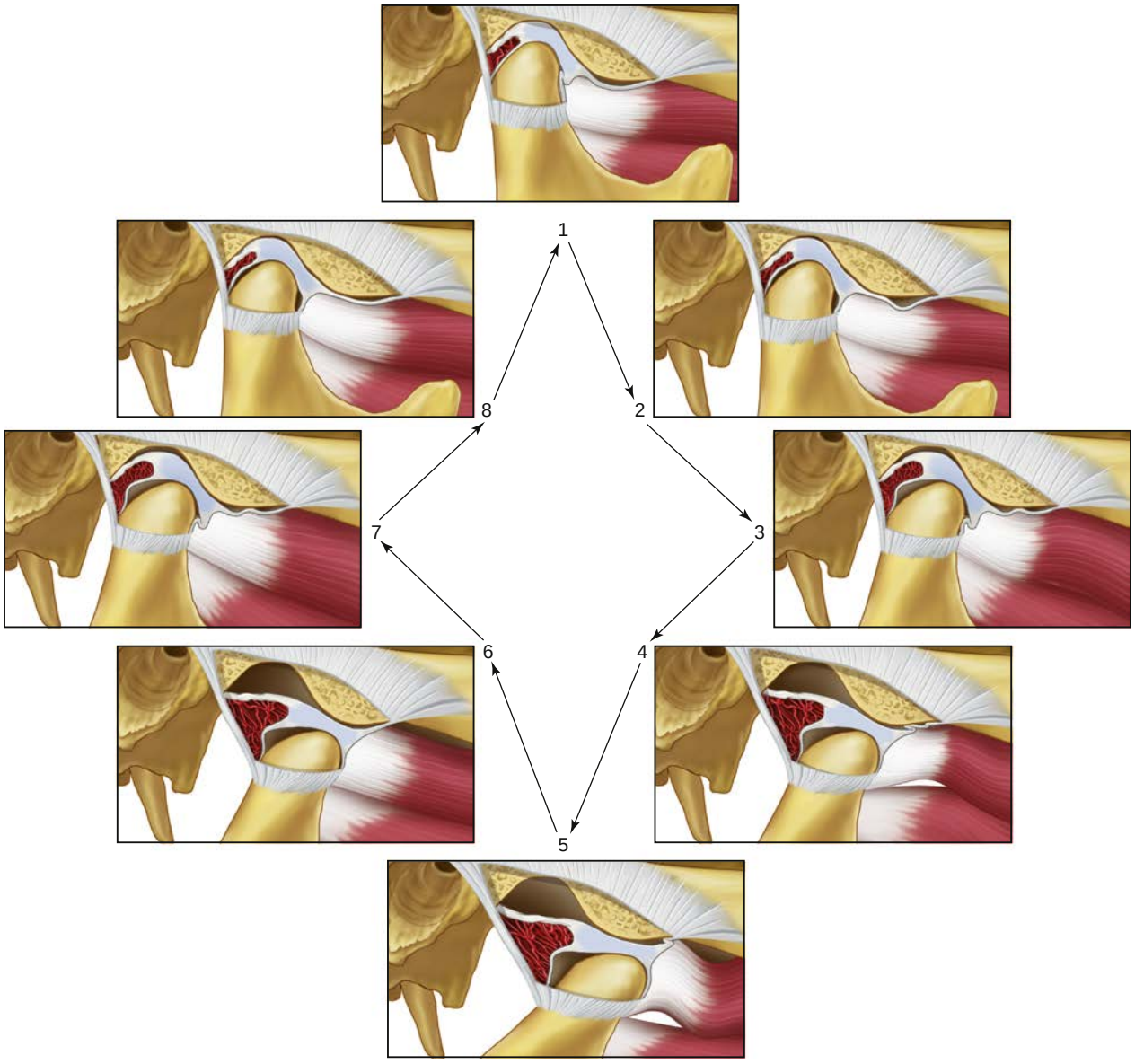
The TMJ is a ginglymoarthrodial joint that is capable of both rotational movements in the inferior compartment and translational movements in the superior compartment (Figure 36-4). During function, the lateral and medial discal collateral ligaments allow for rotational movement of the condyle on the inferior surface of the disc, and the superior surface of the disc translates or slides along the posterior aspect of the articular eminence. Biomechanically, the TMJ exhibits significant mobility. The mandibular condyle freely rotates on the inferior surface of the interarticular disc, and the disc-condyle complex moves within the fossa and translates unimpeded along the posterior slope of the articular eminence. In addition, limited lateral movements are possible. During all of these movements of a normal temporomandibular joint, the interarticular disc is always positioned between the fossa/eminence and the condyle by the action of the superior lateral pterygoid muscle and the uppermost elastic properties of the posterior attachment known as the posterior, superior retrodiscal lamina of the retrodiscal tissue. Translation of the condyle occurs as a result of the action of the inferior lateral pterygoid muscle, which protrudes the mandible, acting in concert with other mandibular depressors of the infrahyoid and suprahyoid musculature. Movement of the disc is also controlled by a second structure. The superior, posterior retrodiscal lamina acts passively to pull the disc posteriorly during opening as the condyle translates anteriorly. The superior lateral pterygoid muscle contracts eccentrically during closure to stabilize the disc against the distal slope of the articular eminence (Figure 36-5). Normal disc/condyle/fossa relationships are demonstrated in Figure 36-6.

Abnormal Biomechanics

Smooth and coordinated opening and closing, in the absence of pain or joint sounds, characterize normal function of all synovial joints, including the TMJ. Signs of a TMD therefore include limited or irregular jaw movements, discomfort, and/or sounds emanating from the joint during function.



• **Figure 36-5** Tomographic imaging of normal translation of the temporomandibular joint. **A,** Closed mouth position. **B,** Open mouth position after rotational and translatory movements.



• **Figure 36-6** Normal functional movement of the condyle and disc during the full range of opening and closing. Note that the disc is rotated posteriorly on the condyle as the condyle is translated out of the fossa. The closing movement is the exact opposite of opening. (From Okeson JP: *Management of temporomandibular disorders and occlusion*, ed 7, St Louis, 2013, Elsevier.)

Impediments to normal joint movement can be extracapsular or intracapsular. A temporomandibular joint assessment must differentiate between the two.

As was previously discussed, extracapsular conditions that affect joint movement typically are caused by muscle dysfunction, although osseous anomalies also may interfere with mandibular movement. These include coronoid hypertrophy, calcified styloid processes, osteochondromatosis, or other bony abnormalities (Figures 36-7 through 36-9).

Synovial chondromatosis is an uncommon arthropathy, but it is one that should be considered in the differential diagnosis of TMJ-pain dysfunction syndrome[6] (Figure 36-10). Limitation of mandibular function caused by calcified bodies found within the TMJ capsule may displace the mandibular condyle, impede mandibular function, and mimic disc displacement or disc interference disorders.

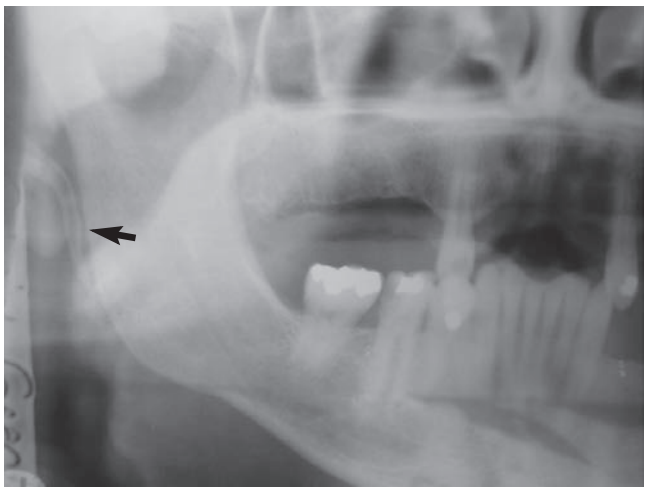
Myofascial pain, myositis, myalgia, and muscle contracture not only can limit mandibular depression but also can result in pain during movement.[7] Myofascial trigger points of the masticatory musculature can refer pain to the TMJ.[8] Care must be taken during the history and physical examination to clearly define the source of the problem. If mandibular dysfunction is not due to extracapsular or myogenous causes, attention should be directed at possible intracapsular disorders.

Intracapsular Pathofunctional Disorders

Intracapsular pathofunctional disorders include anterior disc displacement with and without reduction.



• **Figure 36-7** Hypertrophic hamulus preventing normal mandibular opening.



• **Figure 36-8** Calcified styloid process growing along the posterior border of the ramus, preventing normal mandibular depression.

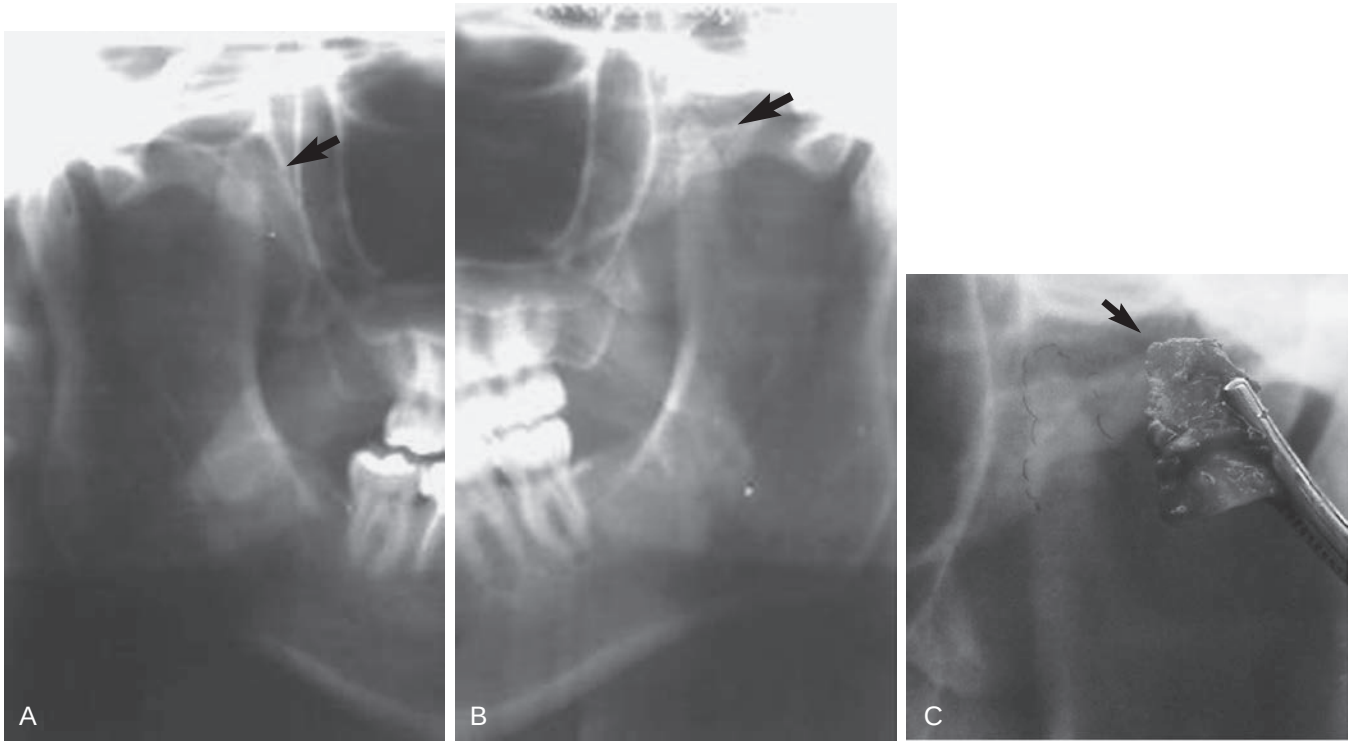
Anterior disc displacement is a partial anterior or anteromedially displaced disc, characterized by joint sounds during function that occur at variable points during mandibular movement (Figure 36-11). Chronic anterior disc displacement may occur for a variety of reasons and may be an adaptive change that occurs within the joint as a result of functional demands (Figure 36-12). Adaptation should not be presumed to be pathologic. Some research indicates that a large segment of the general population, perhaps 90%, exhibits mild disc displacements similar to those of patients seeking treatment. Nearly one third were asymptomatic—that is, without pain or dysfunction—and had documented discal displacement. Therefore, the occurrence of disc displacement is common in the general population, and caution is necessary in differential diagnosis and in determining the need to initiate treatment for asymptomatic individuals based merely on an asymptomatic adaptive disc displacement.[9]

Differential diagnosis involves a physical examination in which the mandibular range of motion is measured, the gait of movement is observed, and the joint is auscultated. Assessing the mandibular range of motion is an important factor in the evaluation for TMDs. A limited mandibular range of motion may be a sign of a biomechanical dysfunction, muscular restriction of movement, extracapsular mechanical factors interfering with movement, or a variety of systemic conditions.

When assessing the mandibular range of motion there is an assumption that normal opening is 40 to 55 mm; however, there are no supporting validated studies. A review of published literature finds that maximal opening varies greatly and is described by several authors as, for example, 39 to 69 mm[10] or 46.9 to 60 mm.[11-13] These data are observational reports only, not taking into account the variations in individual anatomy that might be predictors of an individual's maximum opening. Methods for measuring the mandibular range of motion are also inconsistent; for example, maximum mandibular opening is often measured as the interincisal distance while opening as wide as possible, but inclusion of overbite in the measurement is not consistent.[10] Other literature suggests measurement should begin at the alveolar crest.[14] The lack of standardization in measuring the mandibular range of motion may account for these range discrepancies.

Even accepting a normal range of motion of 40 to 55 mm, as multiple authors have done,[4,15,16] does not eliminate confusion. The normal range of motion is reported anecdotally as less in women, and decreasing with increasing age.[15] Furthermore, range of motion may depend on the height of the patient. A young male of small stature might have a mandibular range of motion of less than 40 mm, while a tall and older female might approach 60 mm. A more accurate measure of normal opening might involve assessment of condylar translation to the crest of the articular eminence. This may be demonstrated radiographically, but the use of x-ray or magnetic resonance imaging (MRI) for this purpose is not suggested; it would be considered overuse of diagnostic imaging.

In anterior disc displacement, soft tissue imaging such as MRI can reveal a displaced disc with improved position during jaw opening. Hard tissue imaging may show an absence of degenerative changes, even though adaptive remodeling of the articular surfaces may occur. Disc displacement with reduction also may be accompanied by pain with joint movement and deviation of the mandible during



• **Figure 36-9** **A-B,** Hypertrophic coronoid processes are visualized radiographically. The surgical specimen has been removed and is shown next to the radiograph **(C).** (Courtesy Dr. Cibele Nasri.)

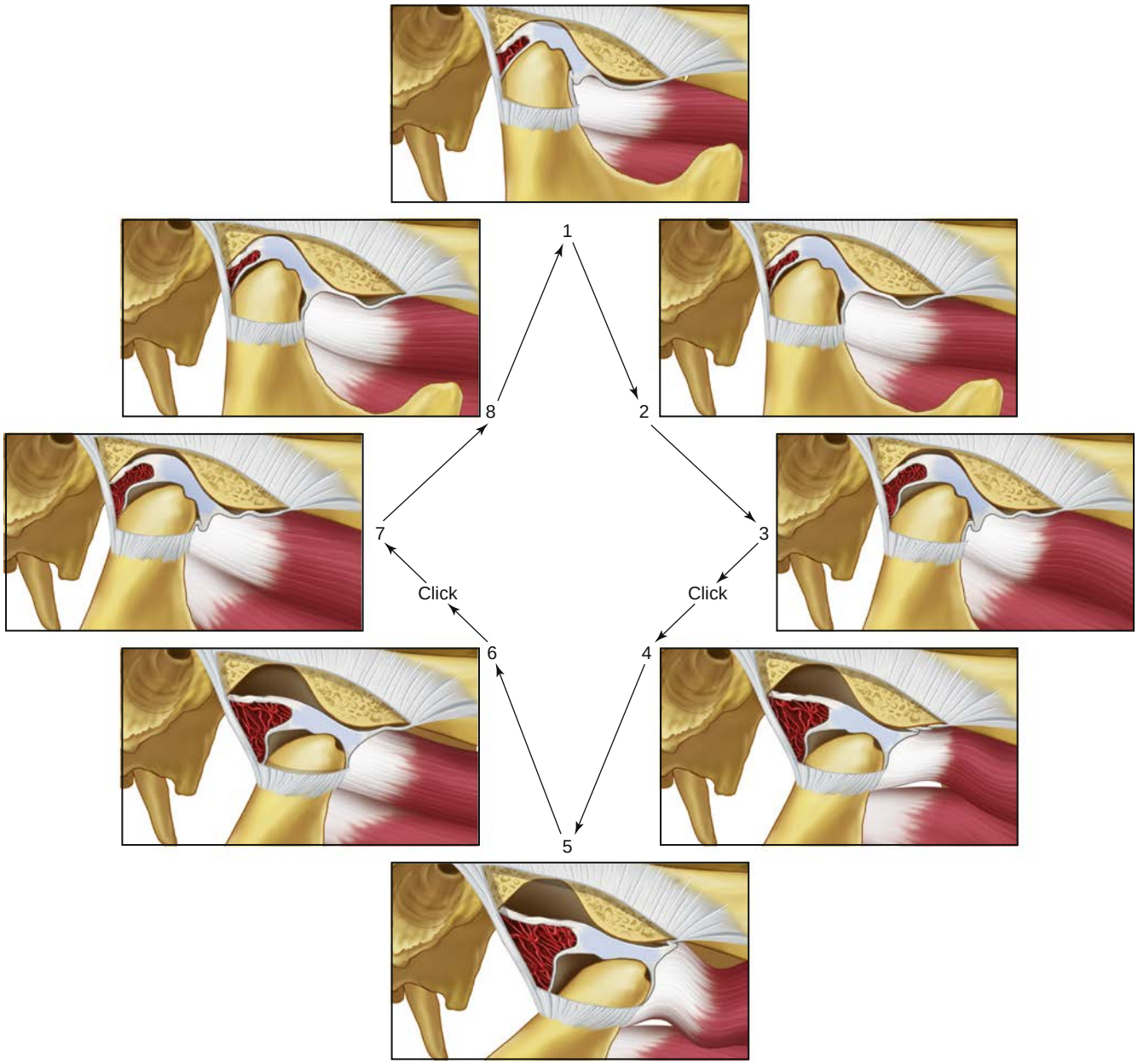


• **Figure 36-10** Synovial chondromatosis. Radiopaque, loose bodies, as seen here, anterior to the left temporomandibular joint within the synovial joint space. (Courtesy John F. Johnson, II, DDS, MS.)

opening, possibly coinciding with a click as the displaced disc returns to normal. No restriction is placed on mandibular movement despite the possibility of an episodic and momentary catch during jaw movement. An abnormal disc/condyle relationship is characteristic of disc displacement with reduction.[4]

Anterior disc displacement without reduction is the state in which the anteriorly displaced disc is maintained in this position throughout translation. This is often referred to as a closed lock. Essentially, the disc no longer allows the condyle to translate along the articular eminence. Thickening of the disc or damage to the posterior attachment may contribute to the disc getting caught or interfering with condylar movement.[4] Disc displacement without reduction is typically chronic, but initially presents as an acute problem. Some patients with anterior disc displacement with reduction evolve to nonreducing disc displacement. However, it is impossible to determine which patients will evolve to more advanced dysfunction.

Although a patient with disc displacement without reduction frequently reports a history of clicking during mandibular movement, a nonreducing disc displacement typically

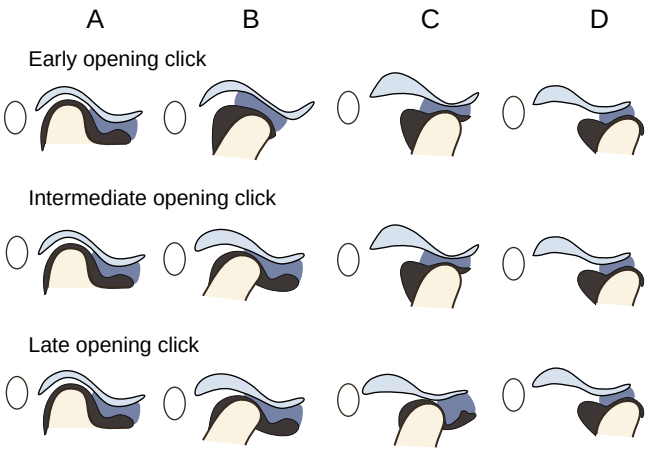


• **Figure 36-11** In position 1, the structural defect (alteration in form) in the condyle and disc. Between positions 3 and 4 the condyle moves out of the defect, creating a click. The condyle returns to this defect between positions 6 and 7. The opening and closing click occurs at the same degree of opening. (From Okeson JP: *Management of temporomandibular disorders and occlusion*, ed 7, St Louis, 2013, Elsevier.)

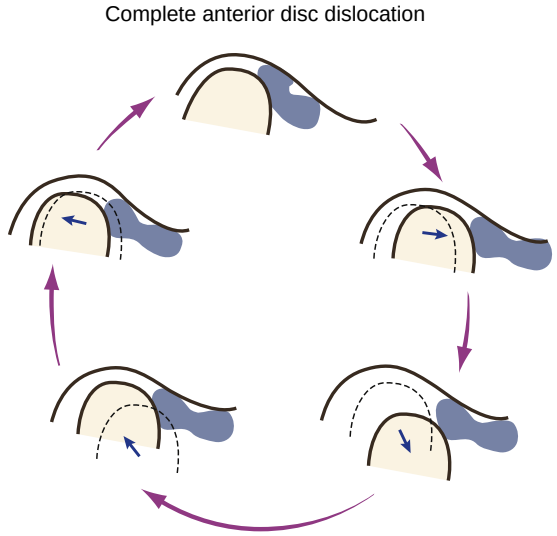
occurs in the absence of joint sounds. Therefore, the presence or absence of joint sounds may not be diagnostic. In fact, patients with chronic anterior disc displacement may have a normal mandibular range of motion with no joint sounds. Soft tissue imaging reveals a displaced disc that does not improve its position during jaw opening. Hard tissue imaging may show degenerative changes. An acute closed lock or nonreducing anterior disc displacement has a sudden onset with nearly immediate limited mouth opening of less than 25 mm. The mandible deflects to the affected side, and lateral movement to the opposite side is limited. Soft tissue imaging reveals the displaced disc, although hard tissue imaging may be normal.[4]

Chronic anterior disc displacement without reduction or chronic closed lock typically includes a history of sudden onset of limited mouth opening with continued limitation of opening for longer than 4 months. Soft tissue imaging shows the displaced disc without reduction. Typically, arthritic or degenerative changes are not extensive[4] (Figure 36-13).

Another post-traumatic condition that may affect mandibular and TMJ function involves intracapsular adhesions. As was previously described, the TMJ functions within a capsular ligament. This ligament exhibits varying degrees of toughness, with the strongest portion at the medial aspect of the superior joint space. The superior/anterior TMJ capsular



• **Figure 36-12** Diagrammatic representation of anterior disc displacement with reduction during early, intermediate, and late condylar translation. **A,** Closed. **B,** Partial translation. **C** and **D,** Full opening. (Adapted from Farrar W, McCarty WL Jr: *A clinical outline of temporomandibular joint diagnosis and treatment*, Montgomery, AL, 1982, Normandie Press.)



• **Figure 36-13** Disc displacement without reduction of the temporomandibular joint. (Adapted from Farrar W, McCarty WL Jr: *A clinical outline of temporomandibular joint diagnosis and treatment*, Montgomery, AL, 1982, Normandie Press.)

ligament is comparatively fragile. A sudden hypertranslation or condylar subluxation could allow the condyle to traumatically encroach on this structure. If injured, bleeding may occur into the superior joint space, resulting in the organization of fibrous bands known as adhesions. These intracapsular adhesions can prevent normal translation of the disc and, while giving the appearance and history of chronic disc displacement without reduction, can actually fixate the disc to the roof of the fossa. MRI or computed tomography (CT) may demonstrate the disc in a normal, closed position.

Another explanation for what appears to be a clinical closed lock in the presence of a normal discal position has been described. A sudden and persistent severely limited mouth opening associated with a total lack of disc translation along the articular eminence may be due to adhesion of



• **Figure 36-14** End-range, bilateral subluxation resulting in a deviation first to the left as the right condyle subluxates, then to the right as the left condyle does the same. After bilateral subluxation, the mandible returns to the midline position. Subluxation may be accompanied by a joint sound that should not be confused with a disc interference disorder.

the disc to the articular eminence secondary to joint overloading. In view of the fact that it is promptly released by lavage (arthrocentesis) of the upper joint space, inefficient lubrication of the joint is hypothesized. It has been postulated that overloading may reduce lubrication and may be responsible for this adhesion of the disc to the fossa and/or eminence. This also may explain the immediate release of the disc following arthrocentesis.[17]

In contrast to hypomobility caused by disc interference or muscle contraction is the chronic subluxation or hypermobility that is seen when, because of laxity of the supporting ligaments, the mandibular condyle translates beyond the articular eminence. Subluxation of the condyle will result in a soft or hard click as the condyle passes beyond the articular eminence at maximum opening. This is accompanied by unilateral or bilateral deflective movements at the end of the opening range. The joint sound associated with a subluxation should not be confused with that of a disc interference disorder (Figure 36-14).

Aside from mechanical dysfunction of the TMJ, inflammation that may accompany abnormal joint mechanics may contribute to the patient's discomfort. Intracapsular swelling from inflammation also may impede joint movement. Inflammation of the joint capsule (capsulitis) or inflammation of the joint lining (synovitis) can result in pain with jaw movement. Intracapsular edema my result in disocclusion of posterior teeth and referred otalgia.

Trauma to the highly innervated and richly vascularized retrodiscal tissue, as might occur with a blow to the jaw that drives the condyle upward and backward, can impart a



• **Figure 36-15** Panoramic view shows mild degenerative changes in the mandibular condylar articulation.

direct trauma to this tissue, resulting in swelling and pain. Pain within the joint may result in secondary muscle splinting or protective guarding of the joints that may cause a more limited mandibular range of motion and pain. Inflammatory mediators within the injured joint may perpetuate pain and dysfunction. Central pain mechanisms may be initiated, resulting in pain referral patterns extending beyond the temporomandibular joints.[18] Synovial fluid may be diminished in quality and/or quantity; this compromises nutrition of the articular surfaces and diminishes protection and lubrication of the joints. Although the quality of synovial fluid within an inflamed joint may be poor, a tendency for excessive synovial fluid formation may result in increased intracapsular pressure, which may lead to further dysfunction and pain.

Evaluation

Regardless of the cause, pain, dysfunctional movements, and sounds during function characterize a TMD. Although trauma may have been the precipitating event leading to the onset of the patient's complaints, other contributing factors may result in lengthier and less productive treatment, if they are not recognized and eliminated. Therefore, the first goal in implementing a well-defined management program is to identify contributing factors. This involves addressing physical, emotional, and psychological factors.

History

A comprehensive evaluation must include a detailed history that reviews the following:

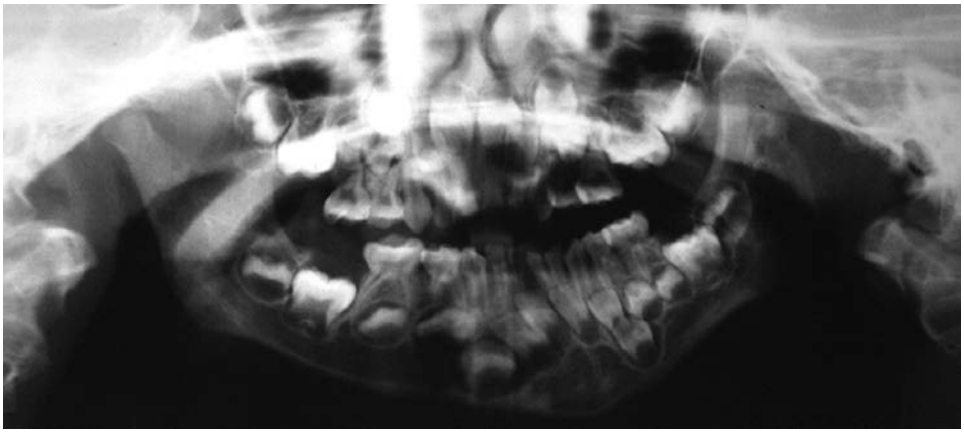
- Chief complaint
- History of the present illness
- Chronology of onset
- Description of any trauma
- Patient's medical and dental histories
- Prior history of joint dysfunction
- Has this individual ever been treated for a similar problem?
- What were the results of that treatment?
- Are any comorbid systemic disorders present?
- Findings of the clinical examination include the following:
  - Evaluation of the muscles of mastication and the supporting muscles of the neck and shoulders
  - Conditions found within the oral cavity that might be contributing to the patient's pain complaints (i.e., an evaluation of the soft tissues, periodontium, and teeth)
  - Myofunctional and/or parafunctional habits
  - Mandibular range of motion measurements
  - Auscultation of the temporomandibular joints during movement
  - Radiologic findings

Diagnostic Imaging

Temporomandibular disorders often involve displacement or dislocation of the interarticular disc and arthritic changes in the bony components of the joint. These alterations from normal anatomy and function may result from various causes, including trauma, degenerative joint processes, developmental anomalies, and neoplasm. It is acceptable to include some form of diagnostic imaging in a temporomandibular joint evaluation to facilitate diagnosis. Various methods of radiologic imaging are available.

Hard Tissue Imaging

The most readily available diagnostic radiograph used in the dental office is the panoramic radiograph. This type of study often is all that is necessary to identify fractures, gross arthritic changes, or hard tissue abnormalities, such as tumors, bone cysts, or malformations (Figures 36-15 and 36-16).



• **Figure 36-16** Condylar aplasia in a 9-year-old child seen on panoramic radiograph.

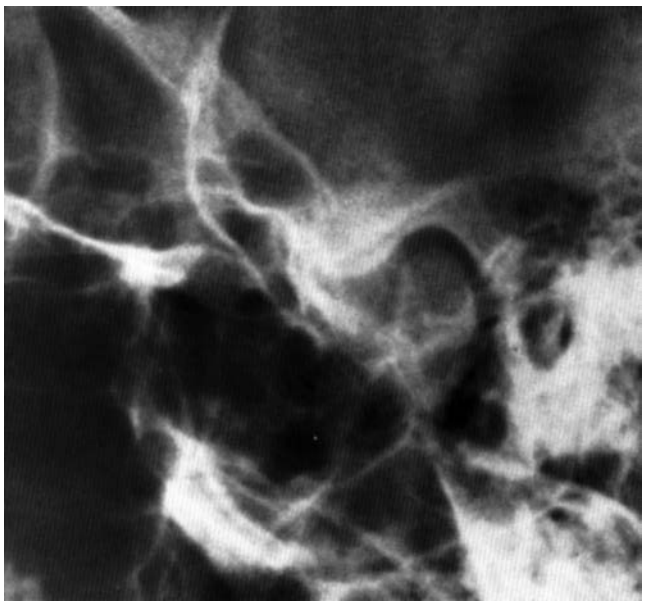
An alternative radiographic study, which is also easily performed in a dental office, is the transcranial view. This study, which uses standard dental x-ray equipment, normally includes views of each condyle in the open, closed, and rest positions. Transcranial radiographs provide information concerning the contours of bony elements. Transcranial radiographs often are inappropriately used to determine condylar position in the fossa—a determination that is not possible with this type of study. As with the panoramic radiograph, transcranial radiographs may be useful in ruling out gross arthritic changes, as well as fractures. Although greater detail is offered on transcranial radiographs, the information provided is similar to that seen on the panoramic radiograph (Figure 36-17).

Tomography offers an evaluation of the osseous structures (Figure 36-18). It is a more accurate study in that it can focus on planes ("cuts") that are only several millimeters thick. This ability enables a tomographic study to evaluate a temporomandibular joint similarly to a loaf of bread, that is, to evaluate one slice at a time. Greater detail of the articular surfaces is rendered. More accurate information regarding condylar displacement and arthritic changes also may be attained.

Cone-beam computed tomography (CBCT) provides superior reliability and greater accuracy than standard tomography and TMJ panoramic projections in the detection of condylar cortical erosion.[19] Although earlier studies reported that CBCT had not been shown to offer significant differences in diagnostic accuracy from that available with conventional tomograms,[20] enhanced osseous detail is obtained with the use of three-dimensional CT (Figure 36-19). In a study comparing imaging from patients diagnosed with osteoarthritis or closed lock of the TMJ to records of non-TMD patients, there were significant correlations between CBCT findings and a clinical diagnosis of TMD.[21]

Soft Tissue Imaging

Although transcranial, tomographic, and cone-beam studies are acceptable for evaluating hard tissues of the temporomandibular joints, they do not demonstrate the

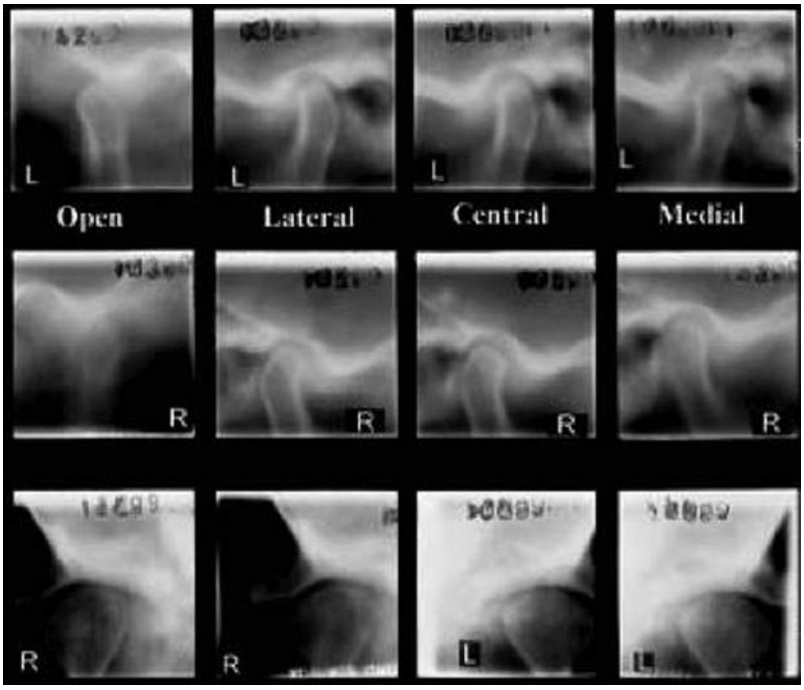


• **Figure 36-17** Transcranial view of the temporomandibular joint, demonstrating normal bony configuration.

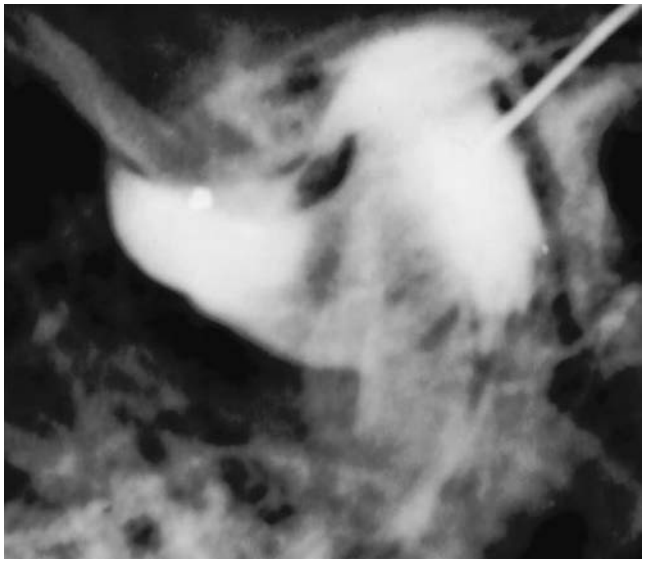
interarticular disc. Various imaging techniques may be used to determine the position of the disc. Arthrography is an excellent method of imaging disc position. This test has been replaced by MRI and is now rarely used, but is of historic value. It is performed by injecting a small amount of radiopaque material into the inferior and/or superior joint compartment. The radiopaque solution

this type of radiographic study include the following: (1) It is often painful for the patient, (2) it requires a great degree of expertise on the part of the radiologist, and (3) it exposes the patient to a significant amount of radiation.

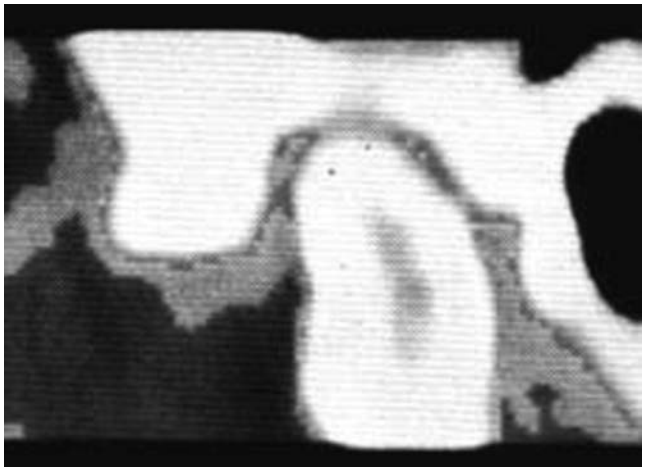
Noninvasive imaging studies include CT scan and MRI. Computed axial tomography has the capacity to image not only the hard, bony tissues but soft tissues as well. Through computer analysis of the x-ray signal, soft tissues



• **Figure 36-18** Tomographic study of a normal temporomandibular joint. Assessment of bony architecture and condyle/fossa relationship is possible on tomographic cuts. Lateral, central, and medial refer to the depth of the cut in each example.



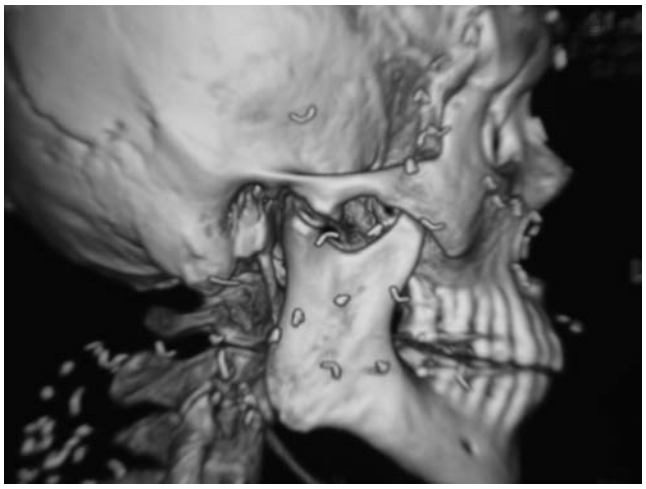
• **Figure 36-19** Radiopaque material injected into the inferior joint space permeates into the superior joint space during an arthrography demonstrating discal perforation.



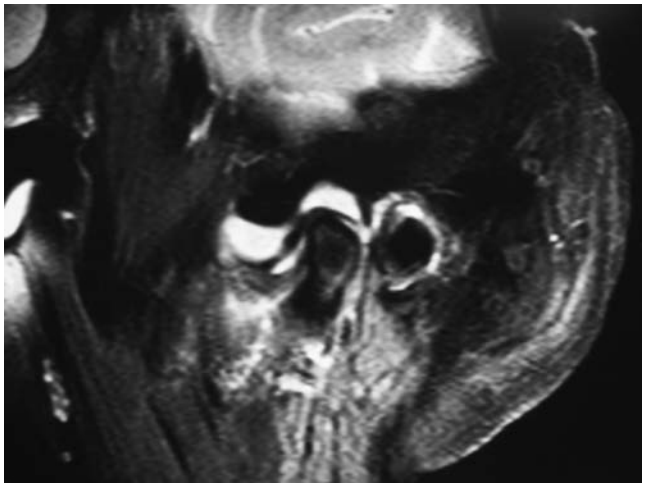
• **Figure 36-20** Computed axial tomography shows anterior disc displacement.

such as the temporomandibular joint disc can be visualized (Figure 36-21). This procedure has proved fairly accurate in its depiction of discal position, although the image often lacks detail. On the negative side is the fact that with this test, as with arthrography, the patient is exposed to substantial radiation.

MRI represents the current gold standard for soft tissue diagnostic imaging technology. It does not use radiation; the image is produced through computer analysis of signals emitted by the oscillation of molecules of water contained within bodily tissues. These signals are produced by placing the patient into a strong magnetic field. MRI is quite effective. The detail of soft tissues revealed by an MRI study is often quite remarkable. Not only can MRI allow visualization of the TMJ interarticular disc, often in more detail than former studies, it also can reveal scar tissue and inflammation (Figure 36-22). In addition, the muscles of mastication can be imaged. No side effects or radiation are associated with MRI. The study is noninvasive and provides a maximum amount of information with the smallest risk.[22-24] The patient experiences no discomfort. A drawback is the cost of this study. Also,



• **Figure 36-21** Three-dimensional computed axial tomography shows degenerative changes in the right condyle and fossa.



• **Figure 36-22** Nonreducing anterior disc displacement seen on T2-weighted magnetic resonance imaging during condylar translation. Note effusion in upper and lower joint spaces.

patients with claustrophobia may have difficulty with the MRI technique, but this has been overcome by the innovation of open MRI.

In cases in which it is necessary to determine the position of a suspected displaced disc, or when confirmation of intracapsular adhesions is necessary, CT or MRI studies may be considered appropriate. Conversely, these imaging studies should not be done routinely for every patient or as initial diagnostic tests. Although panoramic radiographs, transcranial studies, or tomographic images may be considered acceptable initial diagnostic tests, the use of more sophisticated imaging studies should be restricted to those cases for which they are indicated.

Adjunctive Diagnostic Testing

Numerous diagnostic aids may be employed in the evaluation of a TMD. These include movement and sound recording devices, as well as those that monitor muscle activity. Because the diagnosis of a TMD is best made via a meticulous history and clinical evaluation, the use of adjunctive testing devices is not discussed here. Suffice it to say that any adjunctive testing should be secondary to a well-taken history and thorough clinical examination. Adjunctive tests should be used judiciously, and the type of adjunctive diagnostic testing employed should be individualized for the specific patient's need. Consideration of their use depends on the potential for adding significant information to determine a diagnosis or formulate a treatment plan, as well as the cost effectiveness of the test.

• Box 36-1 A Screening Questionnaire for Temporomandibular Disorders

Do you have difficulty, pain, or both when opening your mouth, for instance, when yawning?	Yes ☐ No ☐
Does your jaw "get stuck," "lock," or "go out"?	Yes ☐ No ☐
Do you have difficulty, pain, or both when chewing, talking, or using your jaws?	Yes ☐ No ☐
Are you aware of noises in the jaw joints?	Yes ☐ No ☐
Do your jaws regularly feel stiff, tight, or tired?	Yes ☐ No ☐
Do you have pain in or about the ears, temples, or cheeks?	Yes ☐ No ☐
Do you have frequent headaches, neck aches, or toothaches?	Yes ☐ No ☐
Have you had a recent injury to your head, neck, or jaw?	Yes ☐ No ☐
Have you been aware of any recent changes in your bite?	Yes ☐ No ☐
Have you been previously treated for unexplained facial pain or a jaw joint problem?	Yes ☐ No ☐

From de Leeuw JR, Klasser G, editors: *Orofacial pain: guidelines for assessment, diagnosis and management*, Chicago, 2013, Quintessence.

Assessment of Orofacial Pain Disorders

Because musculoskeletal disorders are the most common sources of orofacial pain, all patients should be screened for TMD and other orofacial pain disorders during a general dental examination. A brief review of the history and use of a screening questionnaire and examination may lead to the diagnosis of a variety of musculoskeletal disorders. The need for a comprehensive history and clinical examination will depend on positive findings and their clinical significance. One option for a screening questionnaire is shown in Box 36-1, and a second option for screening is shown in Box 36-2. Any single positive finding may be enough to prompt a comprehensive examination.

• Box 36-2 TMD—Pain Screener

1. In the last 30 days, how long did any pain last in your jaw or temple area on either side?
   a. No pain
   b. Pain comes and goes
   c. Pain is always present
2. In the last 30 days, have you had pain or stiffness in your jaw on awakening?
   a. No
   b. Yes
3. In the last 30 days, did the following activities change any pain (that is, make it better or make it worse) in your jaw or temple area on either side?
   A. Chewing hard or tough food
      a. No
      b. Yes
   B. Opening your mouth or moving your jaw forward or to the side
      a. No
      b. Yes
   C. Jaw habits such as holding teeth together, clenching, grinding, or chewing gum
      a. No
      b. Yes
   D. Other jaw activities such as talking, kissing, or yawning
      a. No
      b. Yes

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• Box 36-3 Recommended Screening Examination Procedures for Temporomandibular Disorder

- Measure range of motion of the mandible on opening, right, and left lateral movement. (Note any uncoordinated movements.)
- Palpate for preauricular temporomandibular joint (TMJ) tenderness.
- Auscultate and/or palpate for TMJ sounds (i.e., clicking or crepitus).
- Palpate for tenderness in the masseter and temporalis muscles.
- Note excessive occlusal wear, excessive tooth mobility, buccal mucosal ridging, or lateral tongue scalloping.
- Inspect symmetry and alignment of the face, jaws, and dental arches.

From de Leeuw JR, Klasser G, editors: *Orofacial pain: guidelines for assessment, diagnosis and management*, Chicago, 2013, Quintessence, p 26.

The screening examination should include the information in Box 36-3.

TMJ Evaluation

Minimal requirements for the examination of the TMJ include the following:

- Measurement of mandibular range of motion
- Evaluation of mandibular gait
- Auscultation
- Palpation

A description of these examination techniques follows; however, there is a tendency to focus on symptoms and chief complaints, passing over often important steps in the examination and diagnostic process. This can only be avoided by following an examination outline in order to ensure that all etiologic possibilities are assessed. Inconsistent data reporting has been mentioned as problematic when attempting to review the literature. The same may hold true for the examination; inconsistent evaluation of patients may be problematic for attempting to arrive at a diagnosis. Carefully following examination instruments such as the DC/TMD may play an important role in a systematic documentation of symptoms and clinical findings as well as a means by which to monitor a patient's progress.

Clinical observation and the use of a millimeter ruler is the most common method for assessing the mandibular range of motion and gait. Stethoscopic auscultation is the most common technique for detecting joint sounds, although more sophisticated "listening" devices are available.

Range of Motion

As previously noted, the normal mandibular range of motion is generally accepted as 40 to 55 mm,[25-27] but this varies extensively with stature, gender, craniofacial form, and other factors.[28,29] A limited mandibular range of motion, or hypomobility, can result from intracapsular or fibrosis, fracture, ankylosis, and tumor. Extracapsular disorders that limit range of motion include muscle dysfunction, especially dysfunction of muscles involved in mandibular elevation, hypertrophy of the coronoid processes, fractures, and capsular scarring.

Hypermobility with translation of the mandibular condyle beyond the articular eminence may or may not represent a clinical disturbance. Radiographic correlation for clinically evident hypermobility or hypomobility is helpful and is assessed by the relationship of the translated condyle to the crest of the articular eminence.

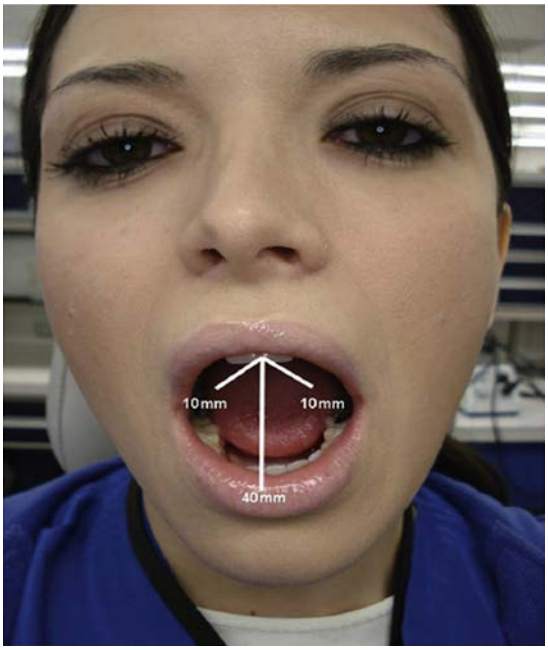
Mandibular range of motion is the measurement of vertical and sagittal opening and lateral movements of the mandible. Three vertical opening measurements are suggested: (1) maximum comfortable opening, (2) full, unassisted opening, and (3) assisted opening.[30] Several techniques and aids for assessing mandibular range of motion are available, ranging from a millimeter ruler to elaborate electrodiagnostic measuring systems.

Maximum comfortable opening is assessed by asking the patient to open the mouth within a comfortable range. The distance between the maxillary and mandibular incisors, that is, the interincisal distance, is measured.[22] Adding overlap to the measurement is suggested. In the edentulous patient, measurement from the crest

of the alveolar ridge is suggested, noting the absence of dentition.

A full, unassisted range of motion is attained by asking the patient to open the mouth as widely as possible regardless of pain. This is called the active range of motion (AROM).

Assisted opening is assessed by asking the patient to open as widely as possible. The clinician then applies gentle, steady force to determine whether further opening is possible. This measurement, also referred to as passive range of motion (PROM), demonstrates the joint "end feel." To test end feel, light force is applied in an attempt to depress the



• **Figure 36-23** The normal opening-to-lateral movement ratio is typically 4:1. Opening should be smooth, pain free, and coordinated, and with an absence of joint sounds.

poor reliability and is difficult to interpret.[23,24]

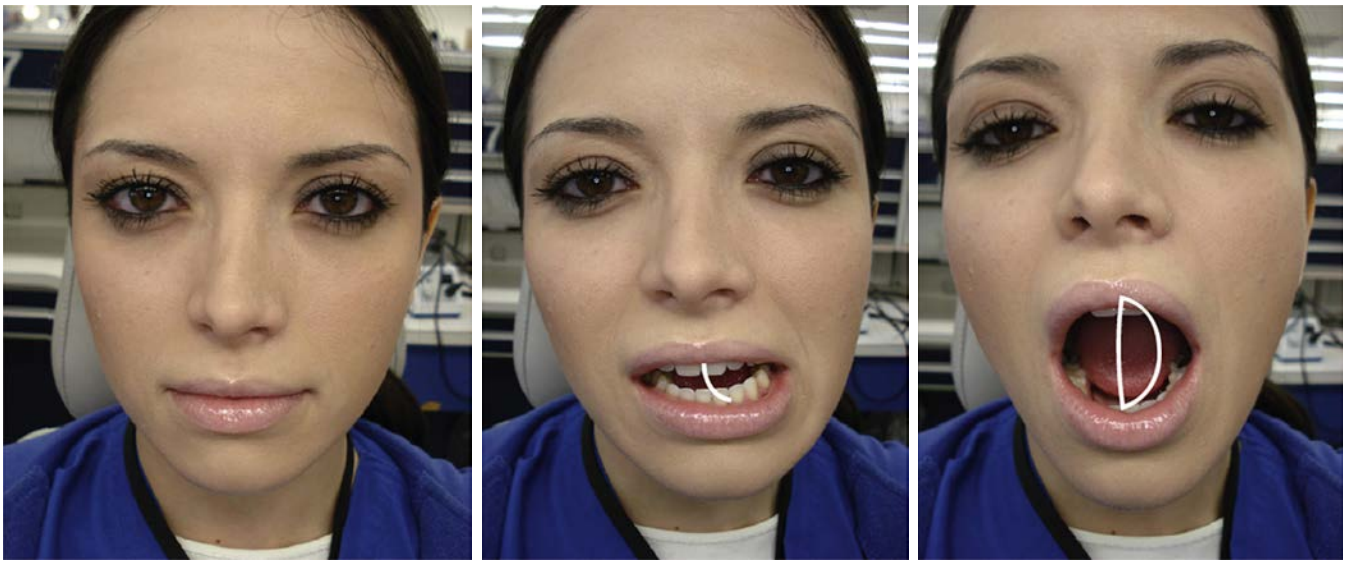
The location of pain provoked when AROM and PROM are tested should be noted. Although this is a reliable sign,[25] the patient's perception of reduced movement, or change in movement, may be more useful than actual measurements.[26]

Gait

Gait is the pattern, direction, and quality of mandibular movements. Abnormal mandibular gait arises from intracapsular and extracapsular disorders. The presence and time of occurrence (early, middle, or late opening and/or closing) of clicking, crepitus, or interference with jaw movement should be documented.[27] Normal opening should be smooth, coordinated, sound and pain free (Figure 36-23). Abnormal or uncoordinated movements are easily observed clinically (Figure 36-24).

Assessment of the opening gait can aid in determining the status of temporomandibular joint biomechanics. The following section is adapted from *A Clinical Outline of Temporomandibular Joint Diagnosis and Treatment,* dated, the observations of Drs. Farrar and McCarty are still relevant.

When the opening-to-lateral movement ratio is observed, 4:1 is considered within normal limits. This would indicate



• **Figure 36-24** Example of deflection of mandibular movement during opening. The mandible deflects to the left, consistent with a left disc interference disorder, preventing normal condylar translation. After reduction of the disc, the condyle is free to translate, and the mandible returns to the midline.

that an opening of 40 mm should be accompanied by lateral movements of 10 mm (Figure 36-25).

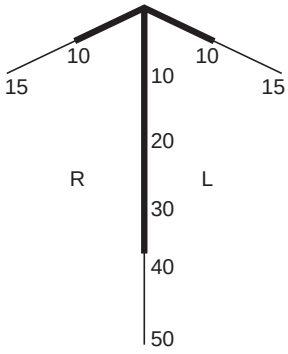
Disc interference disorders often result in a deflection to the affected side during movement with a return to the midline if the disc reduces to a normal or noninterfering position during translation (Figure 36-26). After reduction (the opening click), lateral movements are normal, that is, the 4:1 ratio. The diagram represents disc displacement with reduction of the right TMJ and normal opening that follows a click or disc reduction at approximately 10 mm of opening.

Disc dislocation without reduction that impairs normal translation will result in a lack of lateral movement away from the affected side and a deviation toward the locked joint. Figure 36-27 represents an anterior disc displacement of the left joint that prevents normal translation of that side. Lateral movement away from the locked joint is not possible, and during opening, the mandible deviates toward the locked joint. Note that the sagittal opening is limited to approximately half of the normal opening range, consistent with rotational (hinge) movement only.

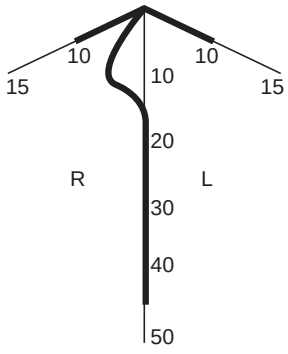
As a disc dislocation becomes more chronic, the opening-to-lateral movement ratio may increase. The opening range may even approach normal, but a deviated opening may still be observed (Figure 36-28).

As a chronic lock enters later stages, the mandibular range of motion may once again approach normal, reassuming the 4:1 opening-to-lateral movement ratio. At this point, the joint or joints may have gone through various adaptive changes, which may be demonstrated on soft tissue imaging.

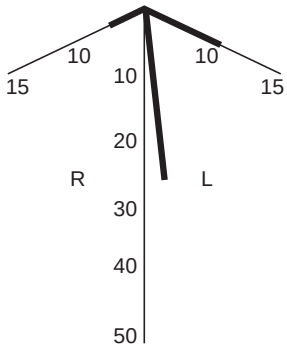
A subluxation occurs when the mandibular condyle translates beyond the crest of the articular eminence. This is considered a hypermobility disorder and may be associated with joint sounds similar to those of a disc interference disorder. As shown in Figures 36-29 and 36-30, this is characterized by unilateral or bilateral deflection of mandibular movement at the end of the opening range.



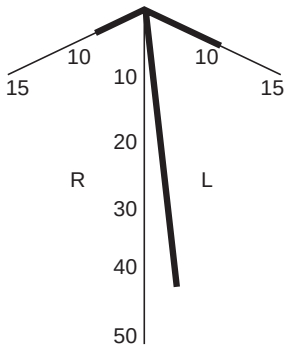
• **Figure 36-25** Normal opening-to-lateral excursion ratio. In this illustration, 40 mm of opening and bilateral movement of 10 mm, or a 4:1 ratio, is considered normal. The opening range and lateral movements may vary with the patient's stature, but the 4:1 ratio should remain.



• **Figure 36-26** Early disc interference. The opening gait in this case demonstrates a sharp, early deflection to the right, followed by a return to midline. Opening beyond that point is seen along the midline. The opening-to-lateral movement ratio is normal, but the deflection with return to midline at the same moment as a click of the right temporomandibular joint is consistent with anterior disc displacement with reduction.

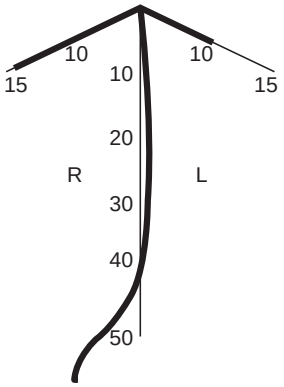


• **Figure 36-27** Nonreducing disc displacement. This illustration maps jaw movement that is limited in opening to approximately 25 mm. The mandible deflects to the left at maximum opening. Lateral movement to the left is normal at 10 mm but is limited to 3 to 5 mm to the right. This is consistent with a nonreducing disc displacement of the left temporomandibular joint. The opening is limited by the nonreducing disc, which causes the mandible to deflect to the affected side. Lateral movement is possible to the side of disc displacement but is limited to the opposite right side because of limited left condylar translation, which prevents movement away from the disc displacement.

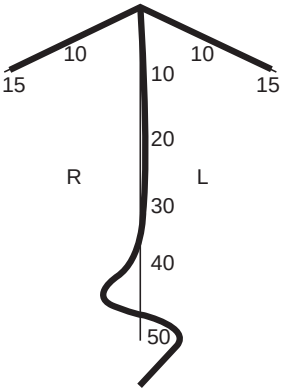


• **Figure 36-28** Chronic anterior disc displacement. If the condition of acute, nonreducing anterior disc displacement seen in Figure 36-27 persists, it may enter a phase of chronic anterior disc displacement without reduction. As the retrodiscal tissues and capsular and collateral ligaments become permanently stretched and the interarticular disc becomes deformed, mandibular range of motion may return to a normal opening-to-lateral excursion ratio. Disc interferences, deviations, and deflections of movement and joint sounds consistent with possible degenerative joint changes may be evident.

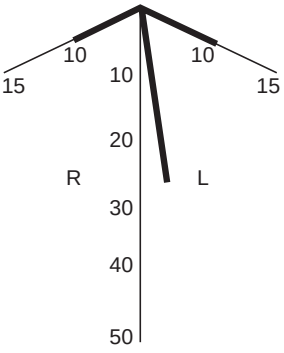
A patient with limited opening and normal lateral movements likely will have an extracapsular source of limited mandibular opening such as muscle dysfunction. In Figure 36-31, the mandibular range of motion demonstrates normal lateral movements and a limited opening with deflection to the left, possibly consistent with left masticatory muscle dysfunction.



• **Figure 36-29** Unilateral subluxation of the left condyle.



• **Figure 36-30** Bilateral subluxation, first left, then right.



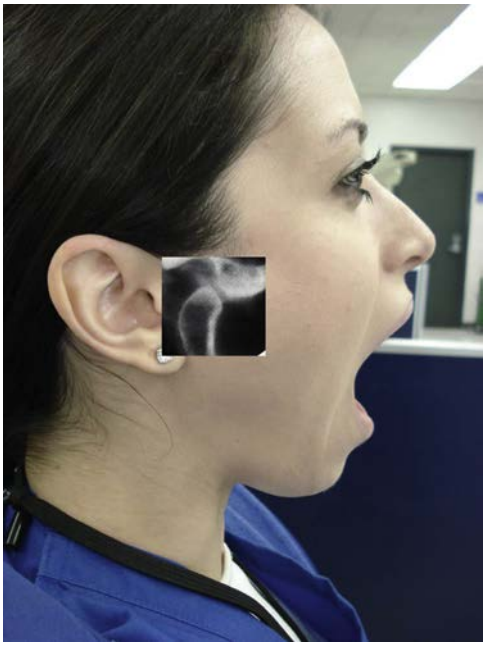
• **Figure 36-31** Muscular restriction of mandibular movement. Another cause of limited mandibular opening is illustrated in this diagram. Lateral movements are normal, but mandibular opening is limited. This opening-to-lateral excursion ratio is 2.5:1, consistent with contracture of jaw elevator muscles. Normal bilateral translation is possible and disc displacement therefore is not likely. Sagittal opening is restricted by mandibular elevator muscle dysfunction.

Auscultation

Intra-articular joint sounds may result from mandibu-



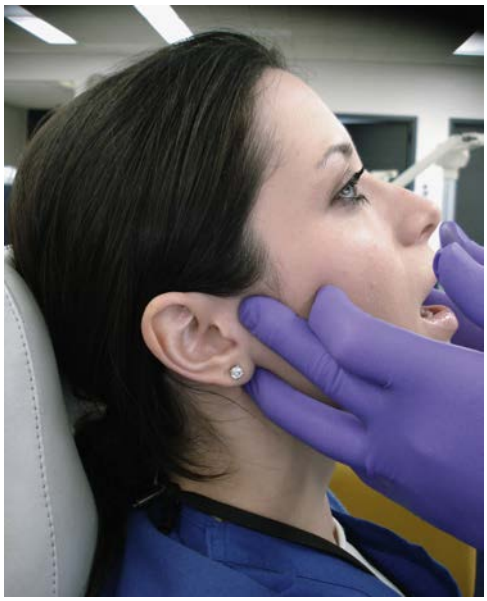
• **Figure 36-32** In the closed mouth position, the condyle is illustrated within the central portion of the temporomandibular joint fossa, behind the posterior slope of the articular eminence. Space for the interarticular disc and retrodiscal tissues is adequate.



• **Figure 36-33** During normal mandibular depression or jaw opening, the condyle rotates on the inferior surface of the interarticular disc. The disc-condyle complex translates forward along the articular eminence. This movement takes place between the posterior slope of the articular eminence and the superior surface of the disc. This illustration shows normal opening with the crest of the condyle approaching the lowest point of the articular eminence.

Sounds may correlate with pain or pathologic function or may be due to functional adaptations not associated with pain or dysfunction. Joint sounds are common among the general population and must be evaluated within the context of other presenting signs and symptoms.[31] Nonpainful joint sounds not associated with impairment of mandibular function do not require treatment.

Auscultation of the temporomandibular joints should discern the presence and timing of early, middle, or late opening and/or closing, clicking, and crepitus, as well as their correlation with interference with jaw movement.

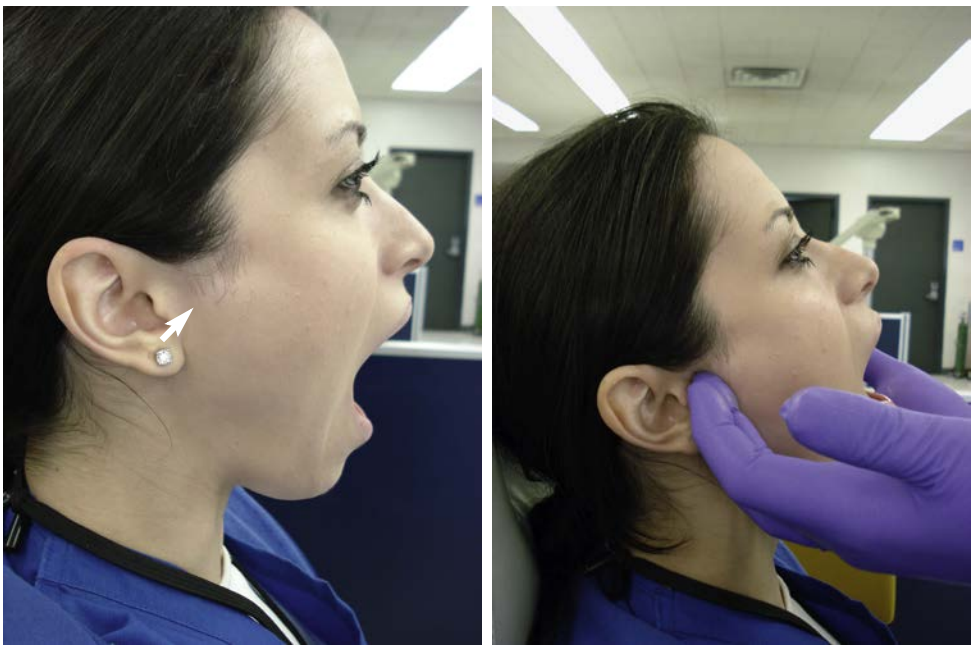


• **Figure 36-34** With the mouth partially open (early translation), palpate the lateral pole to assess capsular tenderness.

Palpation

The temporomandibular joints are palpated bilaterally so that patterns of condylar movement, tenderness, pain, and swelling can be perceived. Temporomandibular joints may be palpated for assessment of tenderness consistent with inflammation of the joint capsule and retrodiscal tissue. Although the predictive value of joint palpation is low in asymptomatic populations,[32,33] positive findings may have clinical significance in symptomatic patients.[34]

During a palpatory examination, movement patterns, tenderness, pain, and swelling are evaluated. The temporomandibular joints should be assessed by direct, gentle palpation of the lateral pole of the condyle (preauricular), as well as the posterior aspect of the condyle in the region of the posterior attachment or retrodiscal tissue (Figures 36-32 through 36-34). Intrameatal palpation achieved by placing the fingers in the external auditory canals and pressing forward during mandibular function may produce artifactual jaw movement and discomfort. The recommended technique has the patient with the mandible in a mild protrusive position and the tip of the index finger gently positioned in the depression formed posterior to the translated condyle. Mild pressure in a forward direction will allow palpation of the posterior-lateral aspect of the condyle and the lateral portion of the retrodiscal tissue (Figure 36-35).



• **Figure 36-35** Full opening (maximum condylar translation) results in the formation of a depression posterior to the translating condyle *(arrow)*. Digital pressure in an anterior direction can be used to assess for posterior capsular pain.

Muscle Evaluation

Local myalgia, myositis, myospasm, muscle contracture, and myofascial pain are conditions that affect all muscles in the body, including the masticatory muscles. These structures must be evaluated for sources of mandibular pain and dysfunction.

The muscles of mastication are palpated bilaterally so that equality of size and firmness can be determined; however, tenderness to palpation is the most important information derived from palpation. The temporalis, deep and superficial masseter, medial pterygoid, and suprahyoid muscles should be examined. Palpation of the lateral pterygoid muscle is difficult in that this muscle is difficult to approach intraorally.[35,36] Evaluation of the lateral pterygoid may be accomplished by functional manipulation and by challenging the muscle to contract against resistance.[37] Myalgia may be exacerbated during this maneuver.

Pressure algometry has been shown to provide reliable measures of muscle and TMJ tenderness[37-39] but is not often used in a clinical setting. Calibration training for finger pressure and site location also can produce reliable data. Palpation pressure for women should be less than that for men[38] and should be adjusted for stature.

Needle electrode electromyography detects abnormal

-

mended. A suggested data collection form for orofacial pain and temporomandibular disorder evaluation is provided in Box 36-4.

Table 36-2 summarizes this text and offers a guide to the most common temporomandibular disorders.

A summary of various stages of disc interference disorders is presented in Figure 36-36.

• Box 36-4 Orofacial Pain and Temporomandibular Disorder Evaluation Form

Patient's Name _____ Date of Examination _____
Review of chief complaints:
1. _____
_____
2. _____
_____
3. _____
_____
Date of onset of symptoms: _____
Chronology of pain onset: _____
Pain location: _____
Pain duration: _____
Pain frequency: _____
Pain quality: _____
Exacerbating factors: _____
Ameliorating factors: _____
Comments:

Facial symmetry: Yes _____ No _____
Comments:

Facial type [by appearance of soft tissues only]:
Class I _____ II _____ III _____
Normal _____ Short _____ Long _____
Ramus height: Equal _____ Unequal _____ (by gross observation)
Note discrepancy in mm: _____
Deviant swallow: Yes _____ No _____
Tongue position and appearance: _____
Parafunctional habits:

_____ Bruxism	_____ Tongue position	Other_____
_____ Clenching	_____ Nail biting	_____
_____ Lip biting	_____ Telephone	_____
_____ Tongue thrust	_____ VDT	_____

Presenting occlusion:
Static occlusion: Normal ___ Malocclusion ___
Mutilated ___ Functional ____
Anterior attrition: None _____ Slight _____ Moderate _____
Severe _____
Posterior facets: None _____ Slight _____ Moderate _____
Severe _____
Freeway space: Within normal limits _____ Minimal _____
Anterior _____ mm; Posterior _____ mm
Loss of vertical dimension: Yes _____ No _____
Anterior _____ Posterior _____
Excessive incisal guidance: Yes _____ No _____
Anterior horizontal overlap: _____%
Anterior vertical overjet: _____ mm
Anterior open bite: Yes _____ No _____
Posterior open bite: Yes _____ No _____ Left _____ Right _____
Anterior cross-bite: Yes _____ No _____
Posterior cross-bite: Yes _____ No _____ Left _____ Right _____
Curve of Spee: Norm ____ Flat _____ Steep _____ Inverted _____
Palatal form: Flat _____ Moderate _____ High _____
Dental midline discrepancy in habitual centric occlusion:
____ Right ____ Left ____ mm
Orthodontic classification:

	R	L
Class I:	_____	_____
Class II—Div 1:	_____	_____
Class II—Div 2:	_____	_____
Class III:	_____	_____

Missing, mobile, or broken down teeth (source of odontogenic pain):
BD = broken down; 1, 2, 3 = mobility; X = missing; N = not replaced; T = tilted; E = extruded; P = possible pain source.

1	2	3	4	4	6	7	8	9	10	11	12	13	14	15	16
32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17

Periodontal status: Excellent _____ Good _____ Fair _____ Poor _____
Hygiene: Excellent _____ Good _____ Fair _____ Poor _____
Temporomandibular joint examination:
Pain upon palpation extrameatally
Lateral pole: _____ Right _____ Left
Posterior capsular area: _____ Right _____ Left
Swelling: _____ Right _____ Left
Auscultation:

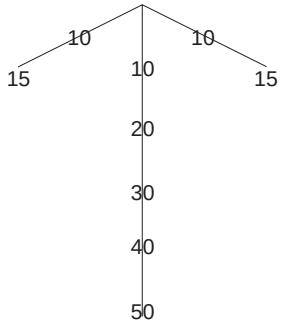
Right opening	Right closing	Left opening	Left closing

• Box 36-4 Orofacial Pain and Temporomandibular Disorder Evaluation Form—cont'd

Rubbing	_____	_____	_____	_____
Clicking	_____ mm	_____ mm	_____ mm	_____ mm
Grating	_____	_____	_____	_____

Functional Analysis

Pattern of mandibular movement:



Widest interincisal opening, including overbite, _____ mm

Deflection at maximum opening:
Left _____ Right _____ _____ mm

Protrusive: _____ mm
Protrusive deviation: Right _____ Left _____ _____ mm

Note pain during mandibular movements with P opening and closing at the point at which it occurs, gait in mm _____

Muscle Evaluation of Head, Neck, and Upper Quarter

0 = no response; 1 = report of discomfort; 2 = facial movement such as palpebral reflex along with a report of pain; 3 = retreat of head in anticipation of palpation along with a report of considerable pain on contact. Note referral patterns under remarks. Note trigger points as "TP" under remarks.

TENDERNESS TO PALPATION										REMARKS
Temporalis										
Anterior	Right	0	1	2	3	Left	0	1	2	3
Middle	Right	0	1	2	3	Left	0	1	2	3
Posterior	Right	0	1	2	3	Left	0	1	2	3
Masseter										
Superficial	Right	0	1	2	3	Left	0	1	2	3
Deep	Right	0	1	2	3	Left	0	1	2	3
Coronoid process	Right	0	1	2	3	Left	0	1	2	3
Lateral pterygoid	Right	0	1	2	3	Left	0	1	2	3
Medial pterygoid	Right	0	1	2	3	Left	0	1	2	3
Digastric anterior belly	Right	0	1	2	3	Left	0	1	2	3
Suprahyoids	Right	0	1	2	3	Left	0	1	2	3
Infrahyoids	Right	0	1	2	3	Left	0	1	2	3
Sternocleidomastoid										
Superior	Right	0	1	2	3	Left	0	1	2	3
Body	Right	0	1	2	3	Left	0	1	2	3
Sternal head	Right	0	1	2	3	Left	0	1	2	3
Clavicular head	Right	0	1	2	3	Left	0	1	2	3
Mastoid process	Right	0	1	2	3	Left	0	1	2	3
Scalene										
Anterior	Right	0	1	2	3	Left	0	1	2	3
Middle	Right	0	1	2	3	Left	0	1	2	3
Trapezius										
Neck	Right	0	1	2	3	Left	0	1	2	3
Shoulders	Right	0	1	2	3	Left	0	1	2	3
Splenius/ Rectus capitis	Right	0	1	2	3	Left	0	1	2	3
Levator scapulae	Right	0	1	2	3	Left	0	1	2	3

Diagnostic Tests

- Stretch and spray
- Manipulation
- Diagnostic analgesic block
- Reposition (wax bite)
- Muscle provocation
  - Opening resistance
  - Closing resistance
  - Protruding against resistance
  - Clenching on teeth
  - Clenching on tongue blade
  - Loading of joint via manipulation
  - Cervical manipulation, compression, or traction

Radiographic Findings

Type of film reviewed:
panoramic radiograph _____ transcranial _____ tomography _____ MRI _____ other _____
Within normal limits: _____
Loss of joint space: _____ Right _____ Left
How determined: _____
Condylar displacement:
Right: _____ Superior _____ Posterior _____ Anterior
Left: _____ Superior _____ Posterior _____ Anterior
How determined: _____
Degenerative changes:
Other:

Recommendation for Additional Studies:

Diagnosis:

Treatment Plan:

Referral to Other Medical Specialties:

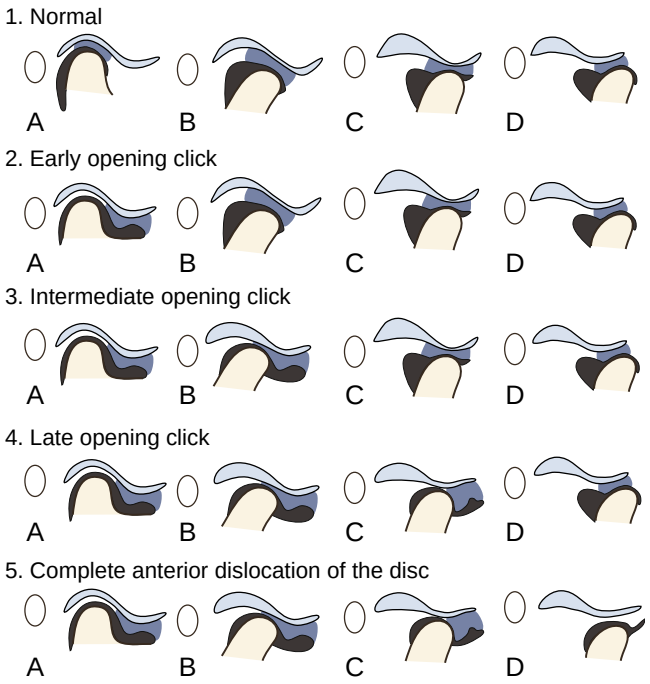
TABLE 36-2 A Simplified Summary for a Diagnostic Approach to Temporomandibular Disorders

Differential Diagnosis	Diagnostic Tests
Congenital or Developmental Disorders	
• Aplasia • Hypoplasia • Hyperplasia • Acquired disorders • Neoplasia	Imaging • Panoramic radiograph • Transcranial • Tomographic
Disc Derangement Disorders	
• Disc displacement with reduction • Disc displacement without reduction • F0B7 Temporomandibular joint dislocation	Physical examination • Range-of-motion studies • Gait of movement • Auscultation • Imaging • Magnetic resonance imaging (MRI)—T1
Inflammatory Disorders	
• Capsulitis/Synovitis • Polyarthritides	History • Trauma • Systemic illness • Physical examination • Joint palpation • Gait of movement • Alteration of occlusion due to retrodiscal swelling • Imaging • MRI—T1 and T2 • Serology • Erythrocyte sedimentation rate (ESR) • C-reactive protein
Polyarthritides	History • Systemic illness • Physical examination • Joint palpation • Gait of movement • Alteration of occlusion due to retrodiscal swelling • Imaging • MRI—T1/T2 • Serology • ESR • C-reactive protein • Rheumatoid panel
Osteoarthritis (Noninflammatory Disorders)	
• Osteoarthritis: primary • Osteoarthritis: secondary • Ankylosis • Fracture (condylar process)	History • Trauma • Systemic illness • Physical examination • Joint palpation • Gait of movement • Alteration of occlusion due to retrodiscal swelling • Imaging • Panoramic radiograph • Transcranial • Tomographic
Masticatory Muscle Disorders	

Myofascial pain	History
	• Regional pain
	• Muscle weakness
	• Fatigue of muscles
	• Limited active range of motion
	• Physical examination
	• Palpation
	  • Myofascial trigger points
	  • Referral patterns
	  • Positive for diagnostic anesthetic block

Myositis	History
	• Local pain
	• Trauma
	• Infection
	• Physical examination
	• Palpation
	  • Local tenderness
	  • Swelling

Myospasm	History • Muscle contraction from which the patient cannot voluntarily relax • Physical examination • Restricted range of motion • May be painful to palpation • Needle electrode electromyography (EMG)
	History • Local pain • Physical examination • Palpation • Local tenderness
Myofibrotic contracture	History • Muscle contraction from which the patient cannot voluntarily relax • Physical examination • Restricted range of motion • May be painful to palpation • Needle electrode EMG
Neoplasia	Imaging • Panoramic radiograph • Transcranial • Tomographic • Computed tomography • MRI



the temporomandibular disc and condyle. These derangements cause the common symptoms of reciprocal clicking and locking. **A,** Closed. **B,** Partial translation. **C** and **D,** Full opening. (Adapted from Farrar W, McCarty WL Jr: *A clinical outline of temporomandibular joint diagnosis and treatment*, Montgomery, AL, 1982, Normandie Press.)

Summary

Dysfunction of the temporomandibular joints and associated structures can be a source of acute and chronic orofacial pain and masticatory dysfunction. Successful treatment depends on an accurate assessment of these disorders. Therefore, the treatment plan must be based on a comprehensive evaluation and accurate diagnosis.

Disorders that may affect the TMJ are similar to those involving other synovial joints; therefore, treatment of patients with TMD should be consistent with that provided to patients with any other musculoskeletal disorder. A clear understanding of the anatomy, biomechanics, and pathologic processes that may afflict the TMJ is necessary if an acceptable course of treatment is to be determined.

An organized approach to the assessment of orofacial pain and of patients with TMD, as well as an accurate diagnosis, is essential. This chapter is intended to provide some basic tools that can be used in assessment of the patient with TMD.

Acknowledgment

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37

Imaging of the Temporomandibular Joint

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The temporomandibular joint (TMJ) has a complex joint architecture comprising the mandibular condyle, temporal bone, and an articular disc. This hard and soft tissue combination has a unique joint orchestra that makes it very difficult to image. Clinical examination alone cannot provide a complete picture of the multitude of challenges associated with the joint. Imaging plays a critical role in the diagnosis, treatment planning, and outcomes assessment associated with the joint. Conventional imaging of the joint with two-dimensional (2D) imaging offers limited information regarding the joint. Advancements in image capture technology and evolution of postprocessing image algorithms are changing the way the TMJ is being imaged and evaluated. Significant developments in imaging technology and evolution of faster acquisition techniques that reduce motion artifacts have paved the way to a more holistic imaging approach. The radiation dose associated with ionizing radiation is a perennial challenge, but good clinical practice strikes a balance between dose and diagnostic-quality images. Various techniques have been described in the literature with specific indications and contraindications.[1] The evolution of lower-dose, three-dimensional (3D) imaging modalities such as cone-beam computed tomography (CBCT) and the ability to modify the acquisition protocols have brought a paradigm shift in the radiographic analyses of the osseous components of the joint.[2,3]

The scope of TMJ disorders includes myofascial pain

of

comprehensive history and clinical exam and a 2D screening exam such as a panoramic radiograph will allow for task-specific evaluation and guide the clinician in choosing the appropriate advanced imaging modality, when indicated, to further evaluate the joint complex.

This chapter provides an overview of existing imaging modalities and their indications and contraindications.

Conventional Imaging

Conventional radiography is the most common 2D imaging modality used to examine the TMJ. It serves as a cost-effective, low-dose diagnostic tool that provides an overview of the joint and is easily accessible to the practitioner. Various projections are used to view specific areas of the TMJ. The objective is to obtain nondistorted, possibly superimposition-free diagnostic radiographs with clear visibility of anatomic detail. With the ubiquitous availability of 3D imaging, the use of 2D imaging is declining, but it is important to appreciate the value of these projections and their use. Routine projections include transcranial, transmaxillary, panoramic, pseudo-tomographic, lateral oblique, submentovertex (basal), and reverse Towne views. A combination of these projections is typically used to evaluate the joint based on clinical symptoms. In addition, conventional linear or multidirectional tomography may be used for sectional imaging of the TMJ.

Film-based imaging continues to be routinely employed in clinical practice. However, the benefits of digital imaging have resulted in an exponential increase in the use of this technology. Many imaging options are available now; their use is facilitated by faster and more efficient digital sensors with higher quantum efficiency, which enables direct or indirect capture of images.[5] The most commonly used technological devices include solid-state sensors such as charge-coupled device (CCD)-based units, complementary metal oxide semiconductor (CMOS)-based units, and others such as photostimulable phosphor (PSP)-based sensors that are widely used in high-volume settings such as a hospitals and trauma centers. Advantages of using digital imaging include reduced doses in



• **Figure 37-1** Transcranial view: Note the superimposition of overlying anatomy on the temporomandibular joint. Only one joint can be imaged at a time. The series shows the position of the condyle during mouth opening. The *arrows* are pointing to the condyle position in relation to the eminence in closed, open, and widely open views.

comparison with earlier-generation film-screen systems; the ability to process images to tease out the signal of interest (postprocessing) without having to re-expose the patient for possible retakes; the ability to transmit, archive, and retrieve images efficiently and in a timely manner with no change in image quality; and the ability to synthesize or reformat images in other planes with the use of image processing algorithms. Such processing and synthesis of 3D volumes are not possible with film-based images unless they are digitized. All advanced imaging modalities use direct-capture electronic sensors.

Conventional imaging modalities are less expensive and more easily accessible than advanced modalities, and they entail lower radiation doses when compared with modalities such as computed tomography (CT). However, image acquisition in two dimensions does not provide a spatial perception of depth. Regional anatomy superimposed on the regions of interest precludes complete evaluation of the TMJ. In addition, image distortion, nonuniform magnification, and the generation of artifacts and other processing errors are potential challenges. Multiple radiographs generally are acquired using differing projection geometry in order to visualize the entire joint and to localize pathology. A single radiograph is seldom diagnostic because the information that is captured is limited to two planes as dictated by the specific projection geometry. The cumulative addition of radiation dose often equals or surpasses the more modern low-dose advanced imaging options such as CBCT.[6]

Transcranial

This method was very popular before the advent of advanced imaging modalities that use low radiation doses, such as CBCT. A transcranial image serves to provide a better view of the lateral aspect of the TMJ than the medial or central portion by virtue of projection geometry. However, most osseous lesions are known to start in this region. Significant superimposition of the mediolateral poles of the condyle occurs in this 2D projection, in addition to other overlying anatomy in the path of the beam as it traverses the skull. Adequate contrast and density are critical for obtaining a diagnostically acceptable image. The lateral portion of the condyle is nearer to the plane of the film and hence appears with relatively greater clarity (Figure 37-1).



• **Figure 37-2** Transmaxillary or transorbital view: Coronal view of the temporomandibular joints. (Courtesy James C. Pettigrew Jr, University of Florida.)

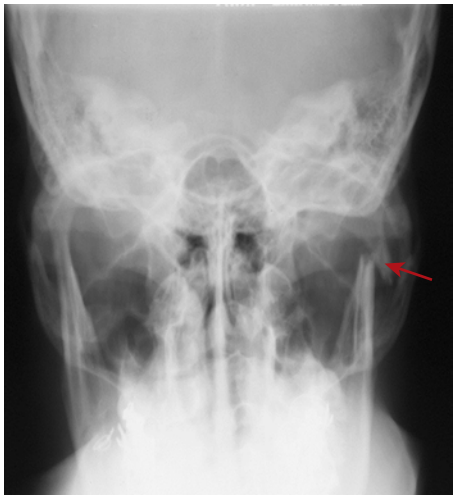
Transmaxillary or Transorbital

In order to better view the medial and central portions of the condyles, it is recommended that an additional coronal view of the TMJ be acquired. This can be achieved with the use of transmaxillary or transorbital projections. Anteroposterior projection geometry places the TMJ closer to the plane of the receptor (Figure 37-2).

Reverse Towne Projection

Another projection that is commonly used to evaluate the condyle is reverse Towne projection, which is a posteroanterior

(PA) projection.[7-9] A PA view is preferred because of the relative proximity of the condyles to the plane of the receptor (film or digital sensor), which results in an image with relatively greater detail. The patient opens the mouth, allowing translation and rotation of the condyle out of the glenoid fossa. This motion may be limited in trauma. However, if obtained accurately, the view facilitates acceptable evaluation of the medial and lateral poles of the condyle without a corrected axis view, but with a good overview of the subcondylar and upper ramal regions to help rule out fractures. Localization of fractures is facilitated because any displacement along the mediolateral axis can be evaluated (Figure 37-3).



• **Figure 37-3** Reverse Towne projection: Open-mouth view enables visualization of the condyles as they translate and rotate out of the glenoid fossa. This view enables bilateral comparison of the two condyles. Note the *arrow* pointing to the left condylar neck fracture.

Submentovertex (SMV) Projection

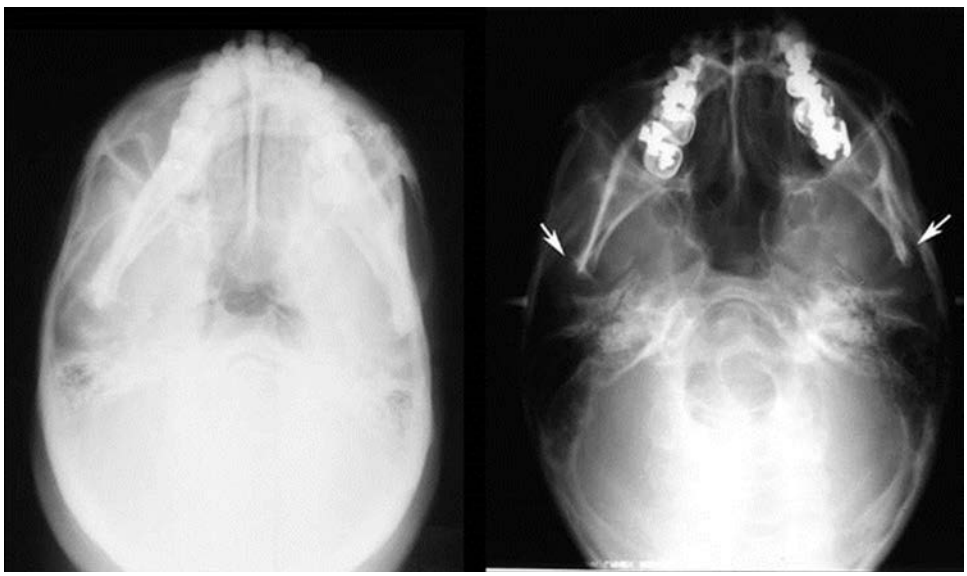
The angulation of the condylar axis with respect to the midsagittal plane can be determined with use of the basal projection, also known as the SMV.[10] The base of the skull is imaged, and the condyles are captured on this projection. However, significant superimposition of the floor of the middle cranial fossa onto the TMJ does not permit a meaningful evaluation. This projection has limited TMJ applications and is most commonly used to acquire corrected-axis tomograms of the TMJ. The mediolateral axes of the condyles are plotted in conventional tomography software to assist with generation of slices parallel to the long axes (Figure 37-4).

Lateral Oblique Views

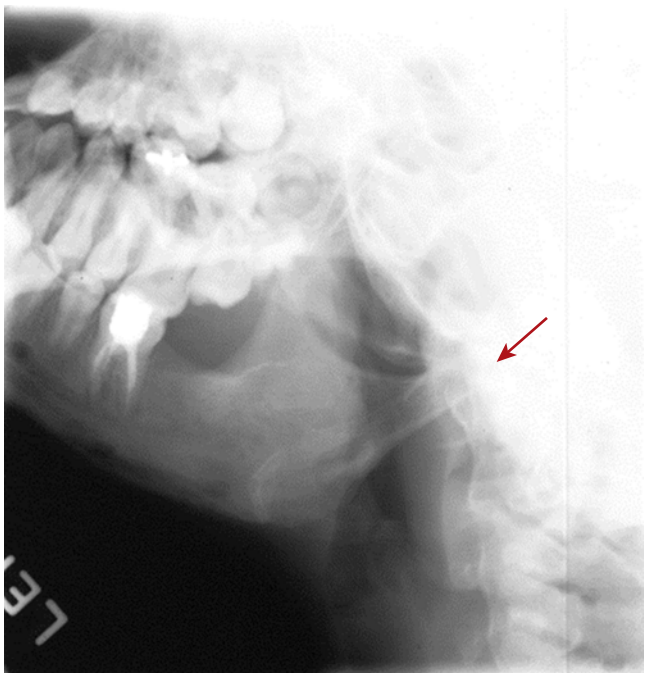
The lateral oblique view of each condyle/ramus, a commonly used projection before the introduction of panoramic radiography, can capture relatively good images of the TMJs, one at a time. In the absence of a panoramic imaging unit, this view provides an excellent option for viewing the condyles and the ramus. The glenoid fossa usually is superimposed by overlying anatomy. The central beam is directed at the midpoint of the ramus (Figure 37-5).

Panoramic Radiography

Panoramic radiographs are used as screening images to evaluate the TMJ. The inherent distortion, magnification, presence of superimposing ghost artifacts, double shadows, and so on prevent a thorough and quantitative examination of the osseous components of the TMJ.[11,12] However, this view allows bilateral visualization of both TMJs, enabling a reasonable comparative evaluation. The patient's position in the focal trough of the panoramic unit, as well as



• **Figure 37-4** Submentovertex view: Also known as the basal view or jug handle view. Enables visualization of the condyles along their mediolateral axis, so the angle with the midsagittal plane can be determined for generation of corrected axis tomograms. *Left* image is showing the right zygomatic arch fracture. The *arrows* are pointing to the zygomatic arches bilaterally.



• **Figure 37-5** Lateral oblique view: Provides an overview of one temporomandibular joint at a time. Superimposition of overlying and transcranial anatomy is a problem. The *arrow* points to the condyle which is superimposed by the transcranial anatomy.

the choice of imaging parameters such as the configuration of the focal trough itself, are of paramount significance in this context to reduce uneven magnification of the areas of interest. Alterations in imaging geometry have been implemented in some panoramic units to limit exposure to the TMJ. Variable magnification of the images in all three axes has been documented to severely impair the ability to make measurements for diagnosis or for treatment planning purposes. Soft tissue components of the TMJ are not captured adequately, and direct visualization of these structures is not possible, as on any other conventional 2D radiographs. Because panoramic radiographs are "Mercator" projections of the area of interest, it is challenging to accurately assess the anatomic area being imaged, but because pantomography has been around for a long time and the focal trough and technique have evolved over time, the depiction of joint anatomy is now well understood.[12]

Modifications of the focal trough, as well as changes in the configuration of motion of panoramic imaging units, have been introduced to generate local views of TMJs, as well as pseudo-tomograms. Pseudo-tomograms are full-thickness images that appear very similar to tomograms. Many modern panoramic units offer various TMJ imaging options, including true linear tomographic capabilities with corrected axis acquisition capabilities. However, these usually are time-consuming procedures that require limited stabilization and positioning devices; in addition, they generate artifacts that may be seen on linear tomography (Figure 37-6).

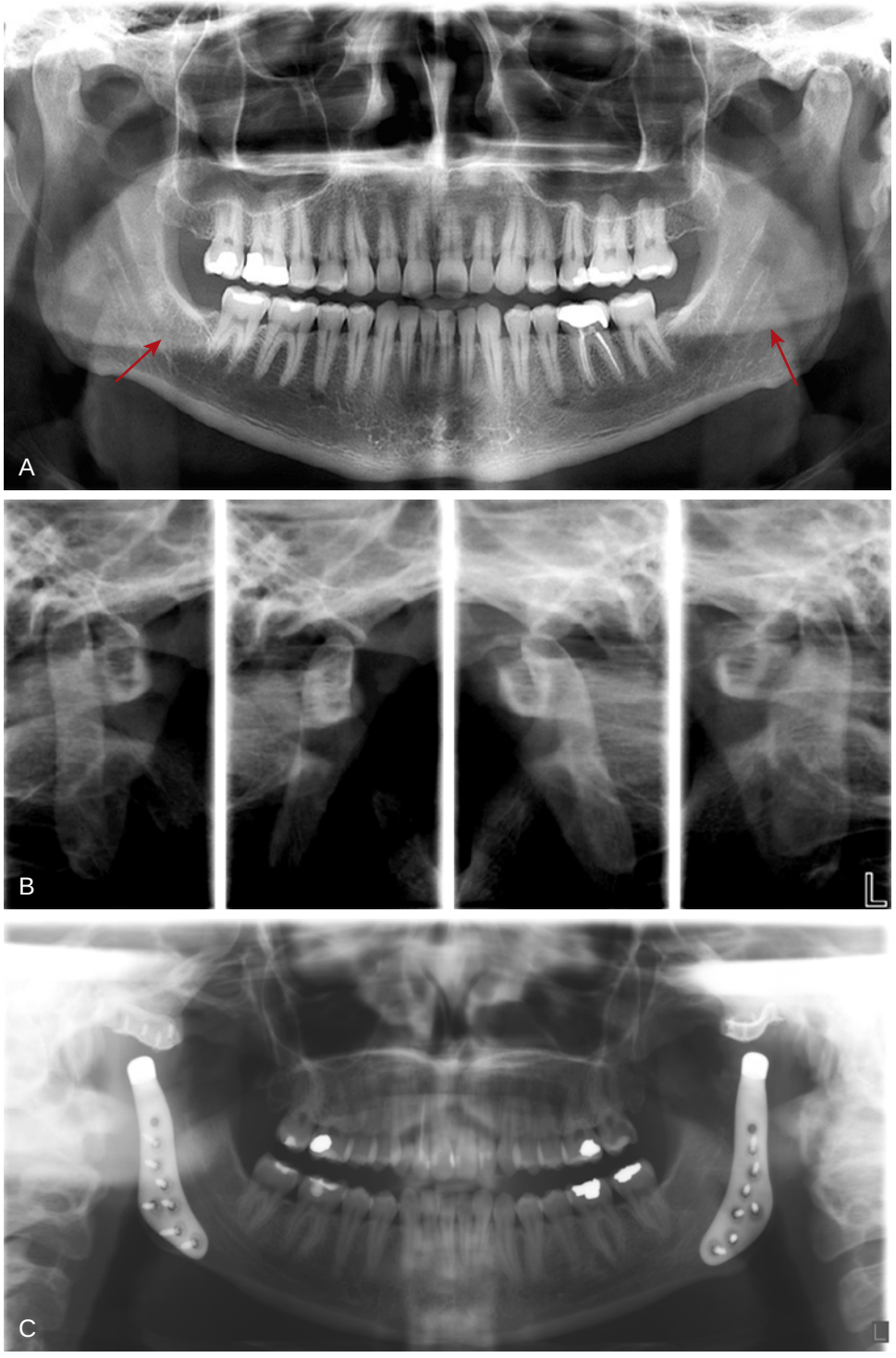
When the clinical examination suggests some form of pathology, panoramic imaging is recommended for initial TMJ screening by the American Academy of Pediatric Dentistry, the American Academy of Orofacial Pain, and the American Academy of Oral and Maxillofacial Radiology.[12] Although panoramic imaging is extensively used in routine clinical practice and is valuable as a screening exam, the coming of multiple field of view (FOV) CBCT machines is changing the imaging approach to TMJ evaluation.

Panoramic imaging is a very good screening imaging modality. With the advent of newer machines with TMJ specific protocols, pseudo-tomogram–like images can be obtained. Significantly less radiation exposure occurs compared to advanced imaging modalities. Major disadvantages of this imaging are altered image geometry and variable magnification in all three axes. Because of the 2D aspect of the imaging, anatomic relationship cannot be evaluated with accuracy. Only osseous components with limited and incomplete depiction of the joint can be evaluated. No soft tissue evaluation can be done.

Conventional Linear and Multidirectional Tomography

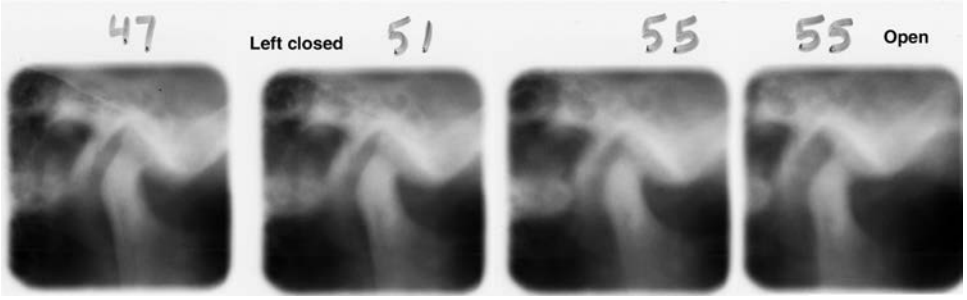
Conventional tomography was extensively used before the advent of CBCT, but the coming of newer 3D imaging modalities has made these methods redundant. Conventional tomography[9-11] is a process by which slices of regions of interest are generated, one at a time, through different types of simultaneous motion of the x-ray source and the receptor (film or digital). Synchronous movement of these two elements about a center of rotation effectively captures a slice of the region of interest placed at this point. Slice thickness varies inversely with the angle circumscribed by the x-ray source during translational or rotational motion. The more complex the motion, the more effective will be the blurring of superimposing anatomy, thus improving visualization detail. However, it should be borne in mind that a decrease in slice thickness beyond a certain value (2-3 mm) will adversely affect contrast as the thickness of imaged tissue lessens. Artifacts are known to degrade image quality in simple motion configurations such as the linear mode. Many panoramic units offer this basic capability for generating linear tomograms. The procedure is very technique sensitive and time consuming, as only one slice is generated at a time. However, it does provide an accurate evaluation of the osseous components of the TMJ. Most panoramic units with true tomographic imaging capabilities offer special positioning devices and programs to correct for the mediolateral angulation of the condylar axis, in order to help generate a true orthogonal view of the anatomy. The condylar angle is assessed with respect to the midsagittal plane with the use of an SMV view that is acquired first.

Multidirectional tomography units use complex motions such as tri-spiral, hypocycloidal, and figure of eight to generate tomographic slices with minimal artifacts and smaller slice thicknesses (Figure 37-7). Computer-driven platforms are used for this purpose. Laser positioning lights and the



• **Figure 37-6** **A,** Panoramic radiograph (sometimes referred to as a Panorex). Note the ghost shadows of the contralateral angle of the mandible on both sides *(arrows)*. Also note the superimposition of overlying anatomy on the temporomandibular joints (TMJs). **B,** Pseudo-tomograms generated from a panoramic unit utilizing a modified acquisition method. **C,** Note the ghost artifacts from bilateral TMJ prostheses. This is a significant problem in patients who have had such surgery. Also C-spine overlap on the anterior portion.

registration of appropriate coordinates in the *x, y,* and *z* axes are possible with such units. This is advantageous for long-term follow-up studies, for which some reproduction of imaging geometry may be required. An SMV may be generated and imported into the software with a flatbed scanner to compute the correction needed to generate orthogonal tomograms. Conventional tomography permits accurate measurement of the regions of interest because magnification is known a priori and stays constant over the entire image.



• **Figure 37-7** Conventional tomograms: Sagittal slices through the temporomandibular joint. Note the condyles in open- and closed-mouth positions.

Advanced Imaging Modalities

Three-dimensional imaging finds numerous applications in diagnostic TMJ imaging, owing to its capability of demonstration.[13,14] Anterior disc displacement is more common and is followed by anterolateral positioning. Disc displacement patterns vary to a large extent, which is very well depicted with magnetic resonance imaging (MRI). Other pathologic entities such as degenerative joint disease, ankylosis, tumors, and developmental anomalies often necessitate 3D imaging. In addition, soft tissue components can be adequately visualized with MRI and the use of appropriate techniques in CT. Advanced imaging modalities provide diagnostic information that also can be quantified to characterize pathology and thus determine the optimal mode of intervention.

CT is also used as a basis for therapeutic options such as patient-fitted total joint replacement. The evolution of better materials and more refined radiographic imaging for preoperative planning has changed the landscape of this procedure. The DICOM data from the scan is used to create an accurate 3D plastic model of the TMJ and associated jaw structures. Stereolithography, CAD-CAM fabrication, or more recently 3D printing technology is used to make a functional 3D model, to best restore the patient to normal joint function. The new joint is created based on this model.[15]

Computed Tomography

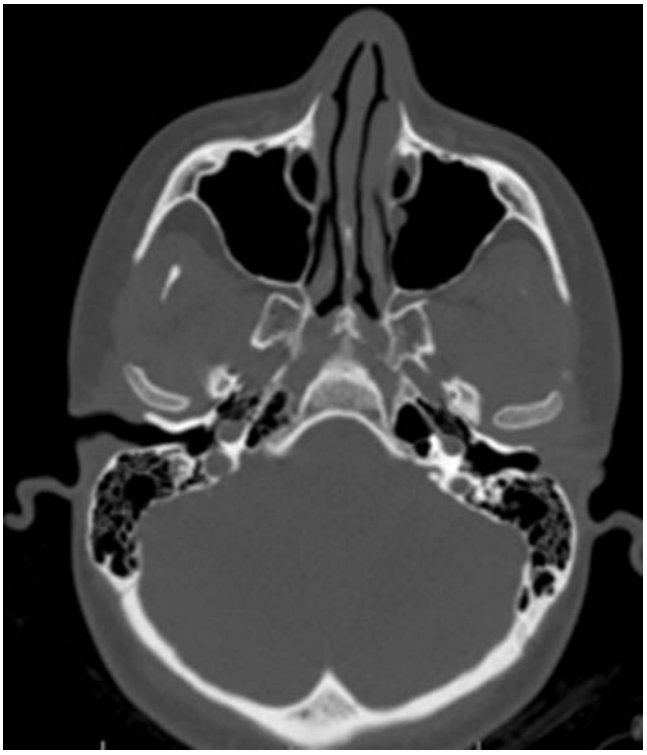
Computed tomography (CT) uses an image-forming algorithm to reconstruct a 3D image data set from multiple 2D images of the TMJ. The patient is positioned on the gantry; the x-ray sources and the electronic detector array rotate around the patient and undergo translation as images are continuously acquired. Direct acquisition in most units occurs in an axial plane, but coronal acquisition can also be achieved.[1] The patient will have to be placed in an uncomfortable position for direct coronal capture to occur. However, images can be synthesized or reformatted in any plane such as sagittal or coronal.[1] This process is referred to as multiplanar reconstruction (MPR). An entire region of interest thus can be examined in a single acquisition. MPR reduces the resolution of images slightly, but contemporary techniques yield adequate imagery for diagnosis. Earlier generations of CT units used less efficient modes of image collection, resulting in longer study times and the potential for motion artifact. Later generations of imaging units are capable of much quicker image generation, such as spiral CT, in which the gantry continues to translate as the x-ray sources and detector array rotate around the patient, thus generating a spiral motion and significantly reducing image acquisition times. Newer units have superior detector technologies and are capable of relatively high spatial resolution. The contrast resolution offered by CT is the highest that can be achieved. Examination of osseous structures with CT, therefore, is considered optimal. However, spatial resolution is still lower than that of digital radiography (DR) in that pixel sizes of the sensors in a CT unit are larger.

CT data can be visualized interactively, in static or dynamic modes, with the use of different display settings. MPR facilitates the generation of images in the coronal and sagittal planes. Scout images are generated first to ensure that the patient has been positioned appropriately in the gantry, and appropriate slices are selected for image generation. The images are displayed as shades of gray that are based on attenuation of the x-ray beam as it passes through the tissues of interest. This value, which is expressed as the attenuation coefficient of the tissue, is compared with the attenuation coefficient of water and is expressed as a logarithmic ratio, resulting in a value commonly referred to as a Hounsfield unit (HU). HU values of different tissues have been identified, thus yielding a range of values that are best for viewing different types of tissue. Further image processing through windowing and leveling of data results in display of desired shades of gray on the image based on the specific diagnostic task. Osseous tissues thus can be best visualized in a bone window setting. Likewise, soft tissue window settings are ideal for viewing such components of the TMJ and adjacent anatomy. The disc usually is difficult to visualize with the use of CT, especially if it is thin and small.[1] Larger discs and posterior attachments may present as areas of differential attenuation, permitting some visualization. Anterior displacement of the disc also may permit visualization. Indirect localization of the disc may occur through observation of displacement of the fat pad adjacent

to the lateral pterygoid muscle attachment to the condylar head. Windowing and leveling can be interactively carried out at the workstation.

For TMJ imaging, closed- and open-mouth views are generated, allowing examination of translation and rotation of the condyles and the dynamic range of motion. The patient must be immobilized during image acquisition by biting down on an object in the open position. CT also allows examination of the glenoid fossa, morphologic alterations or erosions of the condyles, and the articular eminentia and trauma. Perforation of the glenoid fossa into the middle cranial fossa also can be visualized well. If the disc is visualized, sagittal views render the disc much more visible in open and closed positions than do coronal and axial views. However, medial or lateral displacement of the disc may be noted in the coronal view.

CT imaging provides multiple advantages, because 3D information is captured and displayed interactively as a stack of 2D slices in any desired plane through MPR. In addition, 3D volumes can be displayed as surface rendering and volumetric rendering. Surface rendering, as the term implies, generates a surface-only 3D image; volumetric rendering generates the entire volume by making the superficial pixels transparent on the basis of their attenuation properties. In addition, CT is an excellent imaging modality for visualizing osseous components of the TMJ. CT also permits visualization of soft tissue components of the TMJ to some extent, although soft tissue examination is best performed by MRI. CT of the TMJ exposes the patient to higher radiation doses than do conventional techniques. The artifacts in CT may require that the study be repeated or that another modality be chosen. The most commonly seen artifacts include: (1) those induced by metallic fixtures or prostheses in or near the TMJ, (2) restorations such as amalgam and stainless steel crowns that produce a starburst pattern, and (3) motion artifacts induced by patient movement, especially in pediatric patients or those with involuntary movements. Adequate modes of stabilization or a sedation protocol should be used in these instances (Figures 37-8 through 37-10).



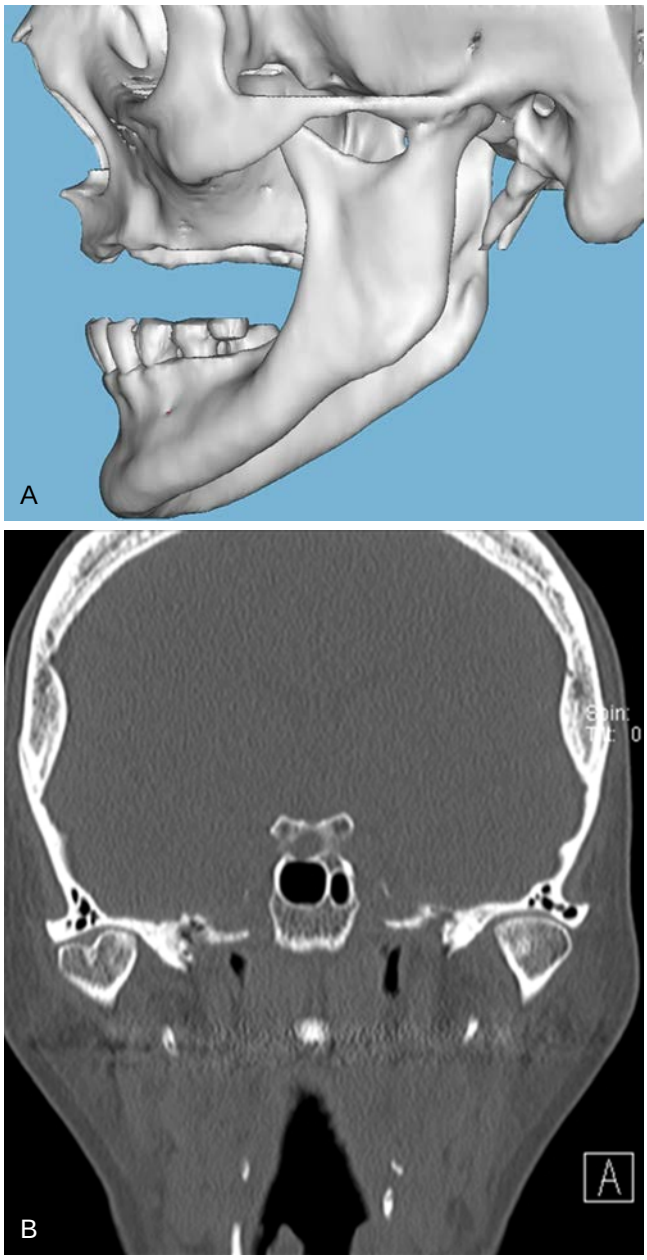
• **Figure 37-8** Computed tomography (CT): Bone window of an axial slice through the temporomandibular joint. Note the condyles.



• **Figure 37-9** Computed tomography (CT): Soft tissue window. Muscle attachments, including the lateral pterygoid muscles, are visible *(arrows)*.

Magnetic Resonance Imaging

MRI is being used increasingly for TMJ imaging and has largely replaced invasive arthrography, because it offers three major advantages: (1) It does not entail the use of ionizing radiation, (2) it provides excellent images of soft tissue components of the TMJ and permits direct visualization of inflammatory changes and the presence of effusion, and (3) it can be acquired in any desired plane. However, bone is not directly visualized on MRI. Detection of joint effusion and osseous changes of varying degrees is well documented,[16] and long-term prospective imaging studies have been advocated to track changes over time.[17] Such studies are useful for evaluating morphologic alterations and remodeling following surgical intervention, or in cases where only nonsurgical therapy is adopted. MRI has also been shown to be nals can be detected with accuracy on MRI.[16] Studies have also shown that MRI and CT can detect occult fractures of the articular eminentia and the glenoid fossa.[18] These



• **Figure 37-10** **A,** Three-dimensional volumetric reconstruction from a computed tomography study showing traumatic ankylosis of the left joint. **B,** Bone window of a coronal slice through temporomandibular joints. Note the right condyle showing bifid appearance.

distinct advantages for several applications make MRI an indispensable tool for diagnosis and treatment planning.

Magnetic resonance images are generated via the magnetic properties of hydrogen atoms in water molecules under the influence of powerful external magnetic fields. Radiofrequency (RF) pulses are delivered at a certain frequency and time interval to the region of interest that helps flip the protons within hydrogen atoms by a certain degree from their original axis of spin. Relaxation of hydrogen atoms upon termination of the RF pulse results in emission of the signal, which then is interpreted by the algorithm and displayed as the signal. Various protocols for MR imaging are based on pulse sequences that are determined by the diagnostic task. Image property varies according to method of acquisition. Differential response of different tissue types in normal and unhealthy states enables the generation of signals that facilitate interpretation of MR images. Image weighting is achieved by alteration of the time of repetition (TR) of the RF pulse and the time of echo (TE) of the signal from tissues of interest. Commonly used weighting includes T1, T2, and proton density. T1 images provide anatomic details, with fat enhancing as a bright signal. Bone appears dark on MRI as hydrogen atoms are tightly bound, failing to generate a signal. T2-weighted images, on the other hand, are appropriate for visualizing inflammatory changes in the capsule, as well as the presence of effusion. Proton density–weighted images provide excellent anatomic detail in that the position of the disc is more clearly outlined in relation to surrounding osseous and soft tissue structures.[1]

Open- and closed-mouth views are generated in MRI studies. The relative positions of the disc and its attachments can be studied at different positions of translocation[17,18,19] of the mandible, thus documenting TMJ dynamics.[17,19]

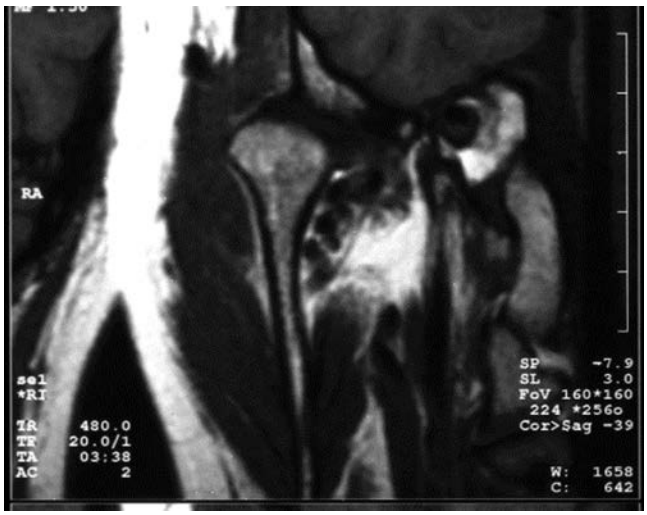
axial projections, as is done in CT. Patients do not have to be positioned differently. Scout images are acquired initially for slice location planning purposes.

MRI of the TMJ yields information that is not captured by any other modality, directly and in a noninvasive pattern.[21-30] MRI imaging of the TMJ provides hard tissue and soft tissue details along with functional information without using ionizing radiation. Extraction of signals of interest within a reconstructed volume using specific exposure and image processing parameters results in the collection of unique data that then can be viewed interactively. MRI thus continues to be routinely used in instances where (1) clinical signs and symptoms warrant such examination for effective definitive diagnoses,[24] particularly in relation to delineation and evaluation of soft tissue components, and (2) other imaging modalities including arthrography[28] are not considered appropriate. Arthrography has been shown to be relatively insensitive for the detection of medial and lateral displacements.[25] Disc degeneration has been shown on MRI to start in the retrodiscal attachment complex.[26]

TMJ imaging by MRI continues to evolve with improving technology. For TMJ imaging, special circular polarized transmission and receiver coils (surface coils) are used to emit and receive signals to enhance resultant image quality.[26,28] One or two coils may be used to capture the signals. Slice thickness of 3 mm or less is used with interslice spacing of 0.3 to 1.5 mm. MRI must be used to determine disc recapture in patients with internal derangement during splint therapy. Preoperative and postoperative images permit evaluation of the functional efficiency of the splint. Studies have shown that the use of high-quality, superconducting receiver coils significantly enhances image quality on low-field and other open scanners[28] (Figures 37-11 and 37-12).



• **Figure 37-11** Magnetic resonance imaging (MRI): Imaging of soft tissue detail, as well as effusion and inflammatory processes, is possible. **A,** T1-weighted parasagittal slices through the temporomandibular joint (TMJ) showing disc displacement without reduction: optimal for visualization of anatomy, condylar and disc position. Condyles are visible with a dark cortical outline and bright fatty marrow *(arrow on the right side).* Disc is visible as graying dark shape anterior to the condyle in the left image *(arrow on the left side)*. **B,** T1-weighted parasagittal slices through the TMJ showing disc displacement with reduction. Disc is pointed on the right image *(arrow on the left side).* **C,** T2-weighted parasagittal slices through the TMJ showing disc displacement with reduction. Note the bright white signal *(arrow on the right side)* representing the joint space effusion.



• **Figure 37-12** Magnetic resonance imaging (MRI): T1-weighted paracoronal slice through the TMJ.

There are multiple advantages that are unique to MRI. MRI imaging yields information that is not captured by any other imaging modality, noninvasively and with no radiation to the patient.[29] Functional and physical evaluation of the joint and joint space components is facilitated by more accurate images.[30] Evaluation of pathologic conditions with inflammation can be done at high resolution.[31] Various imaging protocols are available that can be used to enhance desired tissue with unique interactive data.[32] Disadvantages include potential for artifact generation from field distortions caused by ferromagnetic metallic objects, prostheses, and implants in the maxillofacial region[33] and an inability to image patients with implanted cardiac pacemakers[34] or aneurysm clips in the brain,[35] as well as patients with claustrophobia.[36] However, open units are available for patients with claustrophobia. Such units generally use magnets with lower field strengths, resulting in lower signal-to-noise ratios.

Tuned-Aperture Computed Tomography

Tuned-aperture computed tomography (TACT) is an imaging modality that was developed from the basic principles of tomosynthesis. However, none of the limitations of tomosynthesis apply to TACT. Multiple conventional images of the volume of interest are acquired from different loci in space, resulting in 2D radiographs. Software is used to reconstruct 3D volume with these data. 2D slices then can be generated, or the entire volume can be examined interactively at the workstation in static or dynamic modes. The stack of slices lends itself to image processing like CT (see Figure 37-11). Before the advent and wide availability of cone-beam volumetric imaging, TACT was a promising new modality to get 3D images in less time than conventional tomography and with fewer artifacts compared to CT. TACT was evaluated for TMJ arthroplasty, as it provided images with fewer metal and streak artifacts to evaluate the joint after arthroplasty. Disadvantages include the time required to acquire and reconstruct the images. TACT continues to be evaluated for a variety of diagnostic tasks and is used in medical applications such as mammography.[37,38]

Cone Beam Computed Tomography (CBCT)

CBCT is a relatively new 3D diagnostic imaging modality in dentistry that is finding numerous applications in maxillofacial imaging.[38-43] It uses an x-ray source that delivers a cone-shaped beam, resulting in exposure of the entire volume of interest at the same time and not just one or more slices of the tissue at a time. The result is a faster image acquisition process with significantly lower radiation doses. The linear accuracy of measurements from CBCT scans is very reliable, as the image acquisition is done using isotropic voxels. Because CBCT has poor contrast resolution, scatter artifacts from metallic structures are significantly fewer. First-generation CBCT units were designed to acquire the scan in a supine position, but most current CBCT units are designed to image the patient in a seated or standing position. Most standing and chairless units accommodate patients in wheelchairs. Numerous units are in use, most of which use sensors with high spatial resolution capabilities. Reconstruction times vary according to the unit, but some vendor software can achieve real-time secondary multiplanar reconstructions. Panoramic and other dental modes of view are available in the reconstruction schemes. Field of view and voxel size play a key role in the detection of subtle osseous changes and can help in early diagnosis of arthritic changes; research in this area is emerging and is helpful in developing imaging protocols for evaluation of the TMJ.[44] A new area of emerging research is the ability of CBCT scanners to acquire 3D information using fewer basis projections by modifying the acquisition protocol to do a 180-degree rotation as compared to the conventional 360-degree rotation. This modified acquisition technique is showing promising results in the detection of small and large arthritic lesions associated with the TMJ.[45] This is largely due to the evolution of postprocessing algorithms and small voxel sizes that deliver high-resolution images and better sensors. Newer sensors have resulted in 14-bit capture of data in the recent past and provide an opportunity to postprocess images to glean more valuable diagnostic information. Efforts to achieve 16-bit capture are ongoing. The definitive advantage of increased bit depth in the absence of soft tissue visualization remains to be proved. Cone-beam acquisition does not permit diagnostic imaging of most soft tissue such as muscle attachments and fascial planes, as is seen in conventional CT. Contrast imaging and soft tissue imaging using CT are still best achieved through conventional CT. CBCT does, however, facilitate evaluation of some soft tissue structures such as airway spaces outlined by regional soft tissue, a profile of the patient's face for orthognathic or other reconstructive operative needs, and imaging of subtle calcifications within soft tissue entities. Also available are units that could generate images of selected regions

of the patient's anatomy with the use of smaller detectors and tightly collimated beams, resulting in significantly higher spatial resolution levels. However, these are limited area views, and only a small portion of the anatomy can be captured.

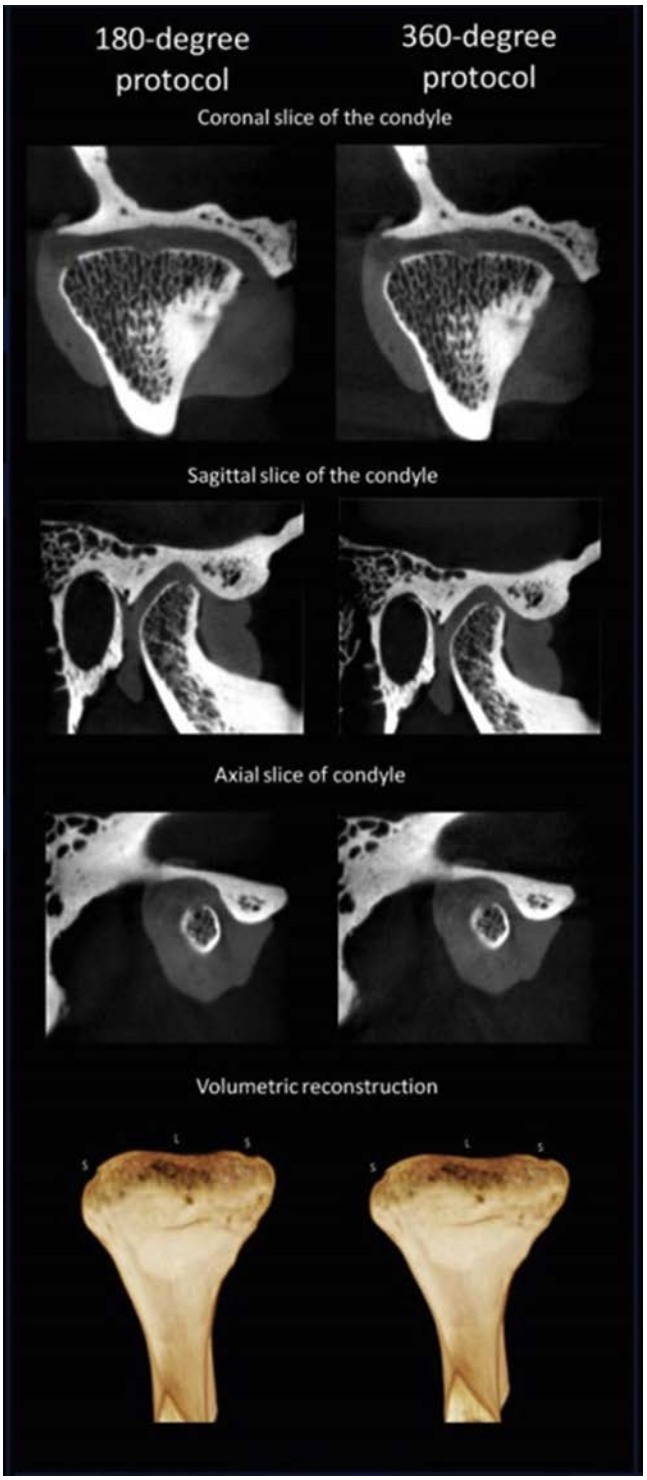
Surface and volumetric reconstructions can be done with CT data for treatment planning purposes. Surface reconstruction yields an image with surface pixels processed

cal treatment planning, simulation procedures, and establishment of visual treatment objectives[46] (Figures 37-13 through 37-17).

A major advantage of CBCT imaging is that it is a low-dose 3D imaging modality with high spatial resolution for imaging the hard tissues in the maxillofacial region. It has a significantly lower radiation dose, lower cost, and smaller footprint compared to multi-slice CTs. A major disadvantage of CBCT in comparison with multi-slice CTs is its poorer contrast resolution, which depicts soft issue details poorly. Other disadvantages such as patient motion artifact and metal artifacts are similar between both imaging modalities.

Functional Imaging

All of the image generation techniques discussed previously fall under the category of morphologic imaging modalities. Functional imaging modalities capture images that provide information on the functional integrity of the region of interest.[47-57] Applications in TMJ imaging are very limited. Examples include evaluation of functional changes following orthopedic treatment,[47] pre-splint and post-splint therapy imaging,[48] condylar hyperplasia,[49] necrosis of the condyle, chronic craniofacial pain refractory to treatment,[50,51] craniofacial osteomyelitis,[52] solid tumor invasion, and so forth. Thus, in instances where such information is needed to evaluate the presence of primary or secondary lesions in the TMJ, functional imaging is used in conjunction with morphologic imaging. These methods include scintigraphy, positron emission tomography (PET), and single photon emission computed tomography (SPECT), among others. Radioactive isotope-labeled tracer agents with short half-lives are administered intravenously, followed by image capture with the use of specialized cameras. Anatomic entities are not well outlined on the resultant images; however, those areas within the volume of interest that take up more of the tracer agent as a result of increased metabolic activity present as bright signals and vice versa. Although the sensitivity of this technique has increased with the use of SPECT, specificity is rather low, leading to false-positive results. Therefore, functional studies should be interpreted with caution. Increased physical activity just prior to imaging is known to generate signals in regions of hyperactivity



• **Figure 37-13** Cone-beam computed tomography (CBCT): Modified and conventional small-volume, low-dose scans: sagittal, coronal slices and volumetric rendering through condyles. Note the condylar surface erosion and defects in both coronal slices and volumetric rendering images through condyles consistent with degenerative changes.

procedure is followed. Therefore, this imaging modality is not selected without prior acquisition of morphologic imaging through CT or MRI; it should be advocated only in those instances where an undisputed indication for such functional assessment exists.



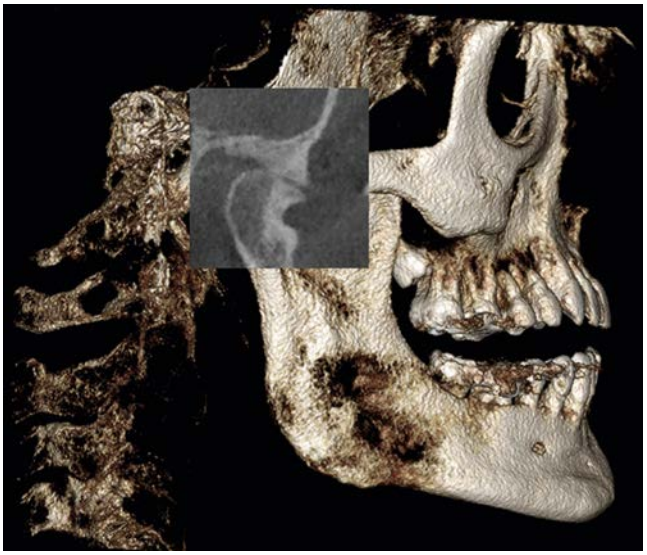
• **Figure 37-14** Cone-beam computed tomography (CBCT): Lateral reconstruction with maximum intensity projection (MIP).



• **Figure 37-15** Cone-beam computed tomography (CBCT): Postero-anterior open-mouth reconstruction with maximum intensity projection (MIP).

Fusion Imaging

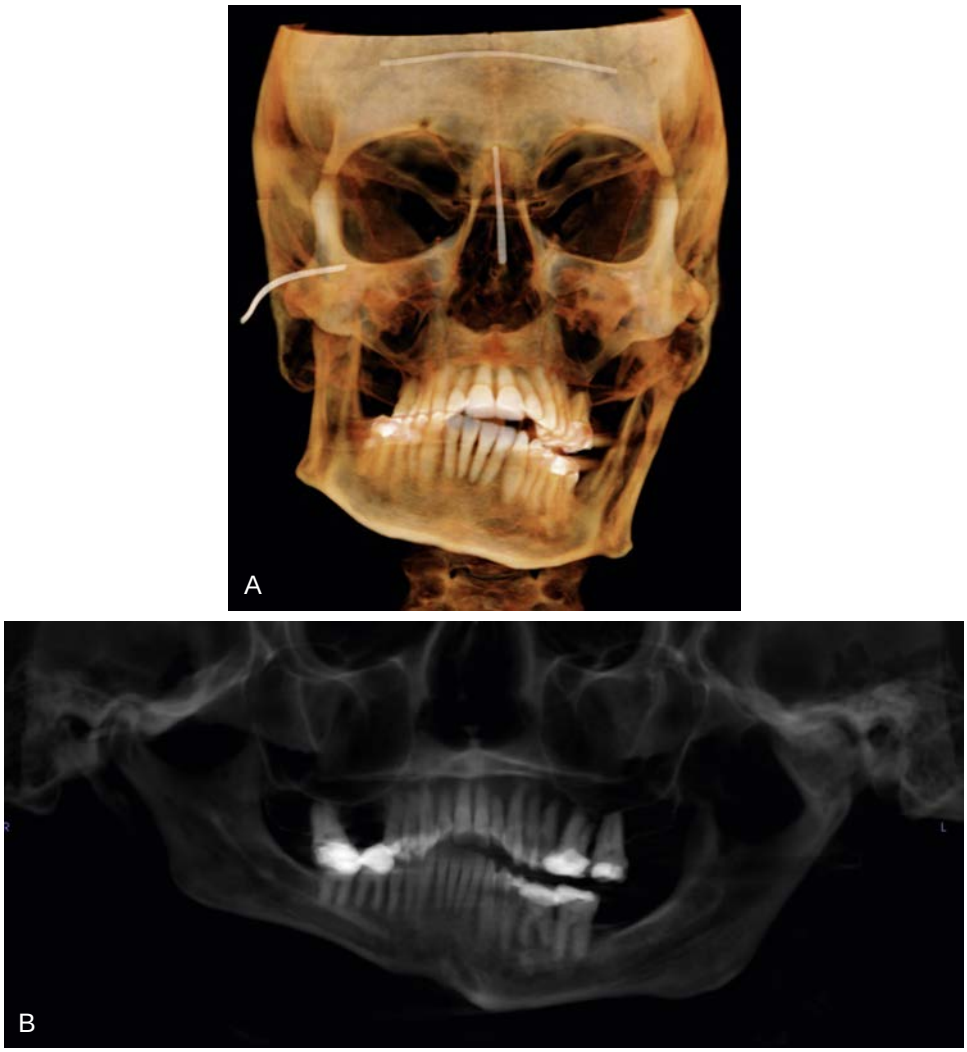
The concept of fusion imaging arose from the need to correlate findings on morphologic and functional imaging studies in a meaningful manner in 3D space. PET/SPECT-CT thus was introduced as a fusion imaging modality.[53-57] Images acquired with the use of the unit would contain both CT and PET/SPECT components, resulting in visualization of data that have been spatially correlated within the volume. It is thus easier to localize areas of increased or decreased metabolic activity to slice planes without compromising visualization of regional anatomy. Post-acquisition fusion of images from two different modalities can be done but is often not as accurate as when images are acquired together. Functional imaging is thus an invasive procedure that has the potential for false-positive results; it must be used only in conjunction with morphologic imaging modalities.[50]



• **Figure 37-16** Cone-beam computed tomography (CBCT): Lateral volumetric reconstruction in a bone window with x-ray window overlapping the right condyle. Note joint space reduction and osteophyte formation on right condyle.

Ultrasonography

Ultrasonography (US) is a noninvasive, inexpensive morphologic imaging procedure that can provide valuable information about TMJ components.[58-61] It may be used as a screening tool to evaluate the osseous contours of joints and may be used to evaluate joint spaces. Good diagnostic accuracy and reliability depend on appropriate use of this technique. The procedure can be completed in a short time. TMJ components present as hyperechoic areas of differing signal intensity, making them distinguishable from each other. Correlation of US findings with results of other imaging modalities such as MRI has shown that morphologic changes can be detected with some accuracy, including measurement of joint spaces as an indication of the presence of effusion as seen on MRI. Effusions present as hypoechoic or anechoic areas on US. Other applications include detection of disc position and dynamic evaluation of TMJ components in motion. More powerful transducers, positioning and size of the transducer for image acquisition, and the expertise of the operator have a direct bearing on image quality. However, it should be noted that evaluation of the medial aspect of the joint continues to be a problem. Some challenges to the routine use of US in diagnostic imaging of the TMJ have arisen, but the future seems to be bright as the technology continues to evolve.



• **Figure 37-17** Cone-beam computed tomography (CBCT): **A**, 3D volumetric rendering showing left condylar hyperplasia. **B,** Panoramic reconstruction from CBCT showing left condylar hyperplasia, joint space reduction, and ankylosis.

Summary

With recent advances in imaging technology and the introduction of newer imaging modalities, noninvasive evaluation of the TMJ has become a more efficient process. Static and dynamic observation of TMJ components is being done with significant reduction of radiation dose and, when necessary, by fusing or co-registering two imaging modalities together. The ideal imaging modality for a specific diagnostic task must be determined on the basis of clinical signs and symptoms, in consultation with a radiologist, because imaging protocols and acquisition schemes constantly change with technological upgrades.

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38

Pathology of the Temporomandibular Joint

ROBERT GASSNER

This chapter on the pathology of the temporomandibular joint (TMJ) consists of three parts. The first part deals with joint physiology and pathophysiology. The second part assesses the plethora of TMJ arthritides. Finally, the last part provides insight into the occurrence of benign and malignant tumors of the TMJ.

Joint Physiology and Pathophysiology

Motion is a fundamental event throughout biology.[1] It is an especially powerful modulator of cellular events, altering and interfering with effects of cytokines and growth factors in the musculoskeletal system.[2] Until recently, mechanical effects on joint tissue, especially the activation of cells such as chondrocytes, synovial fibroblasts, and osteoblasts, were considered beneficial only in disease-free tissue and were regarded as detrimental in the presence of inflammatory disease. When assessing the literature on the TMJ, usually in place of *motion*, the term *mechanical stress* is used in association with breakdown of joint function.[3,4]

This provides a small glimpse of results and work of the past 10 years regarding the interaction of motion and inflammation in articular tissue in vitro and in vivo.[5-12] It reveals how motion provides anti-inflammatory effects even in inflamed articular tissue through intracellular mechanisms. It further outlines how motion-based therapies such as continuous passive motion exert beneficial effects in various states of inflamed joint tissues. The in vitro model compares chondrocyte behavior when chondrocytes are subjected to four different conditions: (1) inflammation (interleukin-1 [IL-1]), (2) motion (cyclic tensile strain[CTS]), (3) inflammation and motion, and (4) experimental control. The in vivo model compares inflamed cartilage behavior when cartilage is subjected to two different conditions: (1) immobilization (IMM), and (2) motion (continuous passive motion [CPM]).

Understanding this can help in the clinical decision-making progress regarding therapeutic regimens of medical, surgical, and/or physical therapy interventions used in the treatment of temporomandibular disorders (TMDs). It can also help in understanding the molecular basis of joint diseases.

Interplay of Cytokines, Growth Factors, and Mechanical Signals

Articular cartilage maintains normal TMJ function through a specialized, hydrated extracellular matrix.[13] The major constituents of fibro-cartilage include type-II collagen fibrils providing tensile strength, and aggregating proteoglycans (aggrecans), nonaggregating proteoglycans, and water providing compressive resilience.[14] Less abundant components, types IX and XI collagen[15] and small proteoglycans,[16] also influence matrix organization.

Glycosaminoglycans are the polysaccharide side chains attached to the core proteins of proteoglycans. The distribution of proteoglycans close to the inferior and superior surfaces[14,17] in a given articular tissue is not uniform.[13,17] Chondroitin sulfate is evenly distributed in cartilage; dermatan sulfate is largely concentrated in the periphery and keratan sulfate in the middle of TMJ discs.[13,17] This may reflect different loading patterns in various regions of the TMJ disc.

Chondrocytes embedded in the articular cartilage express distinct functional properties in development and aging, while maintaining homeostasis in the mature organism and during cartilage remodeling after traumatic or inflammatory injury.[18] Physiologically, these responses lead to the formation or restitution of cartilage extracellular matrix (ECM). Dysregulation of these responses can lead to qualitatively or quantitatively abnormal formation or degradation of ECM, resulting in impaired joint function.[14]

Additionally, mechanical stimuli affect articular chondrocyte metabolism. During normal daily activity, a variety of mechanical forces including stresses, strains, and pressures is distributed within the joint; the long-term stability of the cartilage matrix depends mainly on the response

of chondrocytes to mechanical stimuli [6,19] and their limited capability to balance between anabolic and catabolic processes.[20-22]

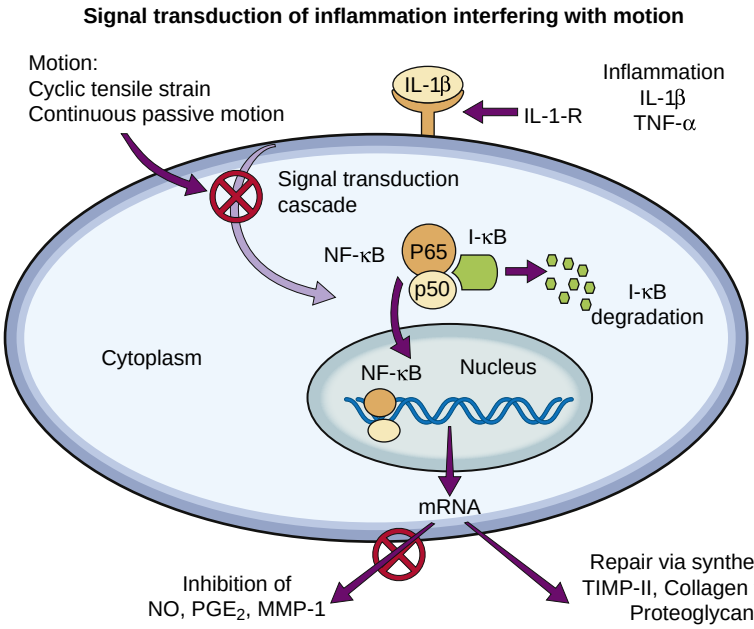
Chondrocyte activation and the induction of anabolic or catabolic responses are thought to be primarily the function of cytokines and growth factors. The catabolic cascade is induced by proinflammatory stimuli such as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α) and is characterized by the secretion of proteases, suppression of matrix synthesis, and inhibition of chondrocyte proliferation. The anabolic process is associated with the secretion of antagonistic cytokines, synthesis of protease inhibitors, production of extracellular matrix, and cell replication.[18]

During inflammation in degenerative TMJ diseases, proinflammatory cytokines such as IL-1 and TNF-α decrease synthesis and increase degradation of proteoglycans and collagens.[19,20,22] Growth factors such as transforming growth factor beta (TGF-β) are unable to stimulate chondrocyte synthesis of collagens and proteoglycans and ultimately reduce the activity of IL-l–stimulated proteinases.[23-25]

It is most important to note that mechanical signals generated by tensile strain of low magnitude (TENS-L) are anti-inflammatory, whereas tensile strain of high magnitude (TENS-H) is proinflammatory and catabolic.[5-8] Both low and high magnitudes of mechanical strain exploit nuclear factor NF-κB as a common pathway for transcriptional inhibition/activation of proinflammatory genes and catabolic processes as described for the intracellular mechanism of action of applied tensile forces in osteoblast-like cells.[26] TENS-L is a potent inhibitor of IL-1β-induced I-κBβ degradation and prevents dissociation of NF-κB from cytoplasmic complexes and thus its nuclear translocation. This leads to sustained suppression of IL-1β-induced NF-κB transcriptional regulation of proinflammatory genes. In contrast, TENS-H is a proinflammatory signal that induces I-κBβ degradation, nuclear translocation of NF-κB, and transcriptional activation of proinflammatory genes (Figure 38-1).

Articular chondrocytes synthesize copious amounts of oxygen with the terminal guanidino nitrogen of the amino acid L-arginine, yielding L-citrulline as a coproduct.[27] Under aerobic conditions, NO spontaneously oxidizes to its stable metabolites, nitrate (NO_3) and nitrite (NO_2). Because the half-life of NO is on the order of seconds, NO production is assessed indirectly by measuring the conversion of ^{14}C-labeled L-arginine to L-citrulline in tissue homogenates or by measuring the accumulation of the stable NO metabolites NO_3 and NO_2 in biological fluids such as the synovial fluid.[6,20-22,28] To date three distinct isoforms of NOS have been identified: a neuronal form (nNOS) initially isolated from brain, an endothelial form (ecNOS) initially isolated from the endothelium, and an inducible form (iNOS) initially isolated from macrophages.[20,22]

The iNOS pathway is principally regulated at the transcriptional level. Proinflammatory cytokines and endotoxin are potent inducers of iNOS in a wide variety of cell types, whereas glucocorticoids and the anti-inflammatory cytokines IL-4, IL-10, and the growth factor TGF-β suppress NO production. NO, acting as a endogenous mediator of catabolic actions, inhibits proteoglycan synthesis directly,[20-22] whereas TGF-β suppresses that NO production, reversing the NO-mediated inhibition of proteoglycan synthesis.[22]



• **Figure 38-1** Scheme: Interaction of inflammatory cytokine interleukin-1 (IL-1) and motion (cyclic tensile strain/CTS; continuous passive motion/CPM). *NO,* Nitrous oxide; *PGE_2,* prostaglandin E_2; *TNF-α,* tumor necrosis factor alpha.

The synovial fluid of arthritic TMJs also contains inflammatory mediators such as IL-1β, TNF, NO, leukotriene B_4, and prostaglandin E_2. Elevated levels of IL-1 and NO in the pathogenesis of arthritic conditions signal downstream events including the induction of matrix metalloproteinases (MMPs), eventually leading to the destruction of stromal tissue.[10]

Matrix metalloproteinases represent a family of structurally and functionally related enzymes responsible for the proteolytic degradation of extracellular matrix. They have been traditionally subdivided into three classes based on their substrate specificity: collagenases, gelatinases, and stromelysins. Their substrates include fibrillar collagen, collagen type IV or denatured collagen (gelatin), and other extracellular matrices (proteoglycan, laminin, fibronectin, casein), respectively. MMPs have been detected in TMJ synovial fluid aspirates and lavage collections, confirming that MMPs are involved in the degenerative component of TMJ disorders.[10,12]

To treat acutely and chronically inflamed joints, both immobilization and mobilization are used as therapeutic measures, with variable success.[29-31] This is partly due to the fact that mechanisms by which these two differing treatments exert their effects remain unclear. Recent in vitro studies demonstrate that biomechanical signals are potent anti-inflammatory signals that attenuate proinflammatory gene induction in chondrocytes. These signals act on chondrocytes in a magnitude-dependent manner. At low magnitudes, biomechanical signals inhibit IL-1β- or TNF-α-induced transcriptional activation of COX-2, MMPs, IL-1β, and other proinflammatory molecules.[32-35] These mediators are involved in cartilage destruction, and by blocking their gene expression, biomechanical signals can potentially attenuate cartilage destruction. Additionally, biomechanical signals upregulate expression of proteins associated with cartilage repair, such as aggrecans, collagen type II, and sulfated glycosaminoglycans. Not surprisingly, mechanical signals intercept the IL-Iβ-signaling pathway and inhibit nuclear translocation of NF-κB and subsequent transcriptional activation of genes under its control.[34,36] Because NF-κB transactivation occurs within a few minutes following activation of chondrocytes with IL-1β or TNF-α, the actions of biomechanical signals are rapid and can be observed within a few hours. Moreover, biomechanical signals act on cells in a sustained manner and can be observed in the presence of an inflammatory stimulus.[34,36] Additionally, mechanistic analysis of the actions of biomechanical signals in vivo is indicated to understand the biological basis of motion-based therapies that may contribute significantly to the healing of inflamed joints.

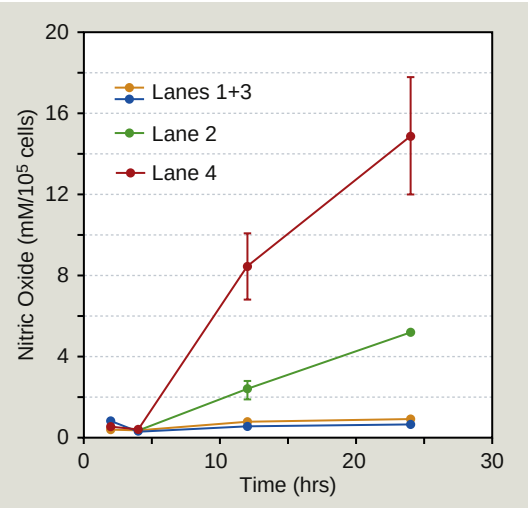
The Arthritic Condition and Cyclic Tensile Strain in Vitro

Mimicking the arthritic condition in in vitro chondrocyte function has to be assessed under at least four different conditions: (1) motion (CTS), (2) motion and inflammation (IL-1), (3) inflammation (IL-1) alone, (4) and experimental control (Figure 38-2). Exposure of chondrocytes to the proinflammatory cytokine IL-1 leads to upregulation of presence of iNOS mRNA and iNOS protein and NO itself via activation of IL-1 receptor on the cell surface and following dissociation of NF-κB from cytoplasmic complexes and thus its nuclear translocation (lane 4). In particular, Figure 38-2 shows that CTS itself does not induce the inflammatory cascade for NO (lane 1), while CTS is clearly downreg-

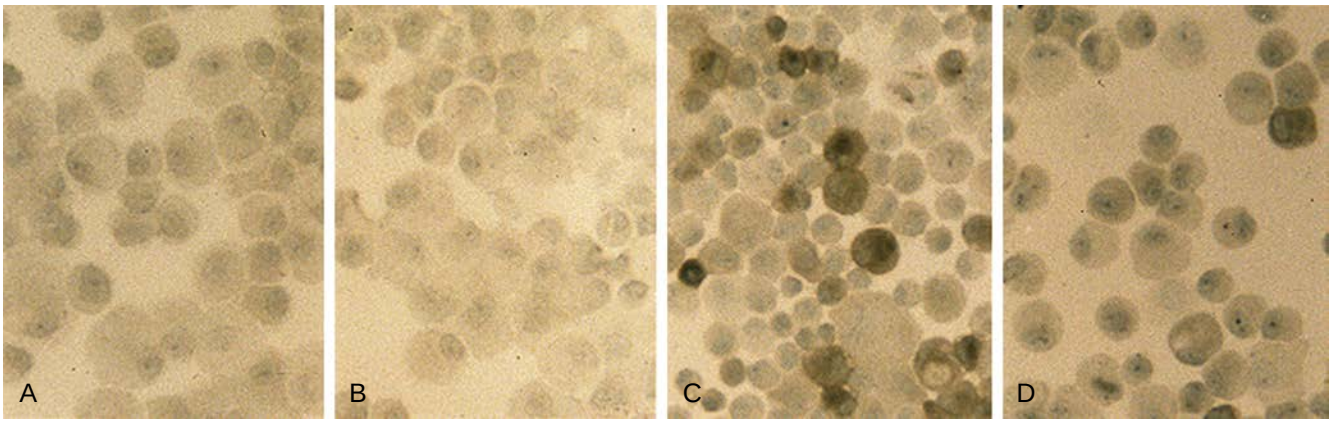
Chondrocytes in the tangential layers of cartilage are most responsive to IL-1β and synthesize high levels of iNOS as compared with chondrocytes in the deeper layers.[20,21] As shown in Figure 38-3, immunochemical staining for iNOS shows the distinct presence of inflammatory response in chondrocytes following exposure to inflammatory signals alone in comparison to simultaneous exposure to

are iNOS-positive cells representing the cells derived from the tangential layer of articular cartilage (see Figure 38-3, *C*). This population of chondrocytes is most likely the one that is also responsive to CTS, showing a 62% decrease of iNOS protein immunostaining (see Figure 38-3, *D*).

These in vitro findings provide evidence that mechanical signals play an important and critical role as modulators of inflammatory joint diseases. CTS functions as a potent effector mechanism for suppressing pathologic effects of IL-1β in vitro through inhibition of inducible



• **Figure 38-2** Nitric oxide (NO): A marker of inflammatory cell response during (*lane 1*) motion (cyclic strain), (*lane 2*) motion and inflammation (interleukin-1 [IL-1]), (*lane 3*) experimental control, and (*lane 4*) inflammation (IL-1) alone. (From Gassner R, Buckley M, Studer R, et al: Cyclic tensile stress exerts antiinflammatory properties by inhibiting iNOS induction in chondrocytes, *J Immunol* 163:2187-2192, 1999.)



• **Figure 38-3** Immunochemically stained protein inducible nitric oxide synthase (iNOS) (brown color) during **(A)** control – no motion, **(B)** motion alone, **(C)** inflammation alone (interleukin-1 [IL-1]) alone, and **(D)** motion and inflammation (IL-1 IL-1β. Motion inhibits inflammation.). (From Gassner R, Buckley M, Studer R, et al: Cyclic tensile stress exerts antiinflammatory properties by inhibiting iNOS induction in chondrocytes, *J Immunol* 163:2187-2192, 1999.)

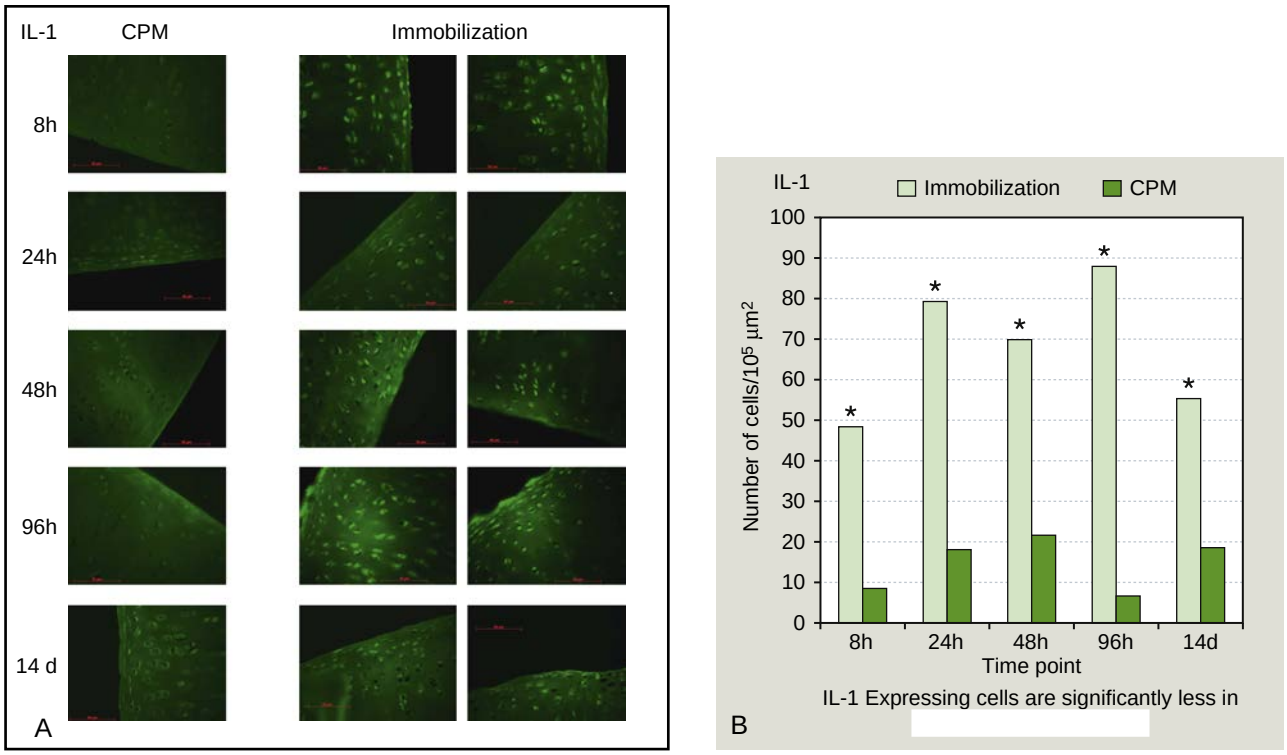
NO production.[5] It is likely that in vivo mechanical signals may exert their effects on arthritic joints in a similar manner by inhibiting the inflammatory effects induced by IL-1β via interruption of iNOS expression. In turn, this would limit the production of NO and its catabolic effects on cartilage. Furthermore, mechanical signals do not only inhibit NO production, but also upregulate proteoglycan synthesis at concentrations of IL-Iβ frequently observed in inflamed arthritic joints, suggesting that the actions of mechanical signals are clinically relevant in suppressing the sustained effects of pathological levels of IL-1β in vivo. Maintaining anabolic capabilities of chondrocytes within inflamed joint tissue is an additional anti-inflammatory asset for the treatment of arthritic conditions.

The Arthritic Condition and Continuous Passive Motion in Vivo

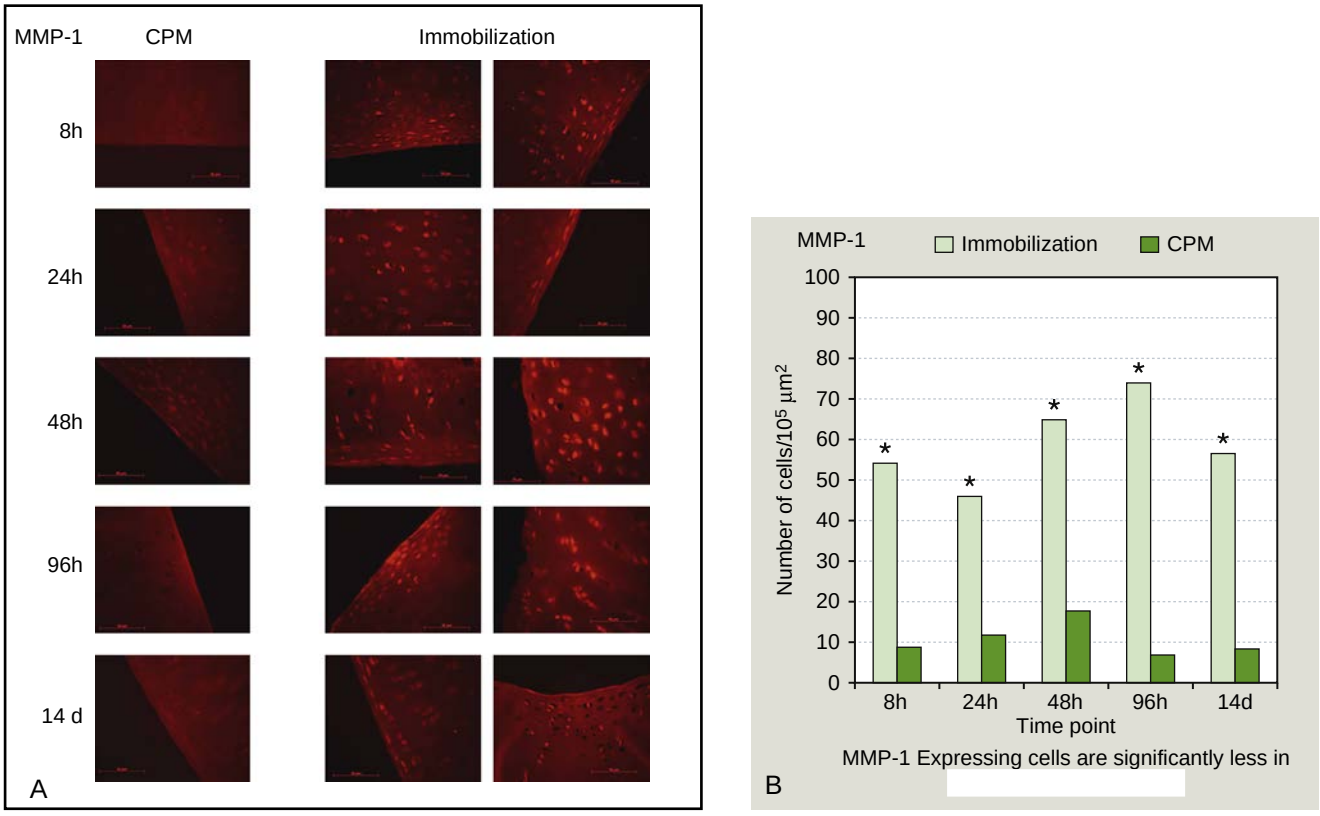
Immobilization versus Continuous Passive Motion

Destruction of cartilage integrity is a hallmark of arthritic conditions as evidenced in a rabbit model of antigen-induced arthritis (AIA).[12] The histopathogenesis of AIA has been well characterized, and the model demonstrates many features of human rheumatoid arthritis (RA), including joint inflammation and damage to articular cartilage via both increased breakdown and decreased synthesis of cartilaginous matrix.[32-34] To evaluate the molecular basis of interaction between motion and inflammation, the in vivo model compares inflamed cartilage behavior where cartilage is subjected to either of two different conditions: (1) IMM or (2) motion (CPM). Given that maintenance of cartilage integrity is due to chondrocyte function, regulation and control of proinflammatory molecules in inflamed cartilage depends on the presence of biomechanical signals. Mobilization clearly prevents cartilage degradation. CPM protects matrix integrity in AIA-afflicted articular cartilage. Inflammation is mainly driven by monocytic cells in immobilized knees as compared with CPM knees. CPM downregulates the proinflammatory cytokine IL-1β mRNA expression and synthesis in inflamed chondrocytes (Figure 38-4). CPM suppresses COX-2 synthesis in inflamed cartilage (data not shown). Finally, CPM suppresses MMP-1 synthesis in inflamed chondrocytes (Figure 38-5). CPM upregulates IL-10 synthesis in inflamed cartilage (Figure 38-6).

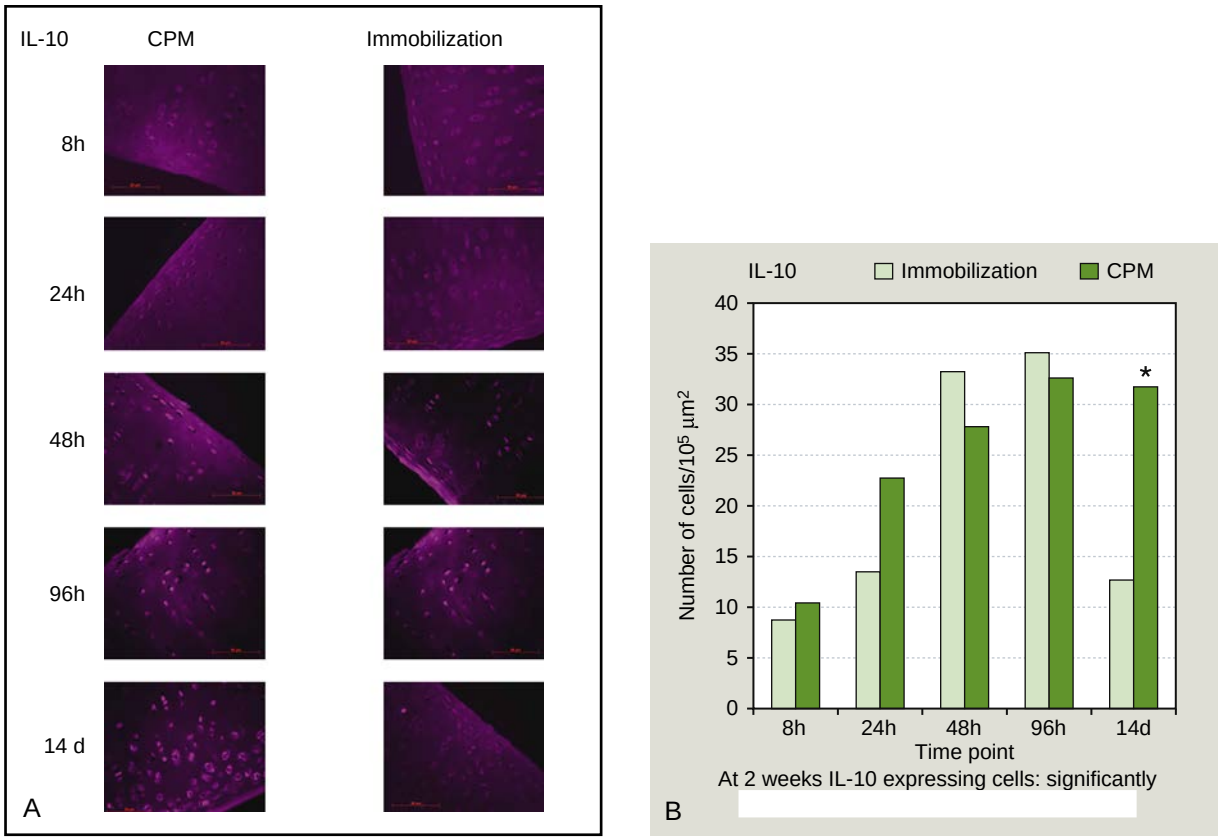
Joint mobilization is suggested to disseminate the inflammatory exudates, whereas IMM is suggested to create a stagnant environment in the synovium, leading to increased inflammation and cartilage damage. Although these effects of mobilization and IMM cannot be excluded, the fact that mechanical signals directly interfere with the proinflammatory gene induction in chondrocytes suggests that mechanical signals regulate inflammation at the intracellular level. The in vitro and ex vivo data demonstrate that chondrocytes are mechanosensitive cells and respond to mechanical signals in a magnitude-dependent manner.[33-38] For example, cyclic tensile or compressive forces, in the presence of inflammatory signals, induce matrix synthesis in chondrocytes and fibrochondrocytes.[35-38] The in vivo findings confirm the in vitro and ex vivo data and demonstrate that mechanical signals act directly on chondrocytes to prevent cartilage destruction due to inflammation. Appropriate mechanical signals play a profound role in attenuating localized joint inflammation in vivo. These signals act on inflamed chondrocytes by two equally important mechanisms. First, these signals are potent inhibitors of proinflammatory gene induction and inhibit expression of catabolic mediators, such as IL-1β, COX-2, and MMP-l. Second, these signals induce expression of the anti-inflammatory cytokine IL-10. Together, the results demonstrate that biomechanical signals have profound effects in minimizing cartilage destruction in a severe



• **Figure 38-4 A,** Rabbit knee with antigen-induced arthritis (AIA)/in vivo conditions: green staining illustrates expression of Interleukin-1 (IL-1ß). **B,** Graphic illustration of Part **A**. (A From Ferretti M, Gassner R, Wang Z, et al: Biomechanical signals suppress proinflammatory responses in cartilage: early events in experimental antigen-induced arthritis, *J Immunol* 177:8757-8766, 2006.).



• **Figure 38-5 A,** Rabbit knee with antigen-induced arthritis (AIA)/in vivo conditions: red staining illustrates expression of Matrix Metallo Proteinase -1 (MMP-1) **B,** Graphic illustration of **A.** (A From Ferretti M, Gassner R, Wang Z, et al: Biomechanical signals suppress proinflammatory responses in cartilage: early events in experimental antigen-induced arthritis, *J Immunol* 177:8757-8766, 2006.)



• **Figure 38-6** **A,** Continuous passive motion (CPM) versus immobilization: CPM upregulates IL-10 synthesis in inflamed cartilage. **B,** Graphic illustration of **A**. (**A** From Ferretti M, Gassner R, Wang Z, et al: Biomechanical signals suppress proinflammatory responses in cartilage: early events in experimental antigen-induced arthritis, *J Immunol* 177:8757-8766, 2006.)

proinflammatory environment and provide continuing evidence that motion-based therapies are more efficacious than perceived earlier.[12]

Arthritides of the Temporomandibular Joint

More than 10% of the population suffers from arthritic diseases leading to pain, loss of function, disabilities, and joint replacement and economically measured as major loss of human productivity and especially early retirement.[5,6,12] In the United States alone, more than 40 million people suffer from some form of arthritis; among these, 12 million have osteoarthritis (OA) and 8 million have RA. Arthritis is also the most common disease affecting the TMJ. All of the arthritic forms that involve other joints in the body occur in this joint, too. Therefore, these conditions are to be considered in the differential diagnosis whenever a patient presents with chronic TMJ pain and dysfunction.[39-45]

Arthritic diseases of the TMJ are inflammation-derived alterations of the synovium, cartilage, and surrounding structures such as the capsule, bursa, tendons, and bone. Similarities of signs and symptoms of the many variants of arthritis necessitate the establishment of a working differential diagnosis based on the patient's history, physical examination, and radiographic evaluation distinguishing these conditions from other causes of TMJ symptoms.

Patient evaluation includes questions regarding swelling, redness, pain at rest, duration of symptoms, rate of onset, location of involved joints, pattern of joint involvement, preceding events such as trauma, and time of day when symptoms are worse. Discussion of medications influencing symptoms and a thorough review of organ systems follows.[39-41,46] Physical examination extends beyond the involved joints, as the skin, heart, lungs, and mucous membranes are often affected by the same disease process. Involved joints are observed for deformity, symmetry, and proximity. Palpation of these areas assesses pain, temperature, and range of motion.

Diagnostic studies also include radiologic studies (magnetic resonance imaging [MRI], computerized tomography [CT] scan, and bone scans), laboratory tests, and synovial fluid analysis.[39-41,43,46] Normal synovial fluid is clear or straw colored and viscous from hyaluronic acid. Viscosity is reduced in inflammatory arthritides, and the synovial fluid flows like water—unlike the stringing produced by normal synovial fluid. Evaluation of cell counts, clot formation, and differences between serum and synovial glucose levels can aid in the diagnosis and differentiate arthritic conditions.

The presence of crystals and evaluation of their size, shape, and compensation under polarized light can be useful in the diagnosis of metabolic arthritides.[39-41]

Classification of Arthritis

Symptoms and signs of the different arthritic diseases are similar. Yet, clinically individual conditions can be distinguished.

1. Traumatic arthritis
2. Degenerative (osteo)arthritis
3. Inflammatory arthritis:
   a. Rheumatoid arthritis
   b. Juvenile rheumatoid arthritis
   c. Psoriatic arthritis
   d. Ankylosing spondylitis
   e. Reiter syndrome
4. Infectious arthritis:
   a. Gonococcal arthritis
   b. Syphilitic arthritis
   c. Tuberculous arthritis
   d. Lyme disease–associated arthritis
5. Metabolic arthritis:
   a. Gout
   b. Pseudogout
6. Arthritides associated with connective tissue diseases: systemic lupus erythematosus, scleroderma, chronic inflammatory bowel disease, reflex sympathetic dystrophy, and sarcoidosis.

Traumatic Arthritis

The immediate intra-articular response of the joint tissues to single or repetitive episodes of acute trauma is release of proinflammatory cytokines starting a cascade of inflammatory events.[46] This response, traumatic arthritis, is manifested in the form of pathologic and clinical states, the nature of which is generally determined by the magnitude of the trauma sustained by the joint tissues.[39,40] *Minor trauma* to the joint tissue may result in compression, or shearing of the retrodiscal tissue and capsule or dislocation of the disc.

Moderate trauma may cause damage to the synovial lining, resulting in subsequent edema and mild serohemorrhagic effusion that can cause hemarthrosis and an inflammatory response in the synovial membrane. This inflammation may eventually result in a hypertrophic synovial response and fibrosis, causing cicatricial contractions and adhesions between the joint components and even fibrous ankylosis. In children, traumatic arthritis can cause growth abnormalities, malocclusion, and facial asymmetry. *Severe trauma*, short of producing a condylar fracture, can cause damage to the articular surfaces, subchondral bone, or both, eventually predisposing to or causing degenerative joint disease.

Clinical Findings

Acute traumatic arthritis presents with severe jaw pain both at rest and with movement. The joint is tender to palpation, is occasionally swollen, and has a decreased range of motion. Effusion in the joint space and edema or hemorrhage in the retrodiscal tissue can cause an increased distance between the articulating components on the traumatized side that results in a posterior open bite. The acute symptoms usually subside within a few days or weeks.[47] In cases of severe trauma, however, the condition may eventually progress to persistent limitation of motion, ganglion formation, intra-articular disc derangement, or degenerative joint disease.

Imaging Findings

As a result of edema and swelling, the intracapsular and capsular structures can increase in thickness. This can be reflected radiographically as an increased distance between the roof of the glenoid fossa and the condylar surface in the closed-mouth position. Late severe traumatic changes in the joint may be manifested as degenerative joint disease or as bony ankylosis.

Diagnosis

A thorough history must be taken and a careful physical examination of the TMJ must be performed after injury to exclude presence of condylar or other mandibular fractures. The diagnosis of traumatic arthritis of the TMJ is based on a history of trauma and on the absence of the characteristic features of the other forms of arthritis. Trauma to the TMJ trauma has been reported, but the long-term benefit of such a procedure is still uncertain.[48,49]

Degenerative (Osteo)arthritis

Osteoarthritis is the most common form of arthritis affecting the human skeleton and is related to increased mechanical loading, physical stress, and traumatic injury of the joint. Consequently, the joints most often affected are the weight-bearing joints such as the hips, spine, and knees. Hand joints are also commonly affected, especially in women. Systemic, genetic, endocrinologic, metabolic, and/or vascular factors, in combination with local mechanical factors, influence the development and progression of the disease.[39-41]

OA is also the most common disease affecting the TMJ. Radiographic evidence of OA of the TMJ occurs in 14% to 44% of symptom-free individuals, and histologic evidence of the disease occurs in 40% to 60% of studied populations.[50] However, clinical evidence of the disease occurs in only 8% to 16% of the population. OA of the TMJ has a strong predilection for women and affects patients at any age, but is more prevalent beyond the age of 40 years. Generally OA is unilateral, although bilateral involvement does occur; in these cases, one side usually shows greater severity.[39-42]

OA characteristically affects the articular cartilage of synovial joints and is associated with simultaneous remodeling of the underlying subchondral bone and secondary

involvement of the synovium. Synonymous terms such as osteoarthrosis, arthrosis, and arthritis deformans are commonly used in Europe, whereas osteoarthritis, degenerative joint disease, and degenerative arthritis are the most commonly used terms in North America.

Clinical Findings

The large weight-bearing joints are predominantly affected by OA. A gradual onset is followed by a chronic course. When the TMJ is affected, the patient usually complains of pain and tenderness in the joint and masticatory muscles. The patient may also complain of jaw muscle fatigue, stiffness and tiredness, difficulty opening the mouth, reduced range of motion, and crepitation during mandibular movements.[51] Osteoarthritis is usually characterized by a lack of morning jaw stiffness; if present, this stiffness lasts no more than 30 minutes.[39,40] The TMJ symptoms may be present in the absence of similar symptoms in other joints of the body. Because of the bony thickening and marginal osteophyte formation in the mandibular condyle, a palpable swelling may occur over the joint.

Although radiographic changes in the TMJ may be observed bilaterally, symptoms may be unilateral. Other associated symptoms include referred head and neck pain and earache. OA may affect the TMJ primarily (primary OA) as a result of the normal wear and tear of the joint components that occur with aging. This form of OA usually begins in the fifth decade of life, with slow onset, and runs a course of mild symptoms. The other form of OA of the TMJ is secondary and is usually associated with macrotrauma or chronic microtrauma. This form affects patients 20 to 40 years old and produces more symptoms than the primary form. In these patients, the symptoms may be associated with chronic myofascial pain and dysfunction (MPD) or intra-articular disc derangement.[39-42,52]

Articular cartilage receives its nutrition from the synovial fluid, not the subchondral bone. After maturity of the epiphyseal plate, perforating vessels can no longer supply the cartilage with nutrients or remove waste products. Changes in the synovial fluid therefore influence the metabolism of the cartilage.[53,54]

Many hypotheses regarding the initial event triggering OA have been postulated, including mechanical, inflammatory, and chemical insults that release collagenases and proteolytic enzymes, causing degradation of the cartilage. Abnormal and repetitive mechanical stresses may exceed the functional capacity of normal articular tissues. The result is a decreased collagen stiffness, leading to increased hydration of the proteoglycan-water gel.[53] Other hypotheses suggest that cartilage breakdown is the result of weakness of the subchondral bone secondary to microfractures from excessive loading. Inflammatory mediators and waste products are also likely causes of degeneration. Alterations of synovial fluid or reduced quantities, causing improper lubrication and nutrition of the cartilage, may also play a role. These phenomena lead to friction of the cartilage and collagen destruction.[55]

Early in OA and chondromalacia, which are indistinguishable, the water content of the cartilage matrix is increased from swelling and breakdown of the collagen fibrils.[41,51,56] Proteoglycans are depleted, and chondrocytes cluster while proliferating in an attempt to repair. These histologic findings are manifested mostly in the deeper layers of cartilage, sparing the superficial layer until advanced disease develops, which may take years.[57] As the disease progresses, chondrocytes degenerate and synovial cells destruct, releasing proteolytic and collagenolytic enzymes; this results in more degradation. As the process advances, tissues lose integrity, and the cartilage splits and fibrillation occurs. This leads to adhesions as the cartilage thins. The marrow contained within the subchondral bone then fibroses. Macroscopic changes identifiable on radiographs include osteophyte formation, sclerosis, surface erosions, subchondral cysts, and deformations. Extra-articular responses such as muscle pain and atrophy may be evident as the mandible length is altered and the occlusion changes.[58]

properties of the joint surfaces, and alterations of the synovial fluid, giving rise to increased friction and adhesive wear, impair disc movement.[45] Degradative products from the OA cartilage are then released into the synovial fluid. When it is produced in large quantities, it cannot be reabsorbed by the synovial membrane or cleared. Mediators of inflammation are also released in response, causing synovitis. The osteoarthrosis and synovitis is termed osteoarthritis. The synovial membrane is not innervated, but the mediators of inflammation produced by the synovium stimulate capsular nociceptors.[61] This leads to joint tightness and continued stretching and elongation of the attachments, causing anterior displacement. Limitation of the mandibular opening can then ensue from the malpositioned disc. The peridiscal tissues, such as ligaments and muscles, are also subject to alteration from the changes in the articular surface. As the posterior attachment elongates, the nociceptors within the tissue are stimulated, causing pain. As the ligaments are subjected to tensile forces from the altered frictional capacity and elongation, they extend beyond their span of elasticity and deform. As they elongate, the collagenous component of the ligament is disrupted and the tissue may rupture or lacerate. It is these ligamentous attachments of the disc that keep it anchored to the condylar head and resist displacement. As the functional limits of the ligament are exceeded, nociceptors are stimulated, causing sprains and pain.[58] Anteriorly displaced discs are also subject to compressive loads placed on their posterior attachment. Maladaption, inflammation, and perforation are then possible as the inflammatory process continues. However, these are not the only adaptive changes that occur. There can be decreased vascularity and elastin content as collagen increases and fibrosis occurs. This can act as a pseudodisc and withstand compressive loads. Autopsy studies revealed that 50% of elderly patients had joint degeneration, although no disc

problems were reported in life. Eighty percent of patients with displaced discs had similar findings. This may suggest that displaced discs are a sign of OA, not a cause of OA.[62]

Classification and findings of TMJ OA should include

eration can be separated into four stages. In the *first stage* of OA, the initial repair stage, an imbalance of synthesis and degradation of extracellular matrix by chondrocytes is encountered. Growth factors, including insulin-like growth [63]

thesis of the extracellular matrix. In the *second stage* of OA, the early stage, extracellular matrix synthesis increases but is exceeded by degradation from the increased activity of proteases. Cartilage swelling ensues, resulting in an irregular surface and a net loss of articular cartilage.[40,58] Characteristic clusters of chondrocytes with increased metabolic activity in the swollen areas are also seen. Chondrocyte and cartilage necrosis follow in all cell layers, leaving attempts at repair disorganized.[59] Synovial fluid analysis during this early stage reveals metabolic products of arachidonic acid, IL-1, IL-6, TNF-α, and other proteases. Arthroscopic examination reveals swelling, softening, and fibrillations. Common clinical complaints during this phase include pain and limited range of motion. In the *third stage* of OA, the intermediate stage, articular cartilage is lost as synthesis is exceeded by degradation. Histologic evaluation reveals thinning, vertical splitting, and fibrillations of the cartilage as clusters of chondrocytes continue to necrose. Staining of proteoglycan continues to be reduced, and the collagen network becomes more haphazard. Biochemical markers such as cytokines and fibronectin continue to fill the joint space. Arthroscopically, cartilage continues to thin, and a displaced disc may be evident. Pain with limited range of motion continues and can now be accompanied by joint clicking. In the *fourth stage* of OA, the late stage, increased degradation exceeds synthesis or reduced degradation equals decreased synthesis. Histologically, fibrillations are extensive, bone becomes denuded, and proteoglycan staining is nearly lost. Extracellular matrix synthesis is reduced, whereas protease activity can be reduced or increased if residual OA is occurring. Arthroscopic evaluation is remarkable for severe fibrillations, exposed bone, disc displacement, and possibly angiogenesis.[39-41]

Imaging Findings

Radiographic studies of OA of the TMJ reveal an incidence of 40% in patients older than 40 years and 100% in patients older than 80 years. Approximately 50% of the population has radiographic changes, but only 30% of these patients are symptomatic.[39,40] Because OA affects the articular cartilage first, the early changes may escape radiographic detection, or the radiograph may only show a reduced joint space, indicating loss of the articular cartilage and/or perforation of the disc. The most common early radiographic change in the condyle is subchondral bone sclerosis because of thickening of the subchondral bony plate. As the disease progresses, there may be flattening and marginal lipping of the condyle and flattening of the articular eminence. In the late stages of the disease, the changes are in the form of erosion of the cortical plate, osteophyte formation, or both. Occasionally, in the late stages of the disease, subchondral bone breakdown may also occur, causing the formation of a bone "cyst" within the condyle.[39,40]

MRI of the TMJ with OA may reveal perforation, damage, or displacement of the articular disc, whereas osseous changes are best delineated by computed or linear tomography.[28,89] High-resolution ultrasonography may also be a valuable diagnostic aid for the detection of abnormal condylar morphology in OA.[64]

Laboratory Findings

early detection of OA. Recent studies using synovial fluid analysis have shown a correlation of pain and disease progression with TNF-α, interleukin 1β, stromelysin, and bradykinin.[65-68] Keratan sulfate levels in the synovial fluid are higher in joints that had arthroscopic evidence of early OA than in normal joints.[65]

The synovial fluid aspirate may show a slight elevation of white blood cells (often less than 2000/μL) and fewer than 30% polymorphonuclear cells, and rheumatoid factor is usually absent.[40] The ESD is usually normal or only slightly elevated, and high values may only be present when the disease has an acute inflammatory component.

Diagnosis

The diagnosis of OA is based mostly on clinical findings and radiographic studies and is usually easy to make when the typical features of the disease are present. The most difficulty is encountered in differentiating OA from early MPD and from RA. Therefore, the differential diagnosis of OA of the TMJ should include RA and its variants, MPD, and various forms of intra-articular disc derangement. Features distinguishing OA from MPD include the more localized nature of the pain, the frequent presence of joint tenderness, and the presence of joint crepitation in the former. When both conditions are present concurrently, as is often the case, the history may help determine which is the primary condition.[40,42]

Inflammatory Arthritis

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic inflammatory disease that primarily affects the periarticular structures such as the synovial membrane, capsule, tendons, tendon sheaths, and ligaments. It secondarily involves the articular cartilage and subchondral bone. The prevalence of RA among the general population is about 2% to 2.5%, with a female-to-male predilection ratio of 2.5 to 3.0:1 and a peak onset of the

• BOX 38-1 Classification Criteria for Rheumatoid Arthritis

Morning stiffness (>1 hour)
Swelling (soft tissue) of three or more joints
Swelling (soft tissue) of hand joints (PIP, MCP, or wrist)
Symmetric swelling (soft tissue)
Subcutaneous nodules
Serum rheumatoid factor
Erosion and/or periarticular osteopenia, in hand or wrist joints, seen on x-ray

The first four of the listed criteria must be continuous for 6 weeks and observed by a physician. Diagnosis requires at least four criteria.

Approximately 50% to 75% of patients with rheumatoid arthritis have involvement of the temporomandibular joint during the course of the disease.[40,57,70-72]

disease between the patient ages of 40 and 60 years.[69,70] To guarantee uniformity in investigational and epidemiologic studies, the American College of Rheumatology has developed classification criteria (Box 38-1).

Clinical Findings

The disease often has an insidious onset and runs a slow, chronic course with progressive destruction of the articular soft tissues and eventual destruction of the cartilage and bone. It has asymmetric, polyarticular involvement, and the small peripheral joints are affected first (wrists, elbows, and ankles). It then progresses symmetrically toward the central skeleton, involving the knee, shoulders, and cervical spine. In the advanced stages, when the inflammatory tissue infiltrates the articular cartilage and bone, erosion and destruction of the articular disc, cartilage, and subchondral bone result.[73]

Such total destruction causes joint deformity and loss of joint function. Joint deformity may also result, in part, from involvement of the tendons, muscles, and ligaments.[39-41,46] RA also has characteristic extra-articular and systemic features that include ocular involvement such as episcleritis, iritis, and keratoconjunctivitis; pulmonary features such as pleurisy, pleural effusion, and fibrosis; cardiac features such as pericarditis and cardiac arrhythmias; vasculitis causing skin ulcerations and osteoporosis; and the presence of subcutaneous nodules in pressure and friction areas in 20% to 25% of patients. Systemic signs and symptoms of RA include fatigue, weight loss, fever, and anemia.[40] When RA is present in combination with anemia, neutropenia, thrombocytopenia, and hypersplenism, the condition is called *Felty syndrome*.[40,74]

A close relationship exists between involvement of the TMJ and the severity of the systemic disease. When the TMJ is involved, it is bilateral in 34% to 75% of those patients.[72] Signs and symptoms of TMJ involvement include deep, dull, aching pain in the preauricular area, especially during function; muscle tenderness with decreased bite force; limited range of motion; crepitation or clicking; and morning joint stiffness.[55,75-77] The pain is occasionally referred to the temporal region and angle of the mandible. As the disease progresses, the condylar bone is resorbed and scar tissue is formed between the joint surfaces and within the joint capsule. This causes further limitation of movement of the jaw.[39,40]

Mandibular movement may be severely limited in the late stages of the disease. This is usually caused by fibrous ankylosis and rarely by bony ankylosis.[78] Perhaps the most striking feature of advanced RA affecting the TMJ is development of a progressive class II malocclusion and anterior open bite deformity with impairment of chewing and phonation. This deformity is caused by loss of normal ramus height secondary to destruction of the mandibular condyles.

Imaging Findings

Because RA is primarily a soft tissue disease, the early stages are characterized by the absence of radiographic changes. Even when these changes are present, they lack specificity and are difficult to interpret. However, with the use of MRI, changes such as disc destruction and/or displacement, condylar cortical bone erosion, joint effusion, and cartilage irregularity and thinning can be seen.[79,80] Once bone is involved in the later stages of the disease, radiographic changes in the TMJ occur in 19% to 84% of patients[55,71]; the incidence and severity of these changes are related to the duration of the disease.

The radiographic features of RA of the TMJ include loss of joint space, condylar destruction, and flattening and anterior positioning of the condyle. This may be accompanied by flattening and anterior positioning of the condyle as well as flattening of the articular eminence and erosion of the glenoid fossa.[81-83] In advanced stages of the disease, the radiographic changes may include a sharp, pointed condyle, osteophyte formation, lipping, shortened posterior ramus length causing premature posterior occlusion, an anterior open bite, and deepening of the antegonial notch.[39,40]

Laboratory Findings

RA has an autoimmune component, with 80% of RA patients testing positive for an immunoglobulin (Ig) directed at the Fc region of IgG known as rheumatoid factor (RF). High titers of RF have been correlated with severe joint destruction and subcutaneous nodules. Testing for RF by latex agglutination or sensitized sheep cell agglutination detects IgM antibodies, although IgG, IgA, IgE, and IgD antibodies have been described. IgM antibodies have the ability of complexing with five IgG molecules and are believed to be the cause of synovial inflammation. Smaller molecules, such as IgG antibodies, are believed to participate in the systemic manifestations and vasculitis common to this disease. Despite the strong association of RF with RA, it is not found only in this disease state. Chronic antigen presentation, as seen in diseases such as bacterial endocarditis, tuberculosis, viral infections, and advanced age, has also resulted in the formation of RF. None of these states is associated

with HLA-DR4, suggesting that the etiology may result from a combination of RF with the genetic antigen.[41,60] Other test results that are less specific for RA include a decreased serum albumin level and the presence of antinuclear antibody (ANA) in 15% of RA patients. HLA-Dw5 and HLA-DRw antigens are also both positive in 50% of RA patients.[39-42,46]

The preliminary diagnosis of RA is frequently based on clinical and radiographic findings, and laboratory tests are used to confirm the diagnosis. The most commonly used test is for RF, which is positive in 70% to 80% of patients with RA. Although the test is not totally diagnostic, it has a good diagnostic and prognostic value when the factor is present in high titers (above 1:1280). In these patients, the disease has a more severe and progressive course. However, the test is also occasionally positive in patients with one of the rheumatoid variants and in approximately 5% of healthy subjects.[84]

The Westergren erythrocyte sedimentation rate (ESR), although not a highly specific test for RA, is elevated in approximately 90% of patients during active stages of the disease, and the test often is used to follow the course of the disease.[77] The complete and differential blood cell counts frequently show a normal white blood cell count, although leukocytosis or leukocytopenia can occur in patients with RA. An elevated platelet count may accompany the stages of high activity of the disease, while mild anemia is reported in approximately 25% of patients. Most of the latter patients have a normochromic or slightly hypochromic, normocytic anemia. Synovial fluid aspirated from a joint with RA is usually cloudy; the viscosity is reduced and the white cell count is high (greater than 20,000/μL).

Diagnosis

The criteria for diagnosis of generalized RA are based on the presence of several clinical, radiographic, and laboratory findings for at least 6 weeks.[39,40,46] The diagnosis of RA of the TMJ is frequently less difficult because involvement of the TMJ often occurs in the advanced stages of the disease and, at that point, the diagnosis of RA has already been established. In these instances, the signs and symptoms, along with the positive radiographic findings, form the basis for diagnosing involvement of the TMJ by the disease.[84] However, in the absence of an already established diagnosis, the differential diagnosis of TMJ involvement should include psoriatic arthritis (PA), ankylosing spondylitis (AS), gout, and OA.

Differentiation of RA from the rheumatoid variants is based on factors such as age of the patient, pattern of involvement (symmetry), number and type of joints involved (polyarticular and peripheral joints), presence of rheumatoid nodules, and, to a lesser degree, laboratory findings (positive RF). Differentiation of RA from OA is less difficult and also is based on the clinical and radiographic findings and, to a greater extent, on some of the laboratory tests.[85]

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA; also juvenile rheumatoid arthritis, JRA) is a chronic inflammatory involvement of the joint lining that has an onset before the age of 16 years. The overall prevalence of JIA is uncertain, but estimates of the number of children affected in the United States range from 30,000 to 250,000.[86] The disease occurs predominantly in girls, with a female-male ratio of 2:1 to 3:1, and it has two peaks of onset, one between the ages of 1 and 3 years and the other between the ages of 8 and 12 years.[39-41]

The reported TMJ involvement in patients with JIA varies considerably, mostly because of the difference in the methods of examination in different studies. Nonetheless, up to 41% of children with JIA have TMJ involvement, with significant adverse effects on occlusion, oral health, and facial growth.[87-89]

Clinical Findings

ciarticular. The latter two are often further subdivided into two subtypes.[46]

Systemic JIA, called *Still disease,* occurs mostly in boys 5 years of age or younger, can affect any joint, and is usually accompanied by several systemic signs, including high fever, a rheumatoid rash, cardiopulmonary involvement, lymphadenopathy, and hepatosplenomegaly. The major complication of this disease is cardiac failure, but the majority of patients go into remission with minimal or no residual articular complications. Generally, patients in this subtype are seronegative for both RF and ANA.

Polyarticular JIA involves more than four joints and has fewer systemic signs. This subtype can be seropositive for RF and ANA in 50% of patients. The major complication of this subtype is the long-term possibility of deformity and disability from the polyarthritis.[74]

Pauciarticular JIA affects girls more often than boys, involves four or fewer joints, and has fewer systemic signs. This subtype usually affects large joints such as the knee, hip,

major hazards of this subtype are iridocyclitis and blindness. The prognosis for articular disability is greater than with the other two forms of JIA.

Although the TMJ can be involved in any of these subtypes, it is mostly affected by the polyarticular subtype. The clinical features of JIA of the TMJ include pain, joint tenderness, crepitation, stiffness, and decreased range of motion.[87-89] Some patients may even develop fibrous or bony ankylosis.

A characteristic feature associated with advanced JIA of the TMJ is a combination of micrognathia and a Class II skeletal deformity[91,92] and is frequently referred to as bird-face deformity. This deformity is a result of the impaired growth of the mandible caused by destruction of the

condylar growth site. Alterations in the soft tissues adjacent to the TMJ, such as scarring of the capsule and ligaments and changes in muscle strength, also can interfere with the normal growth processes of the mandible. The prevalence and severity of such deformity in patients with JIA of the TMJ are influenced by the age of onset and the duration of the disease. The prevalence of this deformity ranges from 0% to 38%.[78,92]

Imaging Findings

The early radiographic changes of JIA of the TMJ may not be visible on a conventional radiograph. However, these changes can be detected on MRI and include cortical bone erosion, disc thinning and perforation, reduction of the joint space, and pannus and effusion in the joint.[92-94] The radiographic changes usually appear late, and the severity of these changes is generally related to the duration of the disease. The radiographic findings in JIA of the TMJ in general resemble those of the adult disease and include erosion of the superior surface of the condyle (leaving a flat, horizontal, or inclined articular surface). The eminence may be eroded and flattened to the same degree as the condyle.

In advanced stages of the disease, these changes may significantly affect growth of the mandible and face. The mandible appears micrognathic, with a downward and backward rotation of the chin and an anterior open bite. This deformity is associated with radiographic evidence of deepening of the antegonial notch.[47,95,96]

Laboratory Findings

Laboratory findings in patients with JIA are not consistent and, when present, the abnormality varies with the mode of onset. RF is positive in 5% to 20% of patients with JIA, mostly with the pauciarticular and polyarticular subtypes, while the ANA test is positive mostly in patients with the pauciarticular subtypes (60% to 80% of these patients). Other laboratory findings, including low-grade anemia, leukocytes, thrombocytopenia, and elevated ESR, may also vary according to the subtype of JIA.

Diagnosis

A diagnosis of JIA of the TMJ is often not difficult to make because involvement of the TMJ usually occurs in the later stages. Because of the presence of fever and generalized arthralgia with the onset of systemic JIA, the differential diagnosis should include bacterial infection, viral polyarthritis, traumatic arthritis, infectious arthritis, and joint involvement with rheumatic fever.

Psoriatic Arthritis

Psoriasis is a dermatologic disease that affects approximately 1% to 2% of the general population. It is characterized by a rash of silvery scales affecting the elbow, scalp, and back. Approximately 5% to 7% of patients with psoriasis develop psoriatic arthritis.[97-99] In 75% of these patients, skin lesions appear before the joint symptoms, whereas arthritis appears first in 10% to 15% of patients; in another 10% to 15% of patients, the symptoms appear simultaneously.[100] PA is an inflammatory, mostly asymmetric, oligoarticular, seronegative arthritis that affects a limited number of joints including those of the hand, knee, and foot.

Reports on the disease incidence relative to sex differ from a predilection for males to equal predilection for males and females.[49,50] The onset of the disease is usually between the ages of 35 and 45 years. PA affecting the TMJ was first described by Franks.[101]

The cause is probably multifactorial, but histocompatibility studies support a propensity for the condition to be associated with several other systemic conditions such as Crohn disease; Reiter, Behçet, and Sjögren syndrome; and aortic incompetence.[46] Heredity and a history of trauma are significant factors in the development of PA.[40,100,102]

Despite the prevalence of PA in other joints, fewer than 35 cases of PA of the TMJ have been reported in the English literature.[103-105] However, some authors suggest that involvement of the TMJ with PA is more common and could be as great as 20%.[106] When PA affects the TMJ, the onset of symptoms occurs by the fourth decade of life and is usually associated with a history of trauma.[107,108]

Clinical Findings

The arthritic changes of PA are mostly limited to the distal interphalangeal and metacarpophalangeal joints, but occasionally may extend to the proximal interphalangeal joints, producing characteristic sausage-shaped digits. Systemic symptoms of PA include fever, fatigue, myalgia, weight loss, and malaise. Joint symptoms include morning stiffness and pain, swelling, and limitation of motion. Other associated symptoms may include nail dystrophy in the form of pitting and oncolysis in 80% of patients, and eye symptoms including conjunctivitis, iritis, and uveitis.[98]

Based on the presence of different clinical features, four distinct patterns of PA are currently recognized: (1) arthritis affecting mostly the distal interphalangeal joints; (2) severe arthritis affecting single or multiple joints, with widespread bone destruction and ankylosis; (3) seronegative polyarthritis that may be difficult to distinguish from seronegative RA; and (4) arthritis that is characterized by the presence of sacroiliitis, spondylitis, and peripheral joint involvement, as well as the presence of HLA-B27 antigen.[40,46]

PA of the TMJ often is unilateral, has a sudden onset, is episodic in nature, and may have a spontaneous remission. Symptoms include pain and tenderness of the joint area and the muscles of mastication, morning stiffness, tiredness in the jaws, joint crepitation, occasional painful swelling of the TMJ capsule, and painful mandibular movements associated with a progressive decrease in the interincisal opening.[103] In severe cases, ankylosis of the TMJ may occur.[104]

Imaging Findings

Radiographic changes associated with PA may be seen in as many as 82% of patients with affected TMJs and include erosion, flattening, osteoporosis, loss of joint mobility, and extreme joint space narrowing. Subchondral bone cysts,

subluxation, and ankylosis are also observed occasionally.[79,106,108,109] The radiographic changes are nonspecific and cannot be easily distinguished from those of other types of arthritis, particularly RA and AS.

Diagnosis

Because the symptoms of TMJ involvement are generally nonspecific, the diagnosis of PA of the TMJ is difficult and is made mainly on the basis of the systemic presentation of the disease. In general, the diagnosis is based on a triad of (1) psoriasis, (2) radiographic evidence of erosive polyarthritis, and (3) a negative serologic test for RF. However, even in the presence of a skin rash, the diagnosis of PA cannot be absolutely confirmed. The differential diagnosis of PA should always include entities such as RA, Reiter syndrome, AS, and gout.

Ankylosing Spondylitis

Ankylosing spondylitis is a disease known by many other terms, but two of the most commonly used are *Marie-Strümpell disease* and *seronegative spondylitis*. It is a chronic and usually progressive inflammatory disease that primarily affects the axial skeleton, most commonly the sacroiliac joint and the vertebral column. When the disease spreads to the peripheral joints, the most commonly affected are the hips, shoulders, knees, wrists, hands, and TMJ. The disease has a prevalence of 0.4% to 1.6% among whites, with a strong familial tendency.[45] It affects both sexes, with a predilection for men up to 10 times greater that for women, and has an onset between the ages of 20 and 30 years.[40,46,110]

When affected, the TMJ is usually involved several years after the onset of the systemic disease and frequently during the late stages of spinal and peripheral joint involvement. Although only sporadic case reports of AS of the TMJ have been published, involvement with AS is reported to occur in 4% to 50% of such patients.[111-113]

Clinical Findings

The clinical signs and symptoms of AS generally arise from chronic inflammation of the synovial tissues and joint capsule and sites of insertion of ligaments and tendons. The inflammation later progresses to ossification and eventually causes limitation of joint motion. In the spine, this results in low back pain and stiffness that are usually worse in the morning but that can be alleviated by mobility and exercise. In the late stages, fusion of the adjacent vertebrae and fixation of the back in extreme flexion causes decreased spinal mobility, lumbar lordosis, and increased thoracic and lumbar kyphosis with limitation of chest movement. The back pain may be referred to the buttocks and the posterior aspect of the leg. Extra-articular manifestations of AS include iritis or anterior uveitis and cardiac symptoms such as aortic insufficiency and conduction defects.[46]

When the TMJ is affected, pain, stiffness, limitation of jaw movements, and, in advanced cases, ankylosis of the joint may occur.[114-116] Often the severity of the TMJ involvement correlates with the severity of the spinal and peripheral involvement, although TMJ symptoms have been reported in patients with only a slightly affected spine.

Imaging Findings

The radiographic features of the disease usually include ossification of ligaments and tendons and sclerotic fusion between the vertebrae. In the late stages of the disease, calcification of the annulus under the paraspinal ligaments gives rise to the characteristic "bamboo spine" appearance. The pelvic radiographs usually show fusion of the sacroiliac joint and sclerotic widening of the margins of the pubic symphysis.[114]

The radiographic features of AS in the TMJ are nonspecific and are observed in 30% of patients. These features usually involve erosive changes in the condyle and fossa, subchondral sclerosis, and osteophyte formation. In the later stages of the disease, narrowing of the joint space and radiographic evidence of restricted anterior translation of the condyle may be detected.[114,115,117]

Laboratory Findings

AS characteristically has a hereditary component; the incidence of occurrence of HLA-B27 antigen is higher in

generally nonspecific and serves only as a rough gauge of the disease. Tests for RF are generally negative.[40,41,46]

Diagnosis

Because of the similarities among RA, PS, and AS, the differential diagnosis should include these entities. However, some features exist that may be helpful in distinguishing AS from the other two conditions. These include involvement of the sacroiliac joint, which, although possible with any of the other types, is only common in AS and is rare in RA. Furthermore, whereas AS may involve peripheral joints, it usually spares the small joints of the hands and feet. Although radiographically apparent erosive changes and narrowing of joint space and osteophyte formation are common in all three diseases, localized or extensive sclerosis is more common in AS, whereas cortical erosion and subcortical bone cyst formation are more common in RA.[39,40,45]

Reiter Syndrome

Classically, Reiter syndrome (RS) is a triad of arthritis, conjunctivitis, and urethritis occurring mostly in men between the ages of 20 and 30 years. More recently, additional frequent features of the disease have been recognized, including mucocutaneous lesions and cardiac and central or peripheral nervous system involvement. The exact cause of the disease is unknown, but the frequent presence of HLA-B27 alloantigen in the patient population has been established. The disease occurs mostly in young men after venereal infection and in both men and women after dysenteric infection.[70] Hans Reiter first described RS in 1916, when a lieutenant in the Prussian army developed the three typical features.[118]

The arthritis in Reiter syndrome often involves multiple joints (resembling RA), but affects mainly the lower extremities. Involvement of the TMJ is rare, but some authors believe its incidence may be grossly underreported because of the lack of specific clinical or histologic features of the disease.[119,120]

Clinical Findings

The manifestations of the disease include development of urethritis, conjunctivitis, and finally arthritis either sequentially or simultaneously. Fever, fatigue, weight loss, and lymphadenopathy often accompany the arthritis. Both the urethritis and the conjunctivitis can develop and resolve without sequelae, or they can cause long-lasting urologic and ocular complications. Skin lesions, known as keratoderma blennorrhagica, may occur on the palms, soles, and glans penis. As many as 80% of patients with Reiter syndrome may show oral lesions in the form of 1- to 10-mm papules on the lips, gingivae, buccal mucosa, and tongue.[107]

When the TMJ is affected, the symptoms are generally acute and asymmetric and include tenderness, erythema, and warmness of the joint.[119]

Imaging and Laboratory Findings

Radiographically, bony changes in the joints affected by Reiter syndrome are only observed in the late stages and consist of erosion of the condyle and loss of the joint space.[119,120] The laboratory findings are mostly nonspecific and may include an elevated ESR, leukocytosis, mild anemia, and negative tests for RF and ANA. Serologic evidence of recent infection and an HLA-B27 marker may be present.[70]

Diagnosis

The diagnosis of Reiter syndrome is clinical and is based on the triad of symptoms that are present in 70% of patients in the first 10 days. However, only the presence of seronegative, oligoarticular, asymmetric arthritis and urethritis is adequate for diagnosis of the syndrome. The differential diagnosis should include PA and other forms of reactive arthritis, such as those associated with ulcerative colitis and regional enteritis and that occurring after intestinal bypass surgery.

Infectious Arthritis

General

Although infectious or septic arthritis of the TMJ is frequently considered a possible complication of such systemic diseases as tuberculosis, syphilis, and gonorrhea, only 22 cases have been reported.[40,121] Some authors attribute the small number of reported cases to misdiagnosis or underreporting and suggest that misdiagnosed septic arthritis in children may account for a significant percentage of cases of mandibular ankylosis.[122,123]

Infectious arthritis can involve the TMJ by direct extension of local odontogenic infections via the pterygomandibular space, from osteomyelitis of the mandible (Figure 38-7), or from parotid, ear, or throat infections.[124] Direct infection can also occur as a result of inoculation of organisms into the joint space during traumatic injury or joint surgery.[125]

The other major route of infection of the TMJ is from a systemic disease such as gonorrhea, syphilis, tuberculosis, or actinomycosis.[40] Risk factors for TMJ infection include the presence of RA, diabetes mellitus, intravenous drug abuse,[126] burn wounds,[127] sexually transmitted diseases,[128] preexisting joint disease,[129] trauma, and steroid therapy.[40,46]

Despite the decreased incidence of some of the systemic infectious diseases known to predispose to septic arthritis, an increase in the frequency of septic arthritis can be expected in the future because of the large number of immunocompromised patients with acquired immunodeficiency syndrome (AIDS) and the wider use of immunosuppressive agents. This form of septic arthritis may be either bacterial (including chlamydia) or fungal in origin.[78,130] Another form of infectious arthritis that can have serious consequences involves infection of a joint prosthesis. Such infection can occur immediately after implant placement or later from hematogenous dissemination of bacteria.[46] However, despite several reports of such infections in the orthopedic literature, only two cases involving the TMJ have been reported.[126]

Clinical Findings

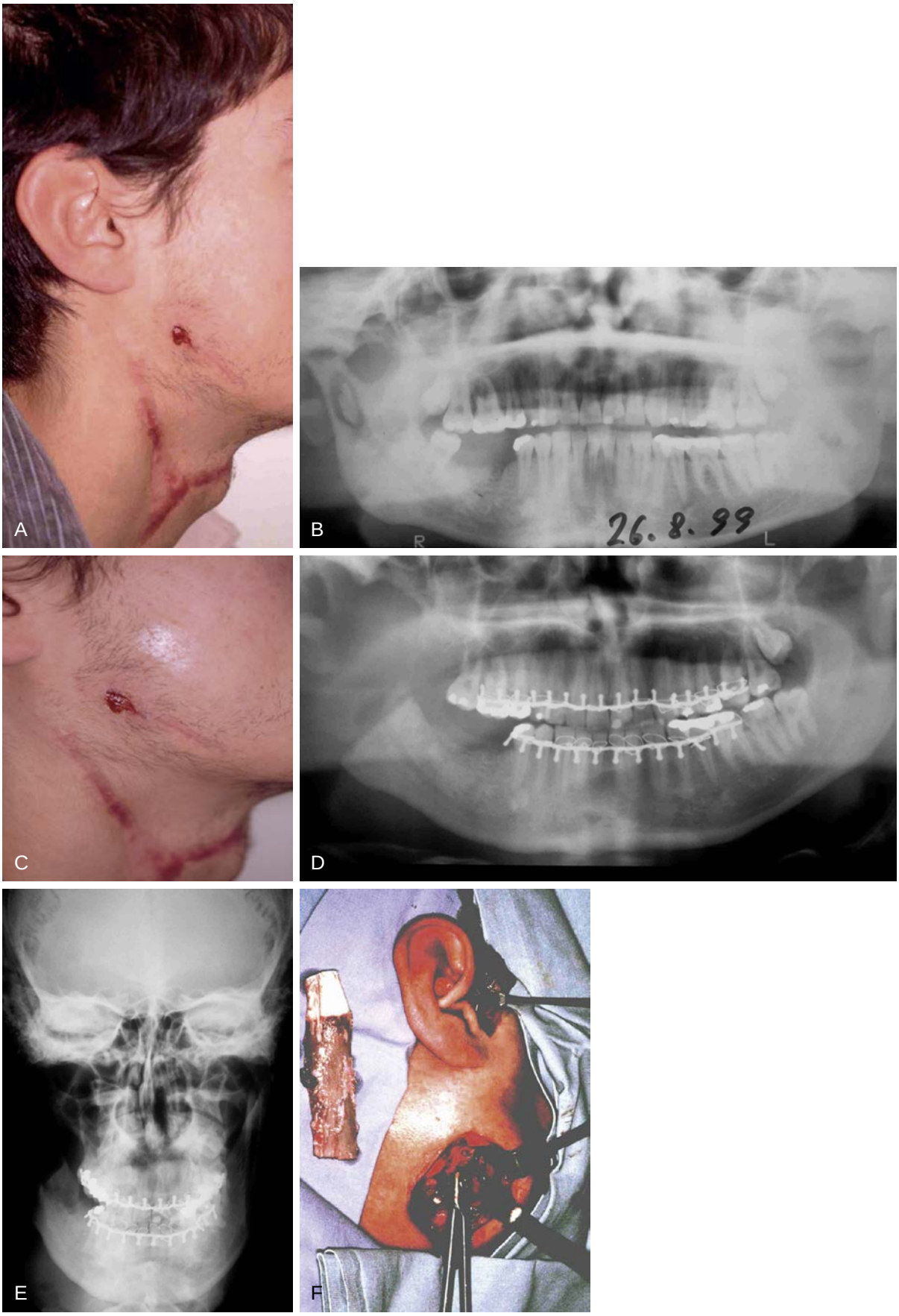
When the cause of the infectious arthritis is systemic, the joint symptoms may be preceded by a prodromal period of symptoms of the primary disease. The acute presentation of septic arthritis includes signs of malaise, fever, chills, sweating, and regional lymphadenopathy. The affected joint (usually one side) is painful, tender, swollen, warm, and erythematous. Movement of the mandible is usually limited and typically elicits severe pain. Occasionally, malocclusion, deviation of the mandible to the contralateral side, and a posterior open bite will occur secondary to the increased amount of joint fluid.

Fluctuation may be present in the region of the joint if the fluid collection is not drained. If septic arthritis is left untreated, it may progress to complete destruction of the condylar cartilage and bone, causing ankylosis, which in children may cause underdevelopment of the mandible and facial asymmetry later in life.

Imaging Findings

Because no bony involvement occurs in the first 7 to 10 days of infectious arthritis, radiographic changes are not demonstrable.[78] However, because of accumulation of intra-articular fluid or pus, a separation of the articular surfaces, in which the mandibular condyle is in a more anteroinferior position, can be seen on either a panoramic radiograph or CT scan of the joint. Later, if the infection is left untreated, bony changes range from destruction of the articular cartilage to total destruction of the joint.

MRI can be used to detect intra-articular pus or accumulation of exudate,[39,40] although it is not helpful in



• **Figure 38-7** Clinical case of infectious arthritis deriving from molar dental infection followed by live threatening mediastinitis and proceeding into condyle osteomyelitis. **A,** Side view of patient with incision scars at the right submandibular neck and pus drainage at the mandibular angle. **B,** Preoperative panoramic radiograph with affected right condyle and TMJ. **C,** Close-up side view. **D,** Panoramic radiograph after resection of right condyle. **E,** Anteroposterior radiograph after resection of right condyle. **F,** Osteochondral rib graft, preauricular and submandibular access.

distinguishing infection from inflammatory, traumatic, or degenerative processes in the joint.[40] A bone scan usually shows an increased uptake in the joint capsule in the presence of septic arthritis, and it can detect bone changes sooner than other imaging studies.[121]

Laboratory Findings

Laboratory tests for septic arthritis in the presence of systemic signs should include a complete blood cell count, a differential cell count, ESR, C-reactive protein determination, and blood culture. Joint fluid should be aspirated for analysis and culture whenever feasible. The aspirated fluid should be examined with a Gram stain, culture, and antibiotic sensitivity testing, a complete blood cell count, and a differential cell count. Glucose and hyaluronic acid levels also should be analyzed. These levels are usually decreased. Typically, the aspirated fluid from an infected joint contains cloudy exudate and sometimes pus. The number of leukocytes is elevated, and the cells are predominantly of the polymorphonuclear type.

Although bacterial growth is obtained in only 62% of cases,[121] when positive it confirms the diagnosis of septic arthritis. The most commonly isolated organism from patients with septic arthritis of the TMJ is *Staphylococcus aureus*,[131,132] although isolation and growth of other organisms, such as gonococci[128] and viruses,[133] have also been reported.

Diagnosis

The diagnosis of septic arthritis should be considered in all cases of monoarthritis associated with high-grade fever, acute severe pain, and tenderness of the TMJ. The diagnosis is confirmed by identification of the organism in the joint aspirate. In the absence of such a laboratory finding, the clinical presentation, radiographic features, other positive laboratory values, and response to antibiotic therapy should provide a basis for the diagnosis.[40,41,134] The differential diagnosis should include RA with acute exacerbation, JIA, PA, traumatic arthritis, viral polyarthritis, disseminated malignancy, and gout.

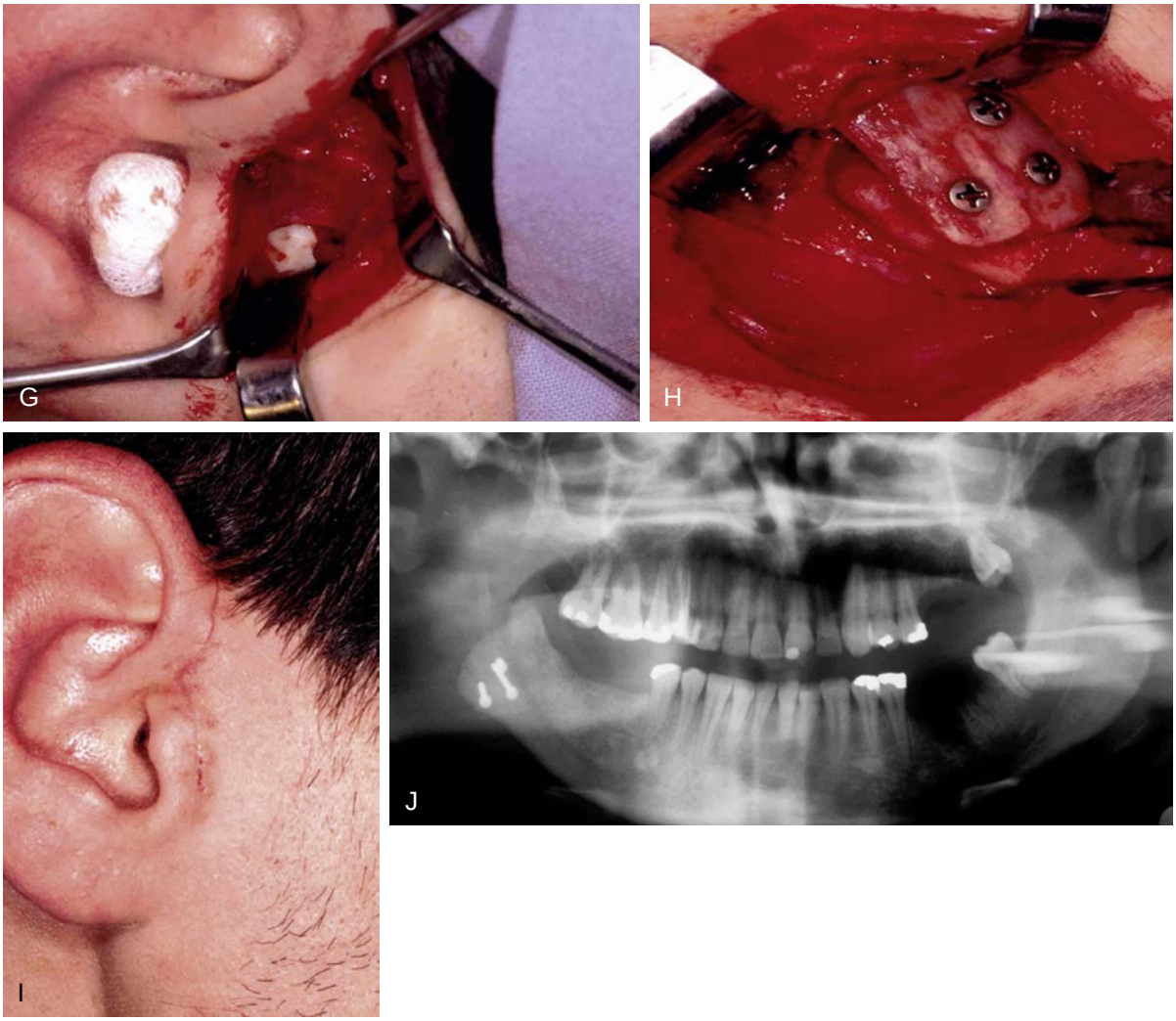


Figure 38-7, cont'd **G,** Preauricular view of inserted graft. **H,** Submandibular view of inserted graft. **I,** Preauricular scar after 2 weeks. **J,** Panoramic radiograph after reconstruction with osteochondral rib graft.

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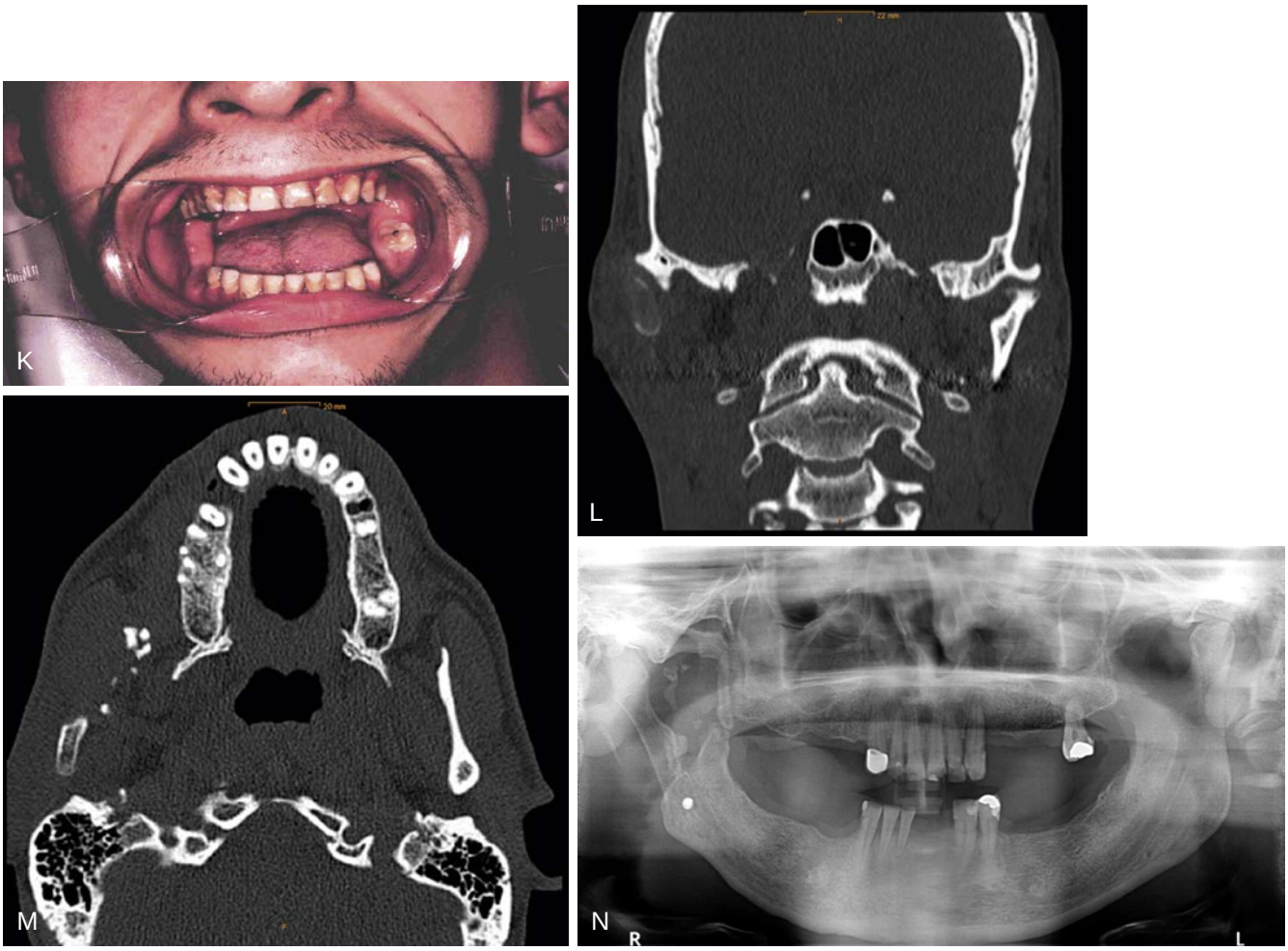


Figure 38-7, cont'd **K,** Mouth opening without mandibular deviation. **L,** Coronal view on patient's computed tomography (CT) scan—10 years after surgery. **M,** Axial view on patient's CT scan—10 years after surgery. **N,** Panoramic radiograph—15 years after surgery.

Lyme Disease–Associated Arthritis

Lyme disease (named after the town of Lyme, CT) is a multisystem disorder that involves the skin, joints, nervous system, and heart. It is caused by the spirochete *Borrelia burgdorferi* and is mostly transmitted by the tick *Ixodes dammini*.[135] Although the disease usually affects only one or two large joints, often the knee, the TMJ can also be involved.[136,137]

Clinical Findings

The initial presentation of the disease is marked by the appearance of a characteristic skin lesion called erythema chronicum migrans (ECM), a clinical marker for Lyme disease. ECM begins as a red macule or papule at the site of a tick or insect bite. Days to a month later, the lesion expands to an average diameter of 10 cm (range, 8 to 68 cm), with partial clearing of the center of the lesion. The outer borders become red and generally flat, while the center is indurated, vesicular, or necrotic. The lesions are usually warm but not painful. They are frequently associated with constitutional symptoms such as fever, malaise, headaches, and regional lymphadenopathy.[138] Generalized lymphadenopathy and splenomegaly are less common findings.

Within a few days to months of the onset of ECM, secondary lesions develop. These lesions are similar in appearance to the ECM but are usually smaller, migrate less, lack the indurated centers, and are not associated with tick bite sites. In some patients, the secondary lesions are associated with a malar rash, conjunctivitis, or, rarely, with a diffuse urticaria.[46] Other systemic signs include neurologic involvement, which appears at the same time as the ECM or weeks to months later. They also include meningoencephalitis, vertigo, short-term memory loss, numbness or tingling of the extremities, atypical facial pain, and bilateral facial nerve paralysis. Cardiac abnormalities are less common, can last from a few days to several weeks, and may be recurrent. They include atrioventricular block, myopericarditis, and cardiomegaly.[138]

Musculoskeletal involvement by Lyme disease occurs in approximately 60% of patients and appears from a few weeks to 7 years after the onset of the disease. The arthritis is usually manifested as a migratory polyarthritis or myalgia

associated with joint swelling. Months to years later, frank arthritis occurs, characterized by intermittent attacks of painful swelling of one or two large peripheral joints such as the knee. The pain is often episodic and of short duration, followed by periods of complete remission and then recurrence. The affected joints are usually swollen and may be warm but are rarely erythematous. Occasionally, joint involvement is polyarticular and symmetric, including the small joints of the hands and feet.

In approximately 10% of patients with arthritic signs of Lyme disease, the condition evolves into chronic arthritis, causing deformity and disability.[46]

Diagnosis

Because many of the signs and symptoms of Lyme disease are nonspecific and may mimic TMJ involvement from other causes, the diagnosis can be difficult, especially in the early stages. Therefore, these conditions should be included in the differential diagnosis. The diagnosis of Lyme disease can be facilitated by a history of tick bite and skin rash. In the absence of such a history, the diagnosis is more difficult, but the presence of an immunoglobulin M antibody to spirochetes may be a helpful diagnostic test.

B. burgdorferi has also been cultured from the skin lesions of ECM and from several body fluids, including the synovial fluid of affected joints.[138,139] Lyme arthritis that persists after antibiotic treatment is correlated with persistence of the spirochete in the synovial fluid.[138,139] Other laboratory findings useful in the diagnosis include an elevated white blood cell count in the synovial fluid (approximately 25,000/μL) that consists mostly of neutrophils, and an elevated serum aspartate aminotransferase.[40,46]

Metabolic Arthritis

Gout and Pseudogout

Gout (uric acid arthritis) and pseudogout (pyrophosphate arthropathy, chondrocalcinosis articularis, and calcium pyrophosphate dihydrate arthropathy) are the two main types of metabolic arthritis affecting the TMJ.[78,140] They are characterized by inflammation of the joint tissues caused by deposition of microcrystals in the synovium. In gout these crystals are sodium urate, and in pseudogout they are calcium pyrophosphate dihydrate.

Gout is characterized by an increase in the serum level of uric acid, generally arising from an inherited anomaly that causes an increase in purine (and uric acid) production and/or a decrease in the excretion of uric acid in the urine. However, it may also be caused by an increase in uric acid production resulting from blood dyscrasias (where cells rich in purine are broken down) or by use of certain medications, such as diuretics.

Pseudogout is regarded by some as an independent disease that often occurs in association with other metabolic diseases, such as hyperparathyroidism and diabetes mellitus.[78] Gout is uncommon in men and women younger than 40 years. It mostly affects men older than 40 years. A suggestion of genetic inheritance exists, with a family prevalence that varies from 40% to 60%. The disease is often associated with tophi (urate deposits) in and around the ear and joints of the extremities, renal disease, uric acid nephrolithiasis, and some degree of renal failure. Although the prevalence of gout is 5% among men 65 years and older and 2% among women of the same age,[140] only a few cases of TMJ involvement have been reported.[140,141] The exact prevalence of pseudogout in the TMJ is uncertain, but it frequently affects persons after the age of 40 to 50 years and has an equal sex predilection.[141,142]

Clinical Findings

The clinical presentation of a metabolic arthropathy is quite characteristic. The onset is usually sudden and is most often monoarticular, affecting the proximal interphalanx of the great toe, the ankle, and the wrists and causing pain and swelling in about 50% to 70% of patients. The affected joint is usually erythematous, warm, and extremely tender. In the acute presentation of the disease, the patient may feel ill and feverish.

When the TMJ is involved, the patient's ability to open the mouth wide and masticate is significantly decreased.[140,142-144] Occasionally, the onset and presentation may be less dramatic in the TMJ than in other joints, and the signs and symptoms are less severe. The latter include mild pain, limited mouth opening, and noise in the joint.

Imaging Findings

Radiographic changes do not become apparent in the joint until several years after the onset of gout. Although no specific radiographic features exist for gout, the changes in the advanced form of the disease have been described as bony erosion, "punched-out" cystic lesions of the bone, bone spurs, and exostoses.

In the case of pseudogout, osseous tophi within the joint and calcification of the disc may be demonstrable in the radiographs. The crystal deposits may have a punctate or linear appearance.[78,142]

Laboratory Findings

Typically, the serum uric acid level is elevated in gout. Aspiration of joint fluid reveals an opalescent fluid. Monosodium urate crystals are present when the fluid is examined under the polarizing microscope. Acute attacks are generally associated with leukocytosis and an elevated ESR. In pseudogout, the serum uric acid is increased in only 30% of patients.[78]

Diagnosis

The diagnosis of gout can be readily made if the disease presents in its acute form. If the symptoms are mild, determination of the serum uric acid level may be helpful. Because the serum uric acid level may also be increased in numerous other conditions, the diagnosis can only be confirmed by identification of uric acid crystals in the synovial fluid or in the surgical specimen. The monosodium urate crystals are needle shaped and have a strongly negative birefringence

vitis (especially in the great toe), a history of renal colic, and a family history of gout make the diagnosis more likely. The differential diagnosis of gout should include septic arthritis, pseudogout, acute RA, PA, OA, and local trauma.

Arthritides Associated with Connective Tissue Diseases

Systemic lupus erythematosus (SLE) is a chronic autoimmune multisystem disease arising from a combination of genetic and environmental factors that interact to cause a state of immune hyperactivity. Systems that SLE commonly may affect include the brain and peripheral nervous system, skin, joints, kidneys, lungs, serous membranes, and components of the blood, but other organs of the body also may be affected. The characteristic immune response is caused by certain self-antigens and involves both T- and B-cell activity. One of the most common symptoms of SLE is symmetric polyarthritis, most frequently occurring in the fingers, knees, and wrists. TMJ involvement has been found in a few studies.[45,145,146] In a controlled study of SLE patients, one third had subjective TMJ symptoms, 22% had clinical signs, and 11% had radiographic changes.[45,146]

Scleroderma

Progressive systemic sclerosis is a generalized disorder of connective tissue recognized clinically by thickening and fibrosis of the skin (scleroderma) and specific forms of involvement

the ages of 30 and 50 years. The disease is three to four times more frequent in women. Because better diagnostic techniques are now available, the prevalence may be higher than previously recognized. The precise incidence remains undefined, but most studies suggest between 4 and 12 subjects per million per year.[147] Characteristic oral manifestations that may complicate dental treatment include limited mouth opening, TMJ dysfunction, mucogingival problems, xerostomia, telangiectasia, increased periodontal ligament width, and osseous resorption of the mandible.[148,149]

Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD) is a disorder showing overlapping features with a number of different connective tissue diseases. Because of the various overlapping features that have been reported, the existence of MCTD as a distinct disease entity has previously been considered controversial. Today, however, it is regarded as a distinct rheumatoid disease, although the exact prevalence is not known.[150] Clinical manifestations of MCTD often include concurrent development of features of SLE, scleroderma, polymyositis, dermatomyositis, and RA, but the overlapping features usually occur sequentially. Because of these overlapping features, it often takes several years to verify the most appropriate diagnosis. Early symptoms include fatigue, myalgia, arthralgia, and Raynaud phenomenon. Nearly all patients have joint pain and stiffness.[150] In a series of 10 patients with MCTD analyzed for signs and symptoms in the masticatory system, all 10 patients showed symptoms or signs of temporomandibular disorders, and 7 had radiographic changes in the TMJ.[151] In five patients with normal-appearing mucosa, histologic examination revealed chronic inflammation.

Sjögren Syndrome

Sjögren syndrome (SS) is a systemic autoimmune disease of unknown etiology and pathogenesis leading to xerostomia and dry eyes.[152] These "sicca" ("dry") symptoms result from an autoimmune process that often may affect other organs, such as neural systems, skin, mucosa, lungs, and kidneys. SS also can develop as a secondary phenomenon, in which the sicca symptoms are associated with RA, SLE, or scleroderma. The prevalence of primary SS, judging from blood donor subjects, has been estimated to be 0.08%. SS is sometimes associated with polyarthritis, and thus the TMJ may also be affected.[45]

Summary

More than 100 heterogenous acute and chronic conditions, some with multisystem involvement, can affect the musculoskeletal system. Clinically, the most important of these conditions that affect the temporomandibular joint (TMJ) complex are the systemic diseases of the musculoskeletal system and the systemic connective tissue disorders. The more common systemic diseases affecting the TMJ are seropositive rheumatoid arthritis and juvenile rheumatoid arthritis. Far less common diseases and disorders are ankylosing spondylitis; psoriatic arthritis; Reiter syndrome, also known as reactive arthritis; gout and calcium pyrophosphate deposition disease; systemic lupus erythematosus; scleroderma; mixed connective tissue disease; and Sjögren syndrome, chronic inflammatory bowel disease, reflex sympathetic dystrophy, and sarcoidosis.

Tumors

Tumors of the TMJ are rare. They may develop from the disc, the synovial membrane, and the articular capsule but also the articulating bones, that is, the glenoid fossa and especially the mandibular condyle. As in most other sites benign proliferations are more common than malignancies. As in other bones, the most frequently occurring malignancy is metastatic carcinoma (Figure 38-8). Despite metastatic lesions, consideration should be given to locally invasive proliferations of lymphocytic, parotid, or middle ear origin.[153-155]

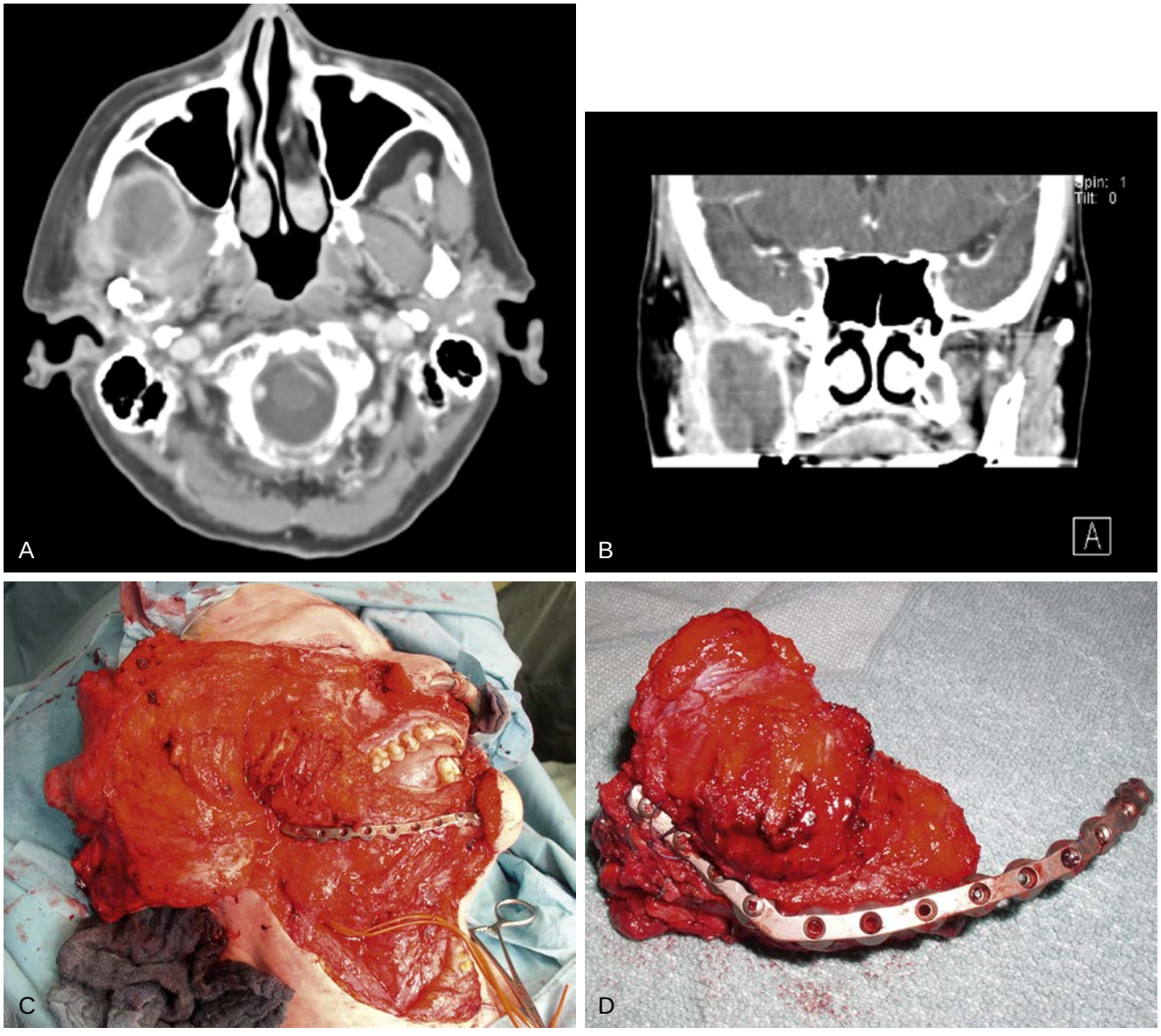
Space-occupying lesions of the TMJ may present with preauricular swelling, pain, trismus, deviation of mandibular motion, and malocclusion. All these symptoms also correlate with far more common entities within the plethora of

temporomandibular disorders. Therefore immediate correct diagnosis of neoplasms in the TMJ is demanding and can be delayed. Radiographic examination and interpretation is necessary, and CT and MRI techniques are often helpful in diagnosis.[153-158]

joint sounds, the following signs are indicative of advanced disease. The tumor mass may extend into the middle cranial fossa through the roof of the glenoid fossa. It may also invade through the glenoid fossa posteriorly and present as a lesion of the external auditory canal or middle ear. Growing laterally, it may mimic a parotid neoplasm, creating a preauricular swelling. Anteromedially it can extend into the infratemporal and pterygopalatine fossae and produce symptoms of cranial nerve involvement. Pathologic fracture with sudden onset of pain may also occur.[153-155]

When formulating a differential diagnosis for any jaw lesion, it is helpful to organize the pathologic entities into several categories and then compare the characteristics of the presenting lesions with those of lesions in each category. In the field of oral and maxillofacial surgery, jaw lesions are suggested to be organized into the following six categories[155-159]:

1. Developmental cysts
2. Odontogenic cysts



• **Figure 38-8** Clinical case of tumor of the temporomandibular joint (TMJ): recurrence of an oral squamous cell carcinoma in the infratemporal region involving the right TMJ. **A,** Axial view on patient's CT scan—recurrence, right infratemporal region. **B,** Coronal view on patient's CT scan—recurrence, right infratemporal region. **C,** Access via soft tissue degloving and temporary zygoma resection. **D,** Resected tumor specimen including TMJ and attached mandibular reconstruction plate from previous surgery.

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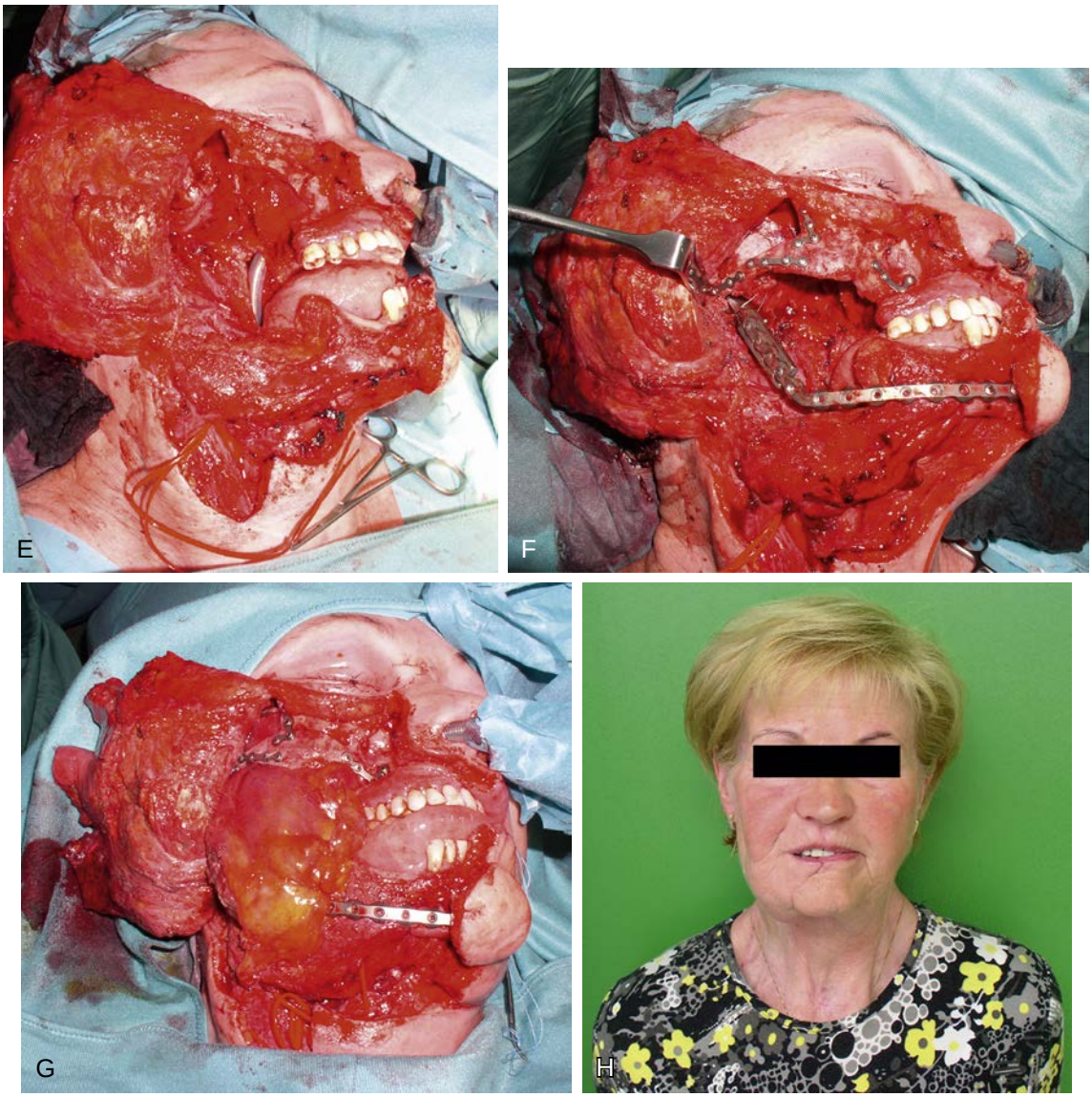


Figure 38-8, cont'd **E,** Empty infratemporal region. **F,** Immediate reconstruction with placement of mandibular reconstruction plate including prosthetic condyle. **G,** Immediate reconstruction with insertion of microanastomosed myocutaneous latissimus dorsi flap. **H,** Postoperative image of patient.

3. Benign odontogenic tumors and lesions
4. Benign non-odontogenic tumors and lesions
5. Inflammatory, metabolic, and genetic disorders
6. Malignant and locally invasive lesions

The presence of developmental cysts, odontogenic cysts, and benign odontogenic tumors in the condyle or TMJ is rare and generally represents an extension of a process that initiated in the tooth-bearing segments of the mandible. Diagnosis and management of those lesions are covered elsewhere and are not discussed here. The benign conditions that are considered here do not all represent neoplasms. Some are cystic lesions but are important in differential diagnosis. Others may be reactive or hyperplastic proliferations, in which the distinction from a benign neoplasm is often unclear.

Benign Tumors, Cysts, and Cystlike Lesions

Condylar Hyperplasia

The articular surface of a normal condyle is composed of fibrocartilage that exhibits appositional growth in contrast to endochondral ossification. Histologic sections of hyperplastic condyles demonstrate the abnormal presence of hyaline cartilage that undergoes ossification and results in abnormal growth. Therefore condylar hyperplasia can have presenting symptoms similar to those of space-occupying benign or malignant lesions, which can displace the condyle from the fossa and cause asymmetry with malocclusion. The etiology of this disorder is not well understood.

Condylar hyperplasia is categorized into two types. The type I deformity, or *hemimandibular elongation*, is the most



Figure 38-8, cont'd **I,** Intraoral soft neopalate of patient 3 years after surgery. **J,** Image of patient 3 years after surgery.

common variant. The mandible is asymmetric, with deviation of the chin to the contralateral side and a concomitant dental crossbite. In patients with the type II deformity, or *hemimandibular hypertrophy*, deviation of the chin is not a prominent feature, but a marked vertical open bite is present on the ipsilateral side of the hyperplasia.[160,161]

Condylar hyperplasia is not a truly neoplastic process but actually a self-limited disorder. Radionuclide bone scans with technetium-99m can be useful in differentiating between active and inactive disorders. Some surgeons favor the use of a high condylar shave to remove the zone of abnormal tissue if the disorder is diagnosed early in its active stage. Removal of only 5 or 6 mm of the most superior condylar surface is usually adequate, and condylectomy is unnecessarily aggressive.[162,163]

Recontouring of the inferior border and angle of the mandible is sometimes necessary to correct the inferior component of the asymmetry. When a bone scan indicates that the process is inactive, orthognathic procedures, such as a vertical subsigmoid osteotomy, can be useful in correcting an open bite while maintaining a functional joint articulation.[162,163]

Chondroblastoma

These tumors develop in the medullary cavity of a bone and are thought to arise from the cartilage of the growth plates. Thus, most cases occur prior to skeletal maturity; the vast majority occur in patients aged 10 to 20 years.

Chondroblastomas usually involve the epiphysis of the distal femur and proximal tibia. These sites are followed in frequency by the proximal humerus and proximal femur. When the tumors develop in more unusual locations, the patients are usually older. Thus, the mean age of patients with tumors of a long bone is 16 years, whereas the mean age in patients with flat and short tubular bone involvement is 28 years.[164] In the mandibular condyle the reported age range has been from 27 to 41 years,[165] and there is a 2:1 male predilection.

Pain is the dominant symptom in the extremities, but swelling or limited motion is prevalent with condylar tumors. Radiographically, they produce a well-defined radiolucency with a sclerotic margin. Flocculent radiopacities may be seen within the lesion.

Chondroblastomas of the skull and facial bones are very uncommon, but it is interesting to note that among the 30 cases reported in a single series, three arose in the mandibular condyle. Twenty-one patients had tumors in the temporal bone, and two of these also extended into the TMJ.[166]

The chondroblastoma is a benign tumor of immature cartilage cells with foci of cartilage matrix formation. The proliferating cell is believed to be a chondroblast. The cells are round to oval, with central or eccentric round to oval nuclei that may have a longitudinal cleft. These cells may be densely packed, and scattered multinucleated giant cells are usually prominent. Interspersed areas show cartilage differentiation and an immature cartilaginous matrix, which appears as an amorphous pinkish tissue. The proportion of these two types of tissue is quite variable. Calcifications tend to form a fine, "chicken wire" pattern around

the chondroblastic cells, although a coarser pattern may be present. Aneurysmal bone cysts develop in about 20% of cases.

Aneurysmal Bone Cyst

Several cases of aneurysmal bone cyst have been reported in the TMJ.[167] These lesions are not actually cysts but rather tumors in which there are widely dilated, blood-filled spaces that are not lined by endothelium. Frequently these tumors occur as a secondary phenomenon within a preexisting pathologic process, most often a giant cell tumor, but also with other conditions such as osteoblastoma, chondroblastoma, and nonossifying fibroma. There is a near-equal distribution between the sexes, and the majority arise in individuals younger than 20 years. In 32 cases in the mandible reported by Trent and Byl,[168] only 2% occurred in the condyle.

The histories concerning the cases in the condyle have varied from rapidly expanding, destructive lesions to incidental findings. The majority of patients had experienced previous trauma.

Pseudocysts

Pseudocysts of the mandibular condyle are asymptomatic radiolucencies with corticated margins. They are seen in the anterior aspect of the condyle and are the result of cupping of the pterygoid fovea; the margins are formed by the dense medial and lateral condylar ridges.

The image is the result of a radiographic distortion when the central x-ray beam does not pass through the condyle at right angles but rather passes obliquely in the horizontal plane and superiorly in the vertical plane. Consequently, the medial ridge is projected posteriorly and superiorly, and the lateral ridge is projected anteriorly and inferiorly. These "lesions" are thus not pathologic processes.

In a Veterans Affairs population of 507 patients aged 22 to 96 years, 9 (1.8%) such cases were found.[169] In a population of 1193 patients aged 18 years and younger, 18 (1.5%) such cases were found.[170]

Idiopathic Bone Cavity (Traumatic Bone Cyst, Hemorrhagic Bone Cyst, Simple Bone Cyst)

Idiopathic bone cavities in the jaw usually are located in the body or symphysis. Approximately 10 cases have been reported in the TMJ.[171] These are essentially asymptomatic lesions. When associated symptoms have occurred, they have usually been caused by a pathologic fracture.

The diagnostic criteria for an idiopathic bone cavity include the presence of a single lesion, the absence of an epithelial lining, and the absence of infection. The lumen should be empty save for some fluid or air. The wall is bony, although a scant amount of fibrous tissue may be present. Many of these cavities appear to undergo spontaneous regression. Similar lesions may be observed in association with other entities, such as florid osseous dysplasia and other fibro-osseous processes.

Central Giant Cell Granuloma

Central giant cell granulomas represent fewer than 7% of all benign jaw tumors; of these, 70% occur in the mandible. The body of the mandible is the area of predilection. There is a female preponderance, and the majority of patients are younger than 30 years. The condyle is an unusual location, although several eases have been reported.[172]

In the condyle, both unilocular and multilocular lesions have been described. Some have been asymptomatic, without functional impairment, even in the presence of preauricular swelling. Histologically, these tumors consist of randomly scattered multinucleated giant cells within a cellular fibrous stroma that also contains extravasated blood. The giant cells are osteoclastic cells, so these lesions represent an osteoclastoma.

A more aggressive giant cell lesion, referred to as a *giant cell tumor,* has been described in the jaws and facial bones but not in the mandibular condyle.[153]

Ganglion and Synovial Cysts

The literature does not always clearly distinguish these two lesions. Whereas the synovial cyst is a true cyst with an epithelial lining, the ganglion cyst is not. *Ganglion cysts* arise in a joint capsule as a consequence of myxoid degeneration of the connective tissue, possibly secondary to a deficiency in the vascular supply. They are not connected to the joint cavity. There is a female predilection with an age range of 30 to 50 years. These lesions are very rare in the TMJ area; only about 10 cases have been reported.[173]

They present as a preauricular swelling, and there may also be joint dysfunction, pain, and tenderness. Bone scans will reveal an increased uptake of technetium-99m. Histologically, these lesions are lined by fibrous tissue and contain a gelatinous material.

Synovial cysts are also uncommon in the TMJ. Five cases have been reported, two of which were associated with a history of trauma.[174] These lesions also present as a preauricular swelling. They are lined by flat or cuboidal cells, which are of synovial origin, and the lumen contains a gelatinous material. These cysts may be the consequence of herniation of the synovium or possibly the result of displacement of tissue during embryogenesis. Following trauma, increased intracapsular pressure may cause degeneration of the adjacent connective tissue.

Hemangioma

Intraosseous Hemangioma

Only five cases of intraosseous hemangioma in the TMJ have been reported.[175] Hemangiomas of bone are found most frequently in the vertebrae and are uncommon in the jaws, where their usual location is in the body of the mandible. These lesions have a 2:1 female-to-male ratio, and there is an age predilection for the second decade.

Among the patients with a lesion involving the TMJ, one was asymptomatic. The others presented with joint pain,

aggravated by movement of the mandible, as well as tenderness over the joint and restricted mouth opening.

Synovial Hemangioma

Synovial hemangiomas are rare lesions, occurring predominantly in the knee joint. They are most unusual in other sites. There is a predilection for female children and young adults.

The findings are typically recurrent, long-standing pain, decreased range of motion, and a spongy, compressible mass over the joint. They may be localized and well circumscribed or diffuse and infiltrative. These hemangiomas are of the cavernous type, with large, dilated, blood-filled vessels that are separated by an edematous, myxoid, or focally hyalinized matrix. Inflammatory cells may also be present. The synovium may develop villous projections, with hemosiderin deposition in the synovial cells.

These lesions may be juxta-articular, intra-articular, or mixed. The intra-articular type is the most frequent, and the tumor is lined by a synovial membrane. The mixed type originates from the synovium and lies both juxta-articularly and intra-articularly, whereas the juxta-articular type is located adjacent to the joint without actual involvement of the synovial membrane.

Radiographs usually reveal nonspecific radiolucencies or opacities. However, the presence of phleboliths is a helpful diagnostic feature.

TMJ involvement has been reported.[176] The case was that of a 43-year-old woman who had been treated for 3 years for masticatory myalgia associated with localized intermittent preauricular pain, restricted motion, and deviation on opening. However, there was no muscle tenderness and no preauricular mass, although there was a painful preauricular depression. Aspiration was not productive. A CT scan showed a soft tissue mass in the posterior portion of the joint. Grossly it was confluent with the synovial membrane.

Arteriovenous Malformation

Facial vascular anomalies are not uncommon findings in maxillofacial surgical patients. Many of these vascular and mortality. Intraosseous AVMs are particularly difficult to diagnose, may not present until adolescence or early adulthood, and often present with symptoms that mimic periodontal disease. Mandibular AVMs account for approximately 1% of all facial AVMs. A small percentage of these present in the TMJ. Death secondary to intractable hemorrhage is reported to occur in approximately 8% of patients.[155]

Treatment of these malformations continues to provide a clinical challenge. Because of the poor prognosis of untreated AVMs, radical cure is mandatory. Treatment modalities used in the past have included radiation therapy, sclerosing therapy, cryosurgery, selective embolization, and surgical resection. Resection of the malformation and the surrounding bone is considered the optimal treatment to prevent recurrence. However, profound surgical hemorrhage and significant postoperative deformity have prompted clinicians to pursue alternative treatments that may have a lower morbidity and mortality. A major advance in the treatment of these malformations has been the development of selective embolization. Selective embolization can serve as the only treatment but is often used as a surgical adjunct to provide preoperative devascularization. Reznik and colleagues[160] and Flandroy and Pruvo[161] described a technique for the treatment of mandibular AVMs in which embolization is performed through direct transosseous puncture. This technique has been further modified to perform the embolization with transosseous microcatheters.

Histologically, AVMs consist of numerous medium- to large-caliber arteries and veins that are directly connected without intervening capillary-size vessels. These vessels are supported by a variable collagenous stroma.

Fibrous Dysplasia

Fibrous dysplasia most commonly presents as an asymptomatic, slow enlargement of the involved bone. Monostotic fibrous dysplasia accounts for up to 80% of reported cases. Jaw involvement is common in this form of the disease. The entire ramus-condyle complex can be involved and present as facial asymmetry.[155] Often the clinical presentation is difficult to distinguish from that of condylar hyperplasia. The radiographic presentation is sometimes similar to that of Garre osteomyelitis.

Following a variable period of growth, fibrous dysplasia frequently stabilizes. Growth typically slows significantly after the onset of puberty. Once pathologic diagnosis is confirmed by biopsy, the only treatment required may be periodic follow-up. However, if significant cosmetic or functional deformity has occurred, surgical intervention with osseous recontouring may be undertaken.[155]

The histologic findings in fibrous dysplasia consist of a cellular, fibrous connective tissue proliferation that contains foci of irregularly shaped trabeculae of immature bone. A relatively constant ratio of fibrous tissue to bone throughout a given lesion has been described as characteristic. The collagen fibers may completely lack orientation or, alternatively, may be arranged in a storiform pattern of interlacing collagen bundles. The fibroblasts exhibit uniform spindle- to star-shaped nuclei. The bony trabeculae assume bizarre, irregular shapes, likened to Chinese characters. These trabeculae do not display any apparent functional orientation. The bone is predominantly woven bone that appears to arise directly from the collagenous stroma without prominent osteoblastic activity. In a mature fibrous dysplasia lesion, lamellar bone may be found. Aneurysmal bone cysts have been reported in association with fibrous dysplasia. It should be noted that fibrous dysplasia shares many microscopic features with the ossifying fibroma.

Nonossifying Fibroma (Fibrous Cortical Defect)

This is a common benign lesion that is generally noted as an incidental radiographic finding in the metaphyses of long bones in skeletally immature patients. It appears to be a self-limiting process that is related to incomplete ossification. It is found almost exclusively in children and adolescents. The lesion frequently resolves spontaneously. The lower extremity is the site of predilection; the distal femoral metaphysis is the most frequent site, followed by the proximal tibial metaphysis.

Occasionally these lesions are multifocal and symmetric. Multiple lesions have been associated with neurofibromatosis and are also found in Jaffe-Campanacci syndrome.

Nonossifying fibromas are typically asymptomatic, but when large, they may cause some expansion and even a pathologic fracture. When found in its typical location, the radiographic appearance is pathognomonic. It appears as an eccentric cortical-based radiolucency with scalloped sclerotic margins. The overlying cortex may be considerably thinned and slightly expanded.

Involvement of the TMJ is extremely rare. Several cases have been reported in the neck of the condylar process.[177-179] These lesions have not caused joint dysfunction and are typically asymptomatic. The jaw lesions appear to be more common in females, whereas in the long bones more males are affected.

Histologically, the lesion consists of a cellular fibroblastic stroma with a storiform pattern. Some multinucleated giant cells and foci of foamy histiocytes are present, and hemosiderin is visible in the stromal cells. Some mononuclear inflammatory cells are usually present.

Cystic change, hemorrhage, and necrosis may occur, and secondary aneurysmal bone cysts have developed. The nonossifying fibroma tends to stabilize at puberty and heals by peripheral sclerosis or solid opacification.

Osteochondroma (Osteocartilaginous Exostosis)

The osteochondroma constitutes about 35% of all benign bone tumors. It is a hamartomatous proliferation that arises from endochondral bone and is thus usually found in the long bones, most frequently the distal metaphysis of the femur and proximal metaphysis of the tibia. Patients are usually younger than 20 years, and there is a 2:1 male predilection. Tumors of the mandibular condyle occur over a much wider age range and have a 2:1 female predilection.

Seventy-five percent are solitary lesions, and 25% are multiple lesions. Multiple osteochondromatosis is an autosomal-dominant hereditary disorder. In these cases, about 11% undergo sarcomatous change, in contrast to 1% of solitary lesions. However, no cases of sarcomatous change have been reported in the mandibular condyle.

Osteochondromas occur infrequently in the mandibular condyle. They form an exophytic mass emanating from the cortex that may cause limited mouth opening, jaw deviation, and unilateral open bite. The radiographic appearance of an osteochondroma of the condyle is pathognomonic. A tapering radiopaque mass extends from the anteromedial aspect of the condyle along the tendon of the lateral pterygoid.

Histologically, the bony mass is covered by a cap of fibrocartilage and hyaline cartilage of varying thickness and cellularity, which is surrounded by the fibrous tissue of the perichondrium. In the deepest aspect of the cartilage, where it interfaces with bone, endochondral ossification occurs.

Spontaneous regression of an osteochondroma has occurred in rare instances.[180] This is most likely due to cessation of growth of the cartilage cap and subsequent resorption and incorporation of the lesion into the cortex through appositional growth. Cessation of growth may also be the consequence of a pathologic fracture. It is also possible that involution of the cartilage cap may result in the lesion resembling an osteoma.

Osteoma

Osteomas occur in several clinicopathologic guises, and frequent sites of involvement include the cranium, mandible, facial bones, orbit, and paranasal sinuses. In the condyle, osteomas usually appear as spherical or lobular enlargements. They may even have a pedicle. They generally consist of dense lamellar cortical bone that is well circumscribed, but a cancellous form also has been described. Although usually occurring as single, isolated lesions, osteomas may also arise in the condyle as part of Gardner syndrome.[153]

Osteoid Osteoma

These tumors are very uncommon in the jaws. One case has been reported in which the inferolateral aspect of the mandibular condyle was involved.[181] The patient was a 21-year-old woman who experienced trismus and spontaneous pain that, in the classic presentation of this tumor, occurred essentially at night. The radiographic appearance was also classic, in that it appeared as a subcortical nodule, 0.8 cm in diameter, with a sclerotic border.

Osteoid osteomas consist of active osteoblasts that deposit abundant osteoid to form a small nidus within normal bone. The lesion generally does not exceed 1.0 cm in diameter.

a limited growth potential and may undergo spontaneous regression.

Benign Osteoblastoma

Osteoblastomas do not occur frequently in the jaws. In this region, the most common site is the body of the mandible, but several cases involving the TMJ have been reported.[182]

Most osteoblastomas arise in the vertebrae and long bones, with a 2:1 male-to-female ratio. The average age of patients is 17 years, and the age range is from the first through eighth decades. The sex and age distributions of TMJ lesions are similar to those in other locations.

They are typically well-circumscribed, solitary lesions that expand within the medullary cavity and exceed 1 cm in diameter. They often produce a tender swelling. When osteoblastomas occur in the TMJ, there is often a history of trauma and, as in other locations, a tender swelling is the frequent presentation. In some cases, there is not only an expanding deformity of the condyle but also a secondary deformity of the glenoid fossa.

These neoplasms, as in the osteoid osteoma, consist of active osteoblasts that lay down abundant osteoid. The osteoblasts are concentrated along the osteoid seams. The fibrous stroma is very vascular with numerous dilated capillaries. Because of the vascularity of the lesion, angiography and scintigraphy are diagnostically useful.

Pigmented Villonodular Synovitis

cial and ligamentous tissues. They are believed to represent a reactive inflammatory process. However, the fact that there may be bone destruction and a significant rate of recurrence suggests a locally aggressive neoplastic process.[183]

Essentially, these are destructive lesions that produce villous and nodular protrusions of the articular and extra-articular synovial membranes. They have been divided into intra-articular (diffuse and localized) and extra-articular (diffuse and nodular) forms. However, the nomenclature and classification involving these lesions have not been consistent.

They are relatively rare lesions, constituting fewer than 5% of all primary soft tissue tumors, and occur over a wide age range, with a peak in the third and fourth decades. Most are located intra-articularly. Eighty percent of cases involve the knee (including both diffuse and local types). The nodular extra-articular form (also called *pigmented villonodular tenosynovitis* or *giant cell tumor of tendon sheath*) is seen predominantly in the finger, carpal, and metacarpal joints.

These lesions are very rare in the TMJ. The majority are extra-articular, although this cannot always be confirmed. Although only about 22 cases have been reported in the literature, approximately a third of them have extended into the temporal bone and middle cranial fossa.[184]

Among the presenting symptoms, preauricular swelling is the most frequent. Hearing loss and tinnitus arising from compression of the auditory canal, as well as pain, trismus, and clicking, may also be present. Some cases have occurred in conjunction with synovial chondromatosis.

Histologically, the lesions consist of fibroblasts, mononuclear histiocytic cells, and irregularly interspersed multinucleated giant cells. Scattered and clustered foamy histiocytes are present, giving the lesion its yellow color, and there is abundant hemosiderin, responsible for the brown color. The hemosiderin may be found in the synovial cells and macrophages or lying free in the proliferative connective tissue, associated with multinucleated giant cells. The irregular villi are covered by thickened synovium or may be denuded. The histiocytes and giant cells are of monocyte-macrophage origin.

The histologic components of the different fibrohistiocytic lesions under this rubric are similar; the distinction is in the clinical presentation and behavior. Localized lesions are well circumscribed and may be partially encapsulated, whereas the diffuse lesions exhibit infiltrative and destructive growth. Thus the overall prognosis is more favorable for localized disease. This issue has not been addressed directly in the reported TMJ cases, but it is clear that many of these cases did behave in an aggressive fashion.

Synovial Chondromatosis

This uncommon entity has generally been considered to represent a non-neoplastic, metaplastic process. However, certain characteristics suggest the possibility that it may be neoplastic. The evidence of monoclonal chromosomal changes has given this theory strong support.[185] In addition, not only may synovial chondromatosis (SC) recur, but also the cartilaginous component may exhibit atypia. Synovial chondrosarcoma has also developed within preexisting SC.[186] In some cases, SC reaches considerable size and behaves in a destructive fashion.[187] SC may develop as a primary lesion or may arise secondary to trauma or another disease process such as osteoarthritis. The aggressive neoplastic features appear to be associated with the primary disease. Thus, it is possible that the primary type is neoplastic and the secondary form is metaplastic.[188]

SC usually affects the joints of the knee, hip, elbow, and ankle; approximately 70% of cases occur in the knee. It is rare in the TMJ; slightly fewer than 100 cases have been reported in the literature. In at least one reported case, the lesion developed from the disc. In the TMJ, SC occurs more frequently in females than in males and usually in the fourth through sixth decades. At other sites, there is a male preponderance and presentation generally occurs two decades earlier.

Pain is the most frequently cited symptom, followed by swelling, clicking, mandibular deviation, and limited mouth opening. CT scans and MRI can be very helpful diagnostically, although the presence of loose bodies in the joint space is not pathognomonic, because they may also be seen with intracapsular fractures and the osteoarthroses.

Initially, the lesion develops within the synovium as a proliferation of undifferentiated cells. Then fibroblast-like cells form a chondroid matrix from which cartilaginous nodules develop. This early phase has been called *stage 1.* Subsequently the nodules begin to lose their attachment and extrude into the joint cavity. The synovial fluid helps to maintain their nutrition and growth. *Stage 2* is the transitional phase, in which there is synovial involvement and detached nodules are found in the joint space. The cartilaginous foci within the synovium and joint space may calcify or even ossify, at which time the term *osteochondromatosis* is appropriate. This process commences at the periphery of the nodule and progresses inward. Eventually the nodules may coalesce to form an

irregular mass. *Stage 3* is advanced disease in which there is no longer synovial involvement and all the nodules have detached. Although the nodules or masses are typically confined to the joint space, in some cases they may erode the underlying bone or joint capsule and invade the periarticular tissues.

Cellular atypia is not unusual in SC, where large cells and binucleated cells may be observed. However, this does not indicate aggressive behavior. The most important consideration in the differential diagnosis is chondrosarcoma.[153]

Malignant Neoplasms

Chondrosarcoma

The majority of reported sarcomas arising in the TMJ have been chondrosarcomas. However, because this amounts to some 14 cases, this is still a very rare occurrence.[189] The age and sex of the patients were not known in three cases. Among the others, the age ranged from 17 to 75 years; four cases arose in the patient's fifth decade. Six patients were female and three were male.

Swelling was a consistent finding and, in most instances, pain or discomfort was also noted. Limited mouth opening and diminished hearing have also been described. Overall, chondrosarcomas constitute about 25% of primary bone sarcomas, with only 1% to 3% arising in the facial bones and jaws.

These tumors develop from mesenchymal stem cells, which show partial chondroblastic differentiation. They are typically slow-growing tumors, and the majority are low grade. They tend to show a lobular growth pattern with hypercellularity. The cells are often pleomorphic and may be binucleated. Malignant cartilage is formed but, in distinction to the osteosarcoma, no osteoid is formed directly from the malignant stroma.

High-grade tumors may metastasize to regional lymph nodes. Low-grade tumors have an excellent prognosis, but recurrences can develop, often after many years.

Synovial Chondrosarcoma

These tumors may arise as a primary malignancy of the synovium or secondarily in a preexisting synovial chondromatosis. They are rare occurrences, and only 21 cases have been reported in the literature. The knee, hip, and ankle are the sites of predilection. The age range of the patients is 30 to 70 years, and two thirds occur in the fifth to seventh decades. There is a female preponderance. The tumors form a soft tissue mass associated with pain and joint dysfunction.

Only six cases occurring in the TMJ have been reported.[190-195] Because there are very close similarities in the clinical, radiologic, and histologic aspects between synovial chondromatosis and synovial chondrosarcoma, the diagnosis may be difficult. Local recurrence and invasion of bone and surrounding soft tissue are clinical features that are also shared by these two entities. Radiographically, in addition to the presence of a soft tissue mass, clumps of ca1cification may be seen within the lesion, and there may be marginal erosion of the articular bone. As in synovial chondromatosis, nodules may be seen grossly, lying free within the joint space and/or the soft tissues.

The histology may also be ambiguous because cytologic atypia is common in synovial chondromatosis. The following histologic criteria are suggested to recognize malignancy:

1. Qualitative differences in the cartilage in different parts of the tumor, in which a clustering pattern is juxtaposed with abundant matrix and tumor cells arranged in sheets
2. Myxoid changes in the matrix
3. Hypercellularity, with crowding and spindling of the nuclei at the periphery
4. Necrosis
5. Permeation of trabecular bone, with "filling up" of marrow spaces rather than a pushing margin[2]

In the series reported by Bertoni and colleagues,[186] the nine patients available for follow-up, in whom the tumors occurred in the lower extremity (knee, hip, and ankle), all developed recurrences following local excision with "lesional margins." In spite of aggressive follow-up surgery, five patients developed metastases.

Synovial Sarcoma

These tumors represent about 5% to 10% of all soft tissue sarcomas. They are the fourth most frequently occurring soft tissue sarcoma, following malignant fibrous histiocytoma, liposarcoma, and rhabdomyosarcoma. They arise near tendons and tendon sheaths and next to joint capsules. They do not arise from mature synovial cells but rather from pluripotential mesenchyme.

Joint involvement per se is very uncommon, occurring in less than 5% of cases. Usually they occur in periarticular areas of the extremities, particularly around the knee, but approximately 9% occur in the head and neck, where the perivertebral structures give rise to most of the tumors, which then present in the pharynx, larynx, or esophagus. The tumors are generally rather slow growing. Up to 50% show calcifications radiographically, a helpful finding diagnostically.

Most cases occur in patients in the 15- to 40-year age range. The four patients with lesions in the TMJ ranged in age from 22 to 57 years.[174] At this site they have tended to present with a preauricular mass, which was painless in some instances.

Histologically, two types of synovial sarcoma may occur: biphasic and monophasic. Both types have occurred in the TMJ. The biphasic tumor consists of plump, uniform spindle cells that resemble a fibrosarcoma but lack a herringbone pattern, and cuboidal to columnar epithelial-like cells that line spaces or clefts and form nests. There also may be a pseudoglandular pattern. Both the spindle and epithelial-type cells stain positively for cytokeratin and epithelial membrane antigen. Mitoses are infrequent, and calcifications may be present.

The monophasic form is usually of the fibrous type, and most of the spindle cells exhibit the same immunohistochemistry as the biphasic form. A monophasic epithelial

form also exists but is very rare. Synovial sarcomas are associated with the chromosomal translocation t (X:18) (p11.2;q11.2).

About half of cases of synovial sarcoma will have local recurrences, even after wide surgical excision and a neck dissection. Most recur within the first 2 years, but recurrence may also take place many years later. Although the lung is the most frequent metastatic site, synovial sarcoma is one sarcoma that may metastasize to the lymph nodes (20% of cases).

Osteosarcoma

Osteosarcomas represent about 30% of all primary bone malignancies, and 6% to 13% involve the craniofacial bones. The maxilla and mandible are involved with almost equal frequency. It is unusual for these tumors to originate in the TMJ.[196] The age of patients with such tumors has ranged from 17 to 69 years.

Patients generally complain of pain, often mild; limited mouth opening; and altered occlusion. Radiographically, the lesions show extensive destruction.

These tumors arise from pluripotential mesenchymal stem cells and may thus show considerable histologic diversity. This includes chondroid and fibrous differentiation. The diagnosis rests on the identification of osteoid formed directly from a malignant stroma.

Lung metastases may occur early in the course of the disease.

Multiple Myeloma

Multiple myeloma represents about 43% of malignant tumors of bone. Most cases arise in individuals older than 60 years, and there is a slight male preponderance.

There appear to be seven cases of multiple myeloma reported in the literature in which there was a mandibular condyle lesion.[197] These patients ranged from 41 to 70 years in age, which is typical for this disease. Two patients had pathologic fractures. The most frequent finding was pain, usually associated with trismus. One patient had a tender preauricular swelling. In some patients, additional bone lesions were found at time of presentation, but in others no additional bone lesions were identified.

Multiple myeloma is a plasma cell dyscrasia in which sheets of proliferating plasma cells form bone tumors. Radiographically, the lesions are typically well-defined radiolucencies that lack a sclerotic rim.

Langerhans Cell Histiocytosis

Approximately 13 cases of Langerhans cell histiocytosis have been reported in the mandibular condyle.[198] The majority were solitary lesions. One patient was found to have additional bone lesions at presentation, and another developed an additional lesion in the bone within 6 months. Four patients were female and nine were male. Three cases occurred in the patients' first decade, three in the third, four in the fourth, and three in the fifth.

All patients had pain in the area of the TMJ. Most had preauricular swelling, and limited mouth opening was also frequently reported. At least four patients developed pathologic fractures. In all cases, a lytic lesion could be identified radiographically within the condyle.

Histologically these tumors consist of sheets of histiocytes with focal collections of eosinophils. Some plasma cells and lymphocytes may also be present. The proliferating histiocytic cells can be identified as Langerhans cells by staining for S100 protein and more definitively by immunostaining for CD1a antigen, as well as by ultrastructural examination and identification of cytoplasmic Birbeck granules.

Although there is still some controversy concerning the nature of these lesions, the finding that these are clonal proliferations suggests that they are indeed neoplasms.

Metastatic Carcinoma

Metastatic carcinoma is the most frequently occurring malignancy of bone. However, the jaws are an uncommon site for metastases, and the condyle is an even less frequent location. In a review of 390 cases of metastatic tumors to the jaws, Hirshberg and colleagues[199] reported that 81% occurred in the mandible but only 11 cases (3.5%) involved the condyle. They also noted that overall there was a female preponderance, probably accounting for the fact that the breast was the most prevalent primary tumor site. Other reported primary sites with metastases to the condyle have included lung, prostate, liver, pancreas, uterus, rectum, and skin of the toe. One particularly unusual report involved a testicular teratoma with metastases to both condyles.[200]

The most prevalent presentation of metastases to the condyle was TMJ dysfunction, but a pathologic fracture may also be found. Although in most cases the patient has a known primary lesion, in some series condylar metastasis was the first sign of a neoplasm in as many as half of the patients. Unfortunately, patients with these metastases have a very poor prognosis, and treatment is generally palliative.

Hypotheses regarding the paucity of metastases to the condyle include the scant amount of red marrow; the separate blood supply from the circular penetrating branches of the maxillary and superficial temporal arteries; the slow circulation; and the limiting osseous plate that shuts off the condylar marrow cavity from the spongiosa of the rest of the mandible.

Other Tumors

Many other tumors have been described as occurring within the condyle. Most of these have been single cases. They have included nodular fasciitis,[201] neurofibroma,[202] malignant schwannoma,[203] leiomyosarcoma,[204] malignant fibrous histiocytoma,[205] fibrosarcoma,[206] and Ewing sarcoma.[207]

Inflammatory, Metabolic, and Genetic Disorders

The inflammatory-metabolic-genetic category accounts for a small percentage of TMJ pathology and includes acromegaly, Garre osteomyelitis, hemifacial hypertrophy, hemifacial microsomia, heterotopic bone formation, phantom bone disease, and septic arthritis. The characteristics of hemifacial microsomia, hemifacial hypertrophy, and acromegaly are well outlined elsewhere in this text and are not discussed in this chapter.

Garre Osteomyelitis

Garre osteomyelitis can be considered a variant of chronic osteomyelitis with a concomitant prominent periosteal inflammatory reaction. This type of osteomyelitis is uncommon. It has been described in the tibia and in the maxillofacial region. In the mandible, it most commonly results from a periapical abscess associated with a molar. It has also been associated with pericoronal infections and infections following tooth extraction.[155] Rarely, this process may involve bone in the area of the TMJ. Patients typically present with a bony hard swelling of the posterior mandible. The overlying skin and mucosa characteristically appear normal. Occasionally the swelling may be tender.

The radiographic appearance is that of a centrally mottled radiolucency similar to chronic osteomyelitis. The peripheral periosteal reaction provides a distinctive radiographic appearance. The mandibular cortex is expanded, with concentric opaque layers (onion skin) noted on occlusal radiographs or CT scans. The clinician must differentiate Garre osteomyelitis from benign mandibular neoplasms. Radiographs are helpful to rule out certain neoplasms, but the radiographic presentation of fibrous dysplasia is often similar. Biopsy for histopathologic examination and bone culture is useful.

Removal of the etiologic agent is of paramount importance in the treatment of Garre osteomyelitis. Some surgeons advocate additional treatment with antibiotic therapy. Others advocate wide exposure of the affected area with perforation of the mandibular cortex to allow for capillary ingrowth.

Heterotopic Bone Formation

Heterotopic ossification is a condition in which mature lamellar bone is formed in tissues that do not normally ossify. Heterotopic ossification is considered to occur in three basic forms: traumatic, neurogenic, and myositis ossificans progressiva. It has also been described, although rarely, following tetanus, burns, poliomyelitis, and some

The onset of heterotopic bone formation usually occurs approximately 2 weeks after injury, although symptoms may not present until 8 to 10 weeks later. A diminished range of motion of the joint is a hallmark characteristic and is often the earliest sign. Patients may also complain of pain, swelling, and local tenderness. Management includes arthroplasty and physiotherapy. Radiotherapy and pharmacologic therapy with agents such as bisphosphonates and nonsteroidal anti-inflammatory drugs have been advocated as prophylaxis to prevent heterotopic bone formation.

Phantom Bone Disease

Phantom bone disease, also known as vanishing bone disease or massive osteolysis, is a rare clinical entity, with approximately 70 cases reported since its initial description in 1838. Only 15 cases have been reported in the maxillofacial region. The clinical course is characterized by a slowly progressive localized destruction of bone. Although the disease is progressive, its course can vary. With time, the bone destruction may spontaneously abate, or the bone may gradually disappear. No effective treatment is known for phantom bone disease.[155] Recently, controversy has developed as to whether this process represents a distinct entity or is a misinterpretation of other pathologic processes. Practitioners are encouraged to consider other pathologic entities when presented with a condition diagnosed as "phantom bone disease."

Conclusion

In the study of temporomandibular disorders, much open mind, because many other conditions can produce similar signs and symptoms. These include arthritides and neoplasms. Although most neoplasms of the TMJ are benign, features that may suggest the possibility of malignancy include swelling, paresthesia, paresis, trismus, and occlusal changes. In addition, there may be auditory changes, including tinnitus and vertigo secondary to eighth nerve involvement and decreased auditory acuity secondary to eustachian tube involvement. When occlusal changes are of sudden onset, the immediate cause may be a pathologic fracture. The development of symptoms of myofascial pain and jaw dysfunction later in life (i.e., beyond the typical 20- to 40-year age range for patients with masticatory myalgia), or failure of the initial treatment for this condition, should make clinicians suspicious of more serious problems.[153-158,208]

The use of good radiographs and other imaging studies is of paramount importance in developing a correct diagnosis. Although the diagnosis is frequently suggested by the clinical and imaging information, in most cases the final diagnosis will only be made by microscopic tissue examination. However, histologic analysis alone is not sufficient. Only by assessing the clinical, radiographic, and histologic information together can the clinician achieve an accurate diagnosis.

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39

Nonsurgical Management of Temporomandibular Joint Disorders

A. THOMAS INDRESANO, CHAN M. PARK

Introduction

Temporomandibular joint (TMJ) disorders are a diverse collection of problems involving the joint itself and/or the surrounding masticatory system. This masticatory system includes the muscles of mastication, their nerve supply, the surrounding afferent neural tracts, central oromotor control, and the maxillary and mandibular dentoskeletal relationship. Given this diversity and the complex cause of the disorders, management is equally diverse. Treatment regimens can be divided into two broad categories: surgical and nonsurgical management. Surgical modalities will be discussed elsewhere in this text.

Accurate diagnosis of the particular TMJ disorder is paramount in determining a treatment regimen. For example, intracapsular joint disorders will be treated differently than musculoskeletal disorders. With virtually all TMJ disorders, however, numerous nonsurgical therapies are part of a treatment regimen (Box 39-1, Figure 39-1).

Philosophies of Treatment

The treatment of TMJ disorders involves philosophical differences among patients and practitioners. These differences often involve what one individual believes is the most appropriate course of treatment. Several treatment philosophies are universally accepted, including the use of a multidisciplinary approach, the use of reversible therapies first, and management of pain by alteration of the disease process.

Multidisciplinary Approach

TMJ disorders, as discussed earlier, involve a variety of diagnoses. The disorders also influence multiple aspects of patients' lives. For example, depression has been positively associated with TMJ complaints, especially painful symptoms.[1-4] Because of this, a sole-practitioner approach to treating TMJ disorders is often inappropriate. A "team" approach is often necessary, using multiple specialties. Professionals from diverse disciplines, such as general dentistry, oral and maxillofacial surgery, orthodontics, physical therapy, occupational therapy, psychiatry, and neurology, are often needed for thorough treatment.

Reversible Versus Nonreversible Treatment

A widely held philosophy is that the most appropriate disease therapy is the least invasive therapy that provides a positive outcome. A large reason for this is that the least invasive therapies are often reversible. Once the therapy is completed, the patient's physiology is not significantly altered. Nonsurgical TMJ therapies often, but not always, fall into this category of reversible treatment.[198] For example, long-term splint therapy can alter disc position and condylar morphology.[5-8] After reversible therapies have been attempted and it has been determined that a disease process has not been adequately interrupted, nonreversible modalities should be initiated.

Pain Management Versus Disease Therapy

Most patient's complaints of TMJ disorders involve pain.[9] Clear delineation must be made within the therapy of TMJ disorders between palliative pain management and a therapy used to *treat* a disease process. Pain can be managed in multiple ways, but the most effective is with removal of the offending stimulus or disease process. During this process, however, medicinal pain management may be necessary. Patients must be educated in the nature of the disease process and what impact each treatment modality will have on that process.

Splint Therapy

The use of occlusal splint therapy for the treatment of TMJ disorders dates back to Kingsley in 1877.[10] Occlusal splints

have, over the years, been advocated for the use of a variety of purposes. It follows that the design of the splints has been modified for each purpose. For example, Sved, Block, and Christensen used occlusal appliances to restore the vertical dimension of occlusion.[11-13] In the 1940s, Thompson advocated mandibular repositioning using intraoral appliances.[14] This form of treatment was postulated to "unload" the condyle. In the 1960s, Ramfjord popularized the use of splint therapy for patients with muscular dysfunction by using electromyographic studies.[15] Further attempts were made to "unload" the condyle in the 1970s and 1980s with anterior repositioning appliances.[10]

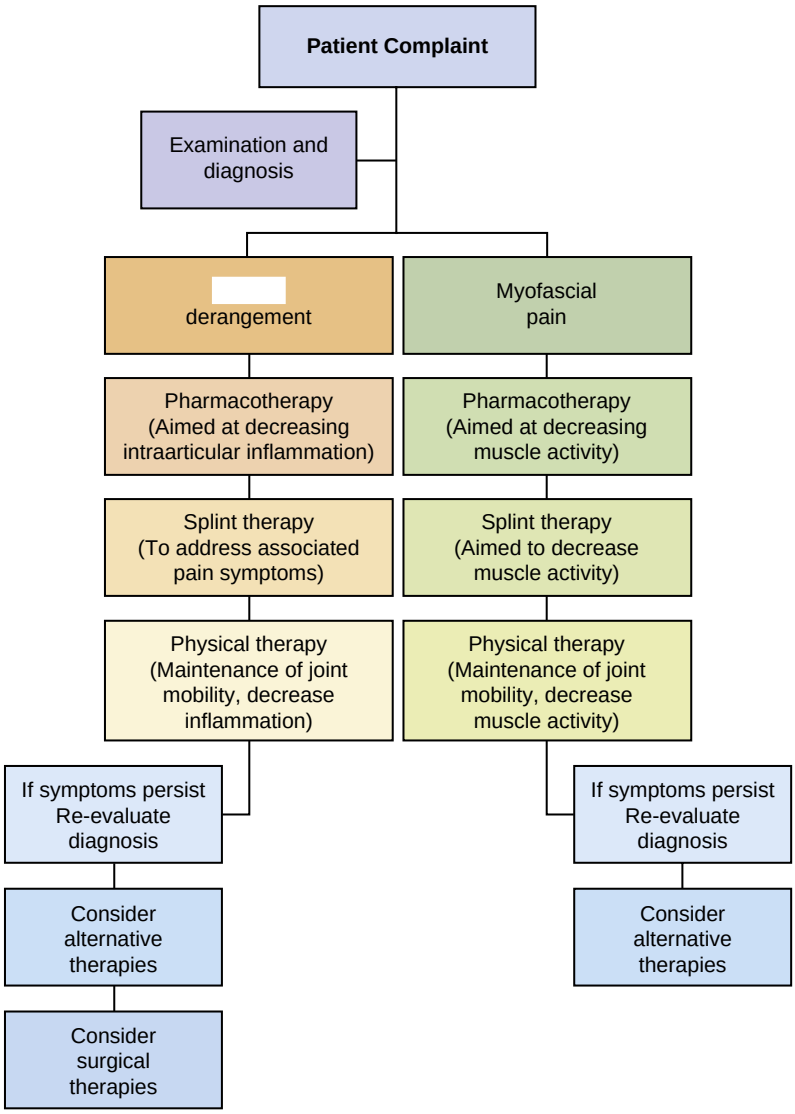
Splint therapy remains a popular method of treating TMJ disorders.[16,17] Several studies have concluded that splint therapy is often an effective therapy, but the type of splint used seems to have little consequence.[18-22] This is likely because the exact mechanism of action of splint therapy is not well understood. This section will highlight the different splints used and their specific uses (Box 39-2).

• BOX 39-1 Nonsurgical Options for Treating TMJ Disorders

Splint therapy
Pharmacotherapy
Occlusal management
Physical therapy
Adjunctive therapies (acupuncture, acupressure, botulinum toxin A, etc.)

Types

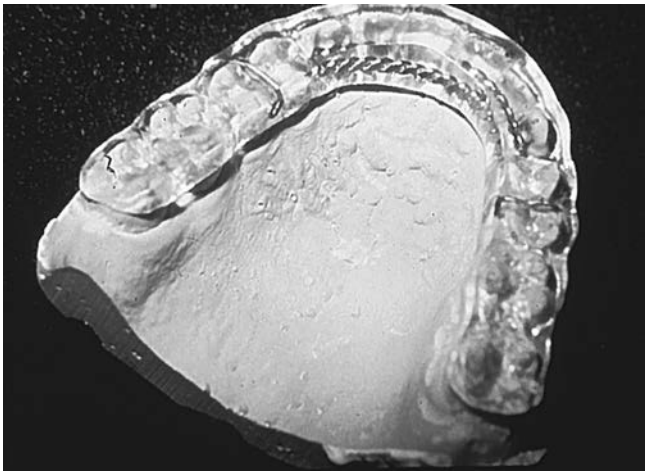
- Stabilization splints: Stabilization splints are the most commonly used splints to treat myofascial pain[23] (Figure 39-2). They consist of acrylic full coverage of the maxillary or mandibular occlusal shelf. Most commonly, there is interdigitation with one arch, but little to no interdigitation with the other arch. Balanced, bilateral occlusal contacts are a must. If any interdigitation



• Figure 39-1 Nonsurgical treatment algorithm of TMJ disorders.

• BOX 39-2 Types of Occlusal Splints Used in TMJ Disorders

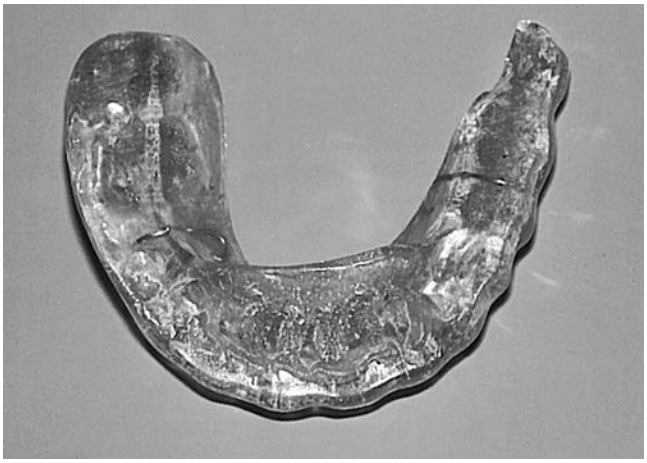
Stabilization splints
Repositioning splints
Pivot splints
Soft splints
Bite plane splints



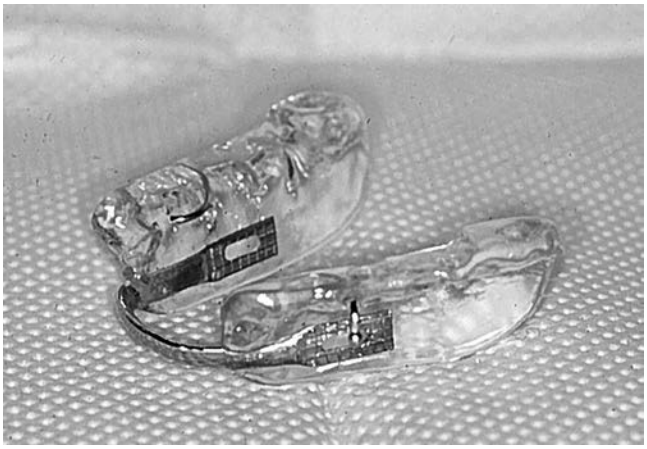
• Figure 39-2 Stabilization splint.

ally constructed in a centric relation. They have been shown to be moderately successful in reducing pain in longitudinal studies.[24] Studies of full-coverage stabilization splints have been shown to have favorable results in symptoms related to joint, muscular, and motion pain, but demonstrate poor results at decreasing joint noise.[25,26] Schmitter et al recently determined that patients treated with stabilization splints were treated more effectively than those with distraction splints.[27] A recent Cochrane Database review of studies using stabilization splints concluded that there was insufficient evidence to support or discourage their use.[28,29] This highlights the need for further well-controlled studies examining their efficacy.

- Repositioning splints: Repositioning splints are primarily used to alter the condylar position at occlusal contact and to recapture a displaced disc (Figure 39-3). They are constructed out of hard acrylic for the maxillary or mandibular arch with cuspal interdigitation or inclines to guide the mandible to a predetermined position. Repositioning splints became popular in the early 1980s with promising results shown to decrease pain and joint noise in patients with anteriorly displaced discs with reduction.[30-32] This initial enthusiasm, however, dwindled with controlled long-term studies showing a high rate of joint noise returning and progressive pain.[33,34] Other studies have shown a significant improvement in pain, but marginal success in "recapturing" discs.[35]

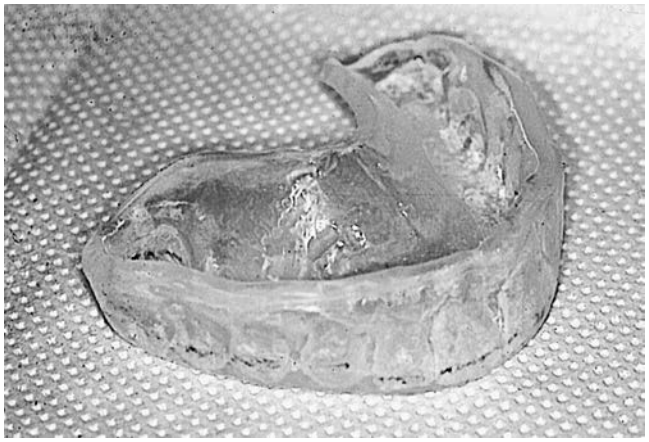


• Figure 39-3 Maxillary anterior repositioning appliance worn unsupervised for 2 years.



• Figure 39-4 A pivot splint. Note that posterior acrylic blocks are thought to gently distract the condylar head when patient is in centric occlusion.

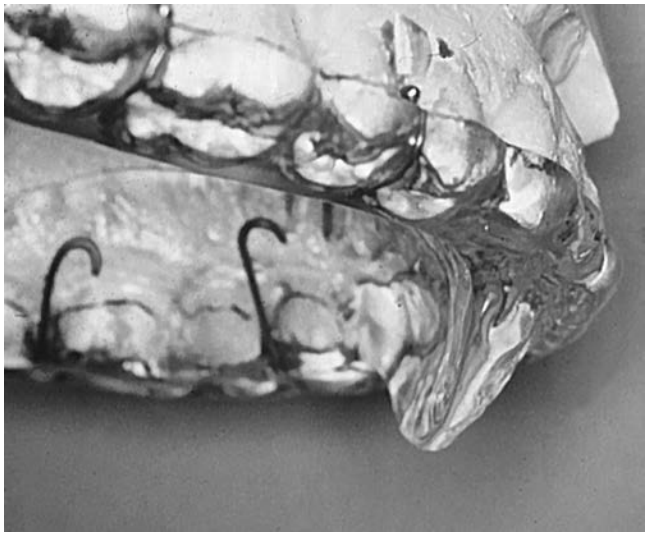
- Pivot splints: First described by Goodwillie in 1881, these splints are designed to "unload" the TMJ and to mildly stretch the joint[10] (Figure 39-4). They can be made for the mandibular or maxillary arch and made unilateral or bilateral depending on the involved joint(s). They were theorized to be useful in patients with intracapsular inflammation. Unfortunately, the elevator muscles of the mandible lie on or posterior to the most distal portion of the dentition. Without the use of a chin cup or other orthopedic device, unloading of the joint is difficult to achieve.[36]
- Soft splints: Soft, or resilient, splints are made from a pliable material and are often effective for immediate results in patients with myofascial pain[37,38] (Figure 39-5). They have an advantage of low cost and ease of fabrication. It is believed, however, that hard splints are superior to their soft counterparts, especially in cases of bruxism.[39,40]
- Bite plane splints: Bite plane splints are used to disrupt mandibular proprioception, thereby decreasing muscle activity[41] (Figure 39-6). They are constructed by indexing only the anterior teeth with no posterior contact.



• **Figure 39-5** Soft splint.



• **Figure 39-7** Patient's occlusion after 2 years of unsupervised wear. Note open posterior malocclusion.



• **Figure 39-6** Lateral view of maxillary anterior repositioning appliance. Note that resting of lower incisors is anterior to this flange.

Prolonged use can cause occlusal discrepancies (Figure 39-7), and stabilization splints are more effective in bruxism cases.

Uses

Myofascial Pain

Numerous studies have shown that splint therapy is effective for myofascial pain. Stabilization splints are the most common splints used.[23] Other forms of splints have been advocated for myofascial pain with similar value; these are effective in 70% to 90% of cases.[10] The exact reason why splint therapy is effective in myofascial pain is not yet determined. Numerous electromyography (EMG) studies have shown a short-term decrease in muscle activity, especially the temporalis and masseter muscles.[42-44] Long-term EMG studies, however, have shown ambiguous results.[45-47] This may be due to a traditionally cyclic nature of symptoms related to myofascial disorders.[48]

A study by deLeeuw et al determined that patients with myofascial pain had a decrease in symptoms with splint in the use of planned actions and rational thinking.[49] It is not clear, however, if the reduction in symptoms caused a decrease in depression or if a decrease in depression caused a reduction in symptoms.

The effectiveness of splint therapy for myofascial pain has been brought into question by a study by Dao et al. positive patient expectations may have an as large or larger role in treatment of TMJ disorders than the biomechanical impact of occlusal appliances.[18,51-53]

The exact reason why splint therapy is effective for myofascial pain is yet to be determined. Further controlled studies are needed to validate any number of theories. The most effective type of splint used is also yet to be definitively determined. It is important, however, to use conservative and reversible appliances because some splints can have adverse effects on a patient's occlusion.[54]

Bruxism

Bruxism can cause several deleterious effects. First, bruxism can cause irreversible wear on the dentition.[55,56] Second, bruxism can also cause moderate hypertrophy of the masticatory muscles, most notably the masseter.[57] Third, bruxism can result in alteration of the TMJ anatomy over time.[58] Lastly, the link between bruxism and myofascial pain is strong and quite possibly causative in many cases.[59,60] Therefore if a patient with bruxism has a myofascial pain component, the same rationale for splint therapy applies.

EMG studies have shown a significant decrease in masseter and temporalis muscle activity with splint use in patients exhibiting nocturnal bruxism.[39,61-63] These studies also

show that the effect of splint therapy is not maintained once splint usage is halted.[61,62] Muscle activity often returned to the pretreatment levels within several weeks after cessation of treatment. Further, a recent study by Raphael et al found pain to improve in patients with bruxism, but the splint therapy had little effect on the severity of the bruxism.[64] This raises questions of the exact mechanism of splint therapy and if there is an exact causative nature of bruxism and myofascial pain.

Splint therapy has been used extensively for various intracapsular TMJ disorders with little definitive evidence indicating their therapeutic value. In attempting to treat anterior displaced discs with or without reduction, splints have been hypothesized to "recapture" a displaced disc into its natural position over the condylar head, especially during function. Cohen and MacAfee submitted that a proper meniscal-condylar position is essential to prevent future degenerative joint disease.[65] This theory, however, has not been supported by further studies. Studies show that recapturing the disc with the use of splints is marginally effective in the short and long term.[66-69] Furthermore, the use of repositioning splints can permanently alter the patient's occlusion. The most effective use is in relation to pain symptoms, where likely the joint is "unloaded" leading to a decrease in inflammation. A decrease in inflammation may result in an increase in the range of motion.[67,70,71]

In the case of anterior displaced discs *with* reduction, the theory is that a "joint unloading" will allow the disc to resume its natural position over the condylar head. Consistent repositioning of the disc has not been proven, but splint therapy has been shown to result in a decrease in joint loading. Nitzan studied the intraarticular pressure within the TMJ with and without an intraocclusal appliance. During clenching there was a decrease in intraarticular pressure of 81.2% with the occlusal appliance in place versus without it.[71] Pivot splints have also been used for joint unloading and have shown that a fulcrum at the second molar area results in 1 to 3 mm of condylar lowering.[70]

Similarly, splints have been used to treat anterior displaced discs *without* reduction. Their effectiveness, however, has been brought into question. A similar "joint unloading" phenomenon has been reported with a decrease in pain.[72,73] It is theorized that over time the retrodiscal tissue becomes more fibrotic, with a decrease in vascularity and innervation.[74-76] A study by Lundh et al, however, found no statistical benefit in pain or range of motion with the use of splints in patients with anterior disc displacement without reduction.[77] Conversely a study by Ohnuki et al observed that pain symptoms improved with splint therapy with patients with anterior disc displacement without reduction. Post-treatment magnetic resonance imaging (MRI) studies, however, revealed that splint therapy had minimal effect on the disc's position.[78] to be determined. Splints do have a role in decreasing joint load, which may lead to an improvement in pain symptoms. Given the lack of a conclusive role, splint therapy, if chosen, should remain conservative and not cause irreversible changes to the occlusion or TMJ anatomy.

Degenerative Joint Disease

Degenerative joint disease includes osteoarthritis and rheumatoid arthritis. Splint therapy has been shown to have a favorable therapeutic index to treat symptoms related to muscle activity and inflammation in the joint as a result of overload. If a patient is exhibiting pain in association with degenerative changes, splint therapy may be effective at treating the symptoms. Splint therapy, however, has not been shown to alter the course of degenerative joint disease.[79,80]

Pharmacotherapy

The treatment of TMJ disorders is often not effective with one modality alone. A complete treatment regimen involves multiple types of treatment reflective of the multifactorial nature of the disease process. Pharmacologic therapy quite often plays a central or adjunctive role in the treatment of TMJ disorders.

Pharmacologic therapy can be divided into two main categories: medications used to treat a certain disorder and medications used to palliate symptoms associated with the disorder. Several types of medication are used for both purposes. Imperative is a detailed discussion with the patient regarding the reason(s) why a certain medication is being prescribed and what is the desired end point. Continuing a medication, especially an analgesic, for an extended period of time is not a desirable method of treating TMJ disorders. Dependency, tolerance, or adverse side effects may occur. Furthermore, giving medications on an "as needed" basis should be avoided as much as possible. Instructions to take a medication "as needed" require the symptom to be present.[72,81,82] This leads to an oscillating or cyclical process to the patient's symptoms. More appropriate is to give medications on a schedule to prevent these variations in symptoms. The goal is to develop an individualized regimen that relieves the symptoms for a period of time, hopefully breaking the disease process and causing permanent improvement.

The categories of various pharmacologic treatment modalities are listed in Box 39-3. The choice of one type of medication over another depends on the TMJ diagnosis

• BOX 39-3 Categories of Medications Used to Treat TMJ Disorders

NSAIDs
Corticosteroids
Analgesics
Muscle relaxants
Antidepressants
Anxiolytics

and the severity of the patient's symptoms. It is not uncommon to use medications from several categories to treat an individual's disease process.

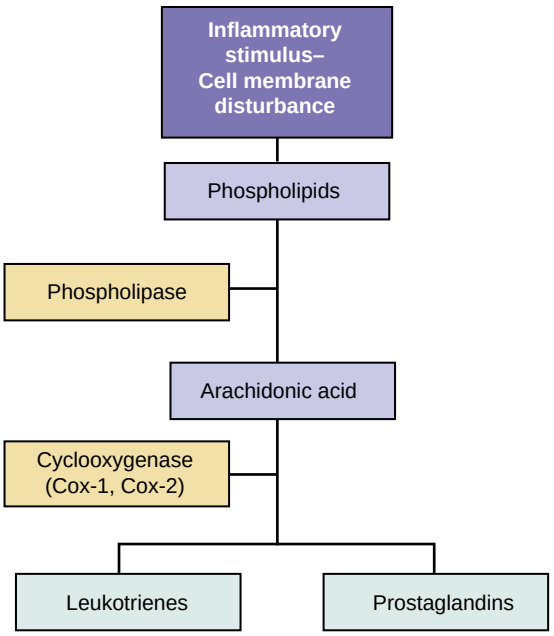
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are used to treat TMJ disorders by two mechanisms: their analgesic effects and anti-inflammatory properties. NSAIDs have been used in myofascial pain syndrome, synovitis, osteoarthritis, and symptomatic disc displacement.[83] NSAIDs' mechanism of action is to inhibit cyclooxygenase from converting arachidonic acid into prostaglandins and thromboxane. Arachidonic acid is released from cell membrane phospholipids in response to noxious stimuli. Prostaglandins promote multiple physiologic effects, including both inflammation and pain (Figure 39-8).

NSAIDs act by temporarily preventing the binding of arachidonic acid to the cyclooxygenase enzyme. The exception to this is aspirin, where the cyclooxygenase enzyme is acetylated. Aspirin's effects take longer to wear off because production of new cyclooxygenase molecules is needed to restore baseline function.[84]

Two different cyclooxygenase enzymes (Cox-1 and Cox-2) produce prostaglandins. Cox-1 is a constitutive enzyme that is stimulated by normal physiologic processes and is always present. It affects platelet aggregation and renal blood flow, protects stomach mucosa, and regulates vasomotor tone.[84,85] The Cox-2 enzyme is increased dramatically with the action of macrophages. This results in the formation of multiple prostaglandins that result in pain, increased swelling, and increased temperature.[86,87]

All NSAIDs are active against Cox-1 and Cox-2, but the degree of effect that a particular NSAID has on either enzyme varies greatly. For example, aspirin is highly selective for Cox-1, whereas naproxen has a relatively equal effect on both enzymes.[86] In general, the greater the effect that a particular NSAID has on Cox-1, the greater side effect profile it has. Most notably, this manifests as gastrointestinal irritation. It follows that NSAIDs should be chosen to maximize their Cox-2 effects and decrease their impact on Cox-1. This idea, though still believed, has been brought into question by reports of selective Cox-2 inhibitors causing various cardiovascular problems.[88,199] Commonly prescribed NSAIDs are shown in Table 39-1. Currently, ibuprofen and naproxen are the most prevalent, after usage of the selective Cox-2 inhibitors has decreased.



• **Figure 39-8** The cyclooxygenase pathway.

Corticosteroids

Various corticosteroids used in TMJ disorders are shown in Table 39-2. Corticosteroids interrupt the inflammatory cascade by completely blocking the formation of arachidonic acid by blocking phospholipase (see Figure 39-8). This results in a greater effect on the formation of prostaglandins than that found with NSAIDs. Their effect on acute TMJ pain and hypomobility is therefore greater than that found with NSAIDs. Long-term use of corticosteroids for the treatment of TMJ disorders, however, is contraindicated. It has been shown that usage of prednisone more than 10 to 20 mg a day for 2 weeks can cause suppression of the hypothalamic-pituitary-adrenal axis.[89] This can result in a Cushing's-like disease process, acute adrenal crisis, hypotension, electrolyte abnormalities, and diabetes. Chronic steroid administration can also result in the formation of osteoporosis including the TMJ. This is because the mandibular condyle has a reduced ability to withstand stress and may go through destructive changes.[90-92]

The use of intracapsular corticosteroid injections is discussed elsewhere in this text. The use of oral corticosteroids should be reserved for significant acute TMJ discomfort or for diagnostic purposes. The course of drug administration should be short and repeated as infrequently as possible. A typical regimen is a tapering dose lasting 5 to 7 days.

Analgesics

Practitioners have a wide array of opinions regarding the role of analgesics in TMJ disorders. Prescribed duration and dosage vary significantly. Patients' attitudes toward analgesics are also variable. Patients must be aware that the use of analgesic medications likely will not "cure" their TMJ disorder. It is permissible for patients to use analgesics for symptomatic relief, but they must be aware that by taking the medication the disease process is not halted.

The use of analgesics in TMJ disorders can be divided into two main categories: narcotic and nonnarcotic analgesics. The primary nonnarcotic medications used are the NSAIDs, which were discussed previously. Acetaminophen is another commonly used nonnarcotic analgesic. Acetaminophen does have some anti-inflammatory properties, but is mainly used for pain relief. High dose or long-term

TABLE 39-1 Nonsteroidal Anti-inflammatory Drugs Used in TMJ Disorders

Category	Generic Name	Brand Name	Usual Dosage	Relative Specificity Ratio of Cox-1 to Cox-2
Salicylates	Aspirin (acetylsalicylic acid) Diflunisal	Bayer Dolobid	650 mg qid (EC) 250 mg bid	166
Acetic acids	Indomethacin Sulindac Diclofenac	Indocin Clinoril Voltaren	25 mg tid 150 mg bid 50 mg tid	60 100 –1.4
Propionic acids	Ibuprofen Naproxen Ketoprofen Flurbiprofen	Motrin, Advil Naprosyn Orudis Ansaid	600 mg tid 375 mg bid 50 mg tid 100 mg bid	15 –1.7 1.2
Fenamic acids	Meclofenamate Mefenamic acid	Medomen Ponstel	50 mg qid 250 mg qid	7
Oxicams	Piroxicam Meloxicam	Feldene Mobicox	20 mg qod 7.5 mg qod	250 –3.0
Pyranocarboxylic acids	Etodolac	Ultradol	300 mg bid	0.1
Naphthylalkanones	Naburnetone	Relafen	1 g qod	
Cox-2 inhibitors	Celecoxib Profecoxib Valdecoxib	Celebrex Vioxx Bextra	200 mg qod 25 mg qod 20 mg qod	0.003 0.026

TABLE 39-2 Oral Corticosteroids Used in TMJ Disorders

Drug	Alternative Name	Relative Potency	Usual Dose
Hydrocortisone	Hydrocortone	1	20-240 mg/day
Prednisone	Deltasone, Orasone	4	5-60 mg/day
Prednisolone	Delta-Cortef	4	5-60 mg/day
Dexamethasone	Decadron	25	0.75-9.0 mg/day
Betamethasone	Celestone	25	0.6-7.2 mg/day

usage of acetaminophen can cause liver dysfunction. It is contraindicated in patients with liver disease or moderate alcohol consumption.

Opioid analgesics are a class of phenanthrene alkaloids with a first known use in sixteenth century Egypt.[93] Multiple opioid receptors have been discovered over the years, but the *mu* receptor has been found to be the principle receptor involved in analgesia.[94] Opioid analgesics act at sites in the brainstem for descending pain inhibition, elsewhere in the brain raising the threshold to a painful stimulus, or peripherally in peripheral nociceptors.[95-99] Opioid analgesics have adverse effects, including decreased gastrointestinal motility, respiratory depression, urine retention, sedation, and nausea and vomiting.

A large drawback to the use of opioids is a potential tolerance to the medication with chronic usage. Physical and psychological dependence on opioids is possible with repeated administration. Commonly used opioid analgesics are shown in Table 39-3 with their relative risk of causing dependence. The tolerance and dependence are both reversible, but the psychological dependence is the most difficult to completely resolve.

If prescribing opioid analgesics for patients with TMJ disorders, it is important to educate the patient on the proper use of the medications and potential risks. Further, a patient's medication intake should be monitored as closely as possible to decrease the abuse potential. Opioids should be prescribed for short durations during times of acute discomfort.

Muscle Relaxants

Muscle relaxants have been used for many years in treating symptoms associated with TMJ disorders. Proper diagnosis is paramount to determine if muscle relaxants are indicated.

TABLE 39-3 Commonly Used Opioid Analgesics in TMJ Disorders

Drug	Alternative Name	Therapeutic Dose	Abuse Potential
Codeine		30-60 mg	Low
Pentazocine	Talwin	50 mg	Low
Propoxyphene	Darvon	32-65	Low
Tramadol	Ultram	50-100 mg	Low
Hydrocodone	Dicodid, in Vicodin	5-10 mg	Moderate
Meperidine	Demerol	50-100 mg	Moderate
Methadone	Dolophine	5-15 mg	Moderate
Morphine	MS Contin	20-60 mg	Moderate
Hydromorphone	Dilaudid	2-4 mg	High
Levorphanol	Levo-Dromoran	2-3 mg	High
Oxycodone	In Percodan	5-10 mg	High

Symptoms associated with myofascial pain, bruxism, and hyperactivity of the masticatory musculature can benefit from muscle relaxants.[100,101] It follows that muscle relaxants will have minimal effects on meniscal disorders. Muscle relaxants are divided into two categories: centrally acting or peripherally acting.

Most commonly, centrally acting muscle relaxants are used to treat TMJ disorders. Antianxiety medications do have centrally acting muscle relaxation properties, but will be discussed elsewhere in this section. Centrally acting muscle relaxants act by diminishing nerve output to voluntary muscles. They involve several areas of the CNS, including the brainstem, thalamus, and basal ganglia. The most commonly used centrally acting muscle relaxants are cyclobenzaprine (Flexeril), carisoprodol (Rela, Soma), and methocarbamol (Robaxin) (Table 39-4).

The most common peripherally acting muscle relaxant is baclofen (Lioresal). Baclofen is an analogue to γ-aminobutyric acid (GABA), which binds to GABA receptors and reduces the release of excitatory amino acids, thus reducing motor tone.[102] Baclofen has been used in traumatic spinal cord injuries, multiple sclerosis, and trigeminal neuralgia in addition to TMJ disorders. Baclofen is reserved for use in patients who are experiencing marked muscle spasms or pain stemming from a neurogenic origin.

An additional method of muscle relaxation is the use of botulinum toxin A (Botox).[103-105] Botulinum toxin A functions by inhibiting the release of acetylcholine from cholinergic neurons, which decreases the transmission of the neural stimulus to the muscle. Botulinum toxin A has been used extensively to treat various dystonic syndromes.[106] Administration of botulinum toxin A requires direct injection into the affected muscle. Most precise administration is accomplished with the use of EMG-guided needles. Repeat dosing of botulinum toxin A is delayed for approximately 6 months, giving time for the botulinum toxin A to defuse from the acetylcholine receptors. Repetitive dosing can result in a tolerance in the recipient muscle.[106] Often botulinum toxin A administration will decrease muscle activity enough that the patient's disease cycle is broken, resulting in an improvement of symptoms for a period of time after the medication has worn off. Some have used botulinum toxin A for treatment of TMJ clicking with success.[200-202]

TABLE 39-4 Commonly Used Muscle Relaxants in TMJ Disorders

Generic Name	Brand Name	Usual Dosage
Centrally Acting		
Cyclobenzaprine	Flexeril	5-30 mg/day
Methocarbamol	Robaxin	1500-4500 mg/day
Carisoprodol	Rela, Soma	1000-1400 mg/day
Chlorzoxazone	Paraflex	750-3000 mg/day
Peripherally Acting		
Baclofen	Lioresal	15-80 mg/day
Botulinum toxin A	Botox	20-100 units/ 6 months

Antidepressants

Several classes of antidepressant medications exist, including tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, and selective serotonin reuptake inhibitors. In general, antidepressants are used to treat a variety of disorders, including depression, eating disorders, chronic pain syndromes, obsessive-compulsive disorders, and sleeping disorders. It is well known that there is a complicated link between chronic pain and depression, and treatment of both entities is often necessary.[107] Magni reported that nearly all patients (97%)

with a chronic pain syndrome without an organic lesion causing the pain were found to have a psychiatric condition compared with 39% of patients with chronic pain resulting from an obvious cause.[108] The majority of patients with TMJ disorders have demonstrated evidence of depression on presentation or through the course of the disorder.[109,110]

For TMJ disorders, tricyclic antidepressants (TCAs) are the most commonly used class of antidepressant medications. TCAs have not only antidepressant properties but have been shown to possess analgesic potential.[111] Amitriptyline, the most commonly used TCA for TMJ disorders, has analgesic properties at low doses, much lower than the therapeutic levels to achieve significant antidepressant effects. Numerous studies have demonstrated their effectiveness in treating chronic pain from TMJ disorders.[112-114] Common side effects include xerostomia, sedation, constipation, and orthostasis[115] (Table 39-5).

Anxiolytics

Anxiolytic medications are occasionally used to treat patients with TMJ disorders. They decrease the anxiety related to the disease process, which often accompanies the depression characteristics. Anxiolytic medications also serve to decrease insomnia and decrease muscle activity, which is often associated with nocturnal bruxism. Anxiolytic medications are often not the only line of treatment for TMJ disorders, but function well as periodic adjunctive therapy.

The most commonly used anxiolytic medications are benzodiazepines (Table 39-6). Their popularity stems from a high selectivity for treatment of anxiety and a larger margin of safety than other medications (e.g., barbiturates). The benzodiazepine receptors in the CNS are coupled with the inhibitory neurotransmitter GABA receptors, leading to an increase in chloride influx. This leads to membrane hyperpolarization and neural inhibition.[116] Benzodiazepines, especially diazepam, have muscle relaxant properties, which can be very effective at treating symptoms associated with nocturnal bruxism. Adverse effects of benzodiazepines include somnolence, muscle weakness, confusion, apathy, and dependency. It is recommended to not use benzodiazepines to treat TMJ disorders for long periods of time. Syrop recommended usage for a maximum of 3 continuous weeks for the treatment of nocturnal bruxism.[83]

Buspirone (BuSpar) is an azaspirodecanedione medication used for anxiolysis. It is not related to benzodiazepines, but has the same anxiolytic properties, without the sedative, anticonvulsant, and muscle relaxant characteristics. It also does not result in physical dependence, as is the case with benzodiazepines. The major disadvantage to using buspirone is a delayed onset to clinical effect of 1 to 3 weeks.

Several other medications are occasionally used for anxiolysis. For example, meprobamate was commonly used before the advent of benzodiazepines, but its popularity has decreased substantially. Antihistamines are used for both their anxiolytic and sedative properties. They have a relatively low toxicity and minimal abuse potential.

Occlusal Management

For many years, dentistry has maintained the position that the cause of TMJ disorders is multifactorial, which usually implies that the profession is unsure about the specific cause. Dental and skeletal occlusion is at the center of a complete maxillofacial examination. This likely has lead to the historical thought that occlusion is the most important etiologic factor in the development of TMJ disorders. Presently, there are no studies that suggest that orthodontics, restorative dentistry, or oral and maxillofacial surgery prevents an individual from developing symptoms or promotes the development of symptoms. The rationale for the treatment of TMJ disorders in association with skeletal malocclusions using orthognathic surgery will be discussed elsewhere in this text.

Anterior Overjet, Overbite, and Open Bites

Numerous sources have suggested that an increase in both the anterior overbite and overjet can predispose individuals

TABLE 39-5 Commonly Used Antidepressant Medication for TMJ Disorders

Class	Generic Name	Brand Name	Usual Dose
TCA	Amitriptyline	Elavil	10-100 mg/day
	Nortriptyline	Pamelor, Aventyl	2.5-75 mg/day
	Doxepin	Sinequan	50-150 mg/day
	Imipramine	Tofranil	10-40 mg/day
	Desipramine	Norpramin	50-150 mg/day
Serotonin modulator	Trazodone	Desyrel	25-50 mg/day
SSRI	Fluoxetine	Prozac	1-20 mg/day
	Paroxetine hydrochloride	Paxil	5-20 mg/day
	Sertraline	Zoloft	50-200 mg/day

TABLE 39-6 Commonly Used Anxiolytic Medications in TMJ Disorders

Class	Generic Name	Brand Name	Usual Dosage
Azaspirodecanedione	Buspirone	BuSpar	15-30 mg/day
Antihistamine	Hydroxyzine	Vistaril	75-300 mg/day
	Promethazine	Phenergan	25-50 mg/day
Carbamate	Meprobamate	Miltown	1.2-1.6 mg/day
Benzodiazepine	Alprazolam	Xanax	0.75-4 mg/day
	Lorazepam	Ativan	2-6 mg/day
	Oxazepam	Serax	30-90 mg/day
	Temazepam	Restoril	15-30 mg/day
	Triazolam	Halcion	0.125-0.5 mg/day
	Chlordiazepoxide	Librium	15-100 mg/day
	Diazepam	Valium	8-40 mg/day
	Flurazepam	Dalmane	15-30 mg/day
	Prazepam	Verstran, Centrax	30-60 mg/day

to mandibular dysfunction.[117-120] There are not, however, suitable studies to support this claim definitively. Many of the currently available studies do not have sufficient numbers, controls, or longitudinal data.

Pullinger et al demonstrated a small but significant correlation between increased horizontal overjet and TMJ disorders.[121] A recent longitudinal study by Pahkala and Qvarnstrom supported this conclusion. Excessive overjet was the only variable that correlated with an increased risk of TMJ disorders.[122]

Definitive data regarding anterior open bites are not available. Numerous studies suggest that there is a higher percentage of open bites in patients with TMJ disorders.[121,123,124] No longitudinal studies, however, have determined that the open bite is the *cause* of the TMJ disorder. More likely, the open bite is a result of the TMJ disorder, possibly because of an alteration in the disc position or condylar resorption.

Therefore minimal conclusions can be made in regard to overjet, overbite, and open bites. There is likely a slight increase in TMJ disorders in patients with an increase in horizontal overjet. Therefore a treatment recommendation *may* be made to correct excessive horizontal overjet. Further longitudinal studies are necessary to completely describe the role, if any, overjet, overbite, and open bites play in TMJ disorders.

Angle's Classification and Anterior Contact

As discussed in the previous section, an increase in horizontal overjet may correlate with a small increase in TMJ disorders. It follows that this increase in horizontal overjet is often associated with an Angle's class II, division 1 occlusion. Studies have found that there is a small increase in TMJ disorders in Angle's class II patients compared with the overall population.[125-128]

regarding the impact of these occlusal schemes on either the success or failure of restorative dentistry treatment outcomes or on the prevention of TMJ disorders.

A study by Okano et al demonstrated a decrease in

overlay-constructed occlusal patterns, not patients' natural occlusions.[129] Conversely, Belser and Hannam found there

have had minimal change on bruxism long term when splint usage is discontinued.[62,131] Therefore an alteration in occlusal scheme (i.e., usage of an occlusal splint) does not significantly decrease muscle activity long term. These results suggest that altering the occlusal scheme probably has little effect on oral habits or the development of intraarticular TMJ disorders.

Missing Posterior Teeth

Historically, it was believed that missing posterior teeth lead to TMJ disorders and the associated pain and dysfunction. Restoring the posterior occlusion would treat these symptoms.[132-134] Many studies have investigated whether missing posterior teeth increased the risk of intraarticular TMJ

disorders or increased the risk of symptoms and if restoring posterior occlusion would treat TMJ disorders.

Loss of posterior teeth has been positively correlated with osteoarthritic changes.[135-138] Tallents et al also found an association between missing mandibular molar teeth and the presence of disc displacement.[139] This has not, however, correlated with the development of symptoms.[140,141]

Several studies have shown that restoring missing posterior teeth does not decrease the prevalence of TMJ disorders.[121,142,143] A longitudinal study by Witter et al demonstrated that loss of posterior teeth did not increase the risk of TMJ disorders.[144] They also suggested that removable partial dentures do not prevent TMJ disorders and do not improve oral function. Lederman and Clayton found dysfunction in 68% of patients with fixed partial dentures in all posterior quadrants.[145] These observations pose two concerns: restorative dentistry to restore posterior occlusion is not justified as a solution to prevent TMJ disorders, and even if a symptomatic patient is restored, he or she may continue to have pain. There are other possible causes for facial pain in a patient with missing posterior teeth.

Centric Relation Versus Maximal Intercuspation

A widely debated question is whether a discrepancy between initial occlusal contact and maximal intercuspation increases the risk of developing TMJ disorders. Numerous epidemiologic studies have been done investigating the degree of TMJ disorders in relation to centric relation and/or maximal intercuspation slides.[125,127,146] The current literature does not strongly support the role of dental occlusion as an etiologic factor in TMJ disorders from the standpoint of centric relation and/or maximal intercuspation slides.[147] Several studies, however, have been done showing that alteration of the vertical dimension or introducing occlusal interferences (i.e., with "high" restoration) can incite pain and synovial changes.[148-150]

It follows that occlusal adjustments should not be used to treat TMJ disorders.[151,152] Most telling was a Cochrane Database publication concluding that there is an absence of evidence that occlusal adjustment treats or prevents TMJ disorders and cannot be recommended for the management or prevention of TMJ disorders.[153] Therefore occlusal adjustments are only recommended when TMJ pain symptoms have been introduced by recent restorative dentistry or occlusal changes. The traditional recommendation to eliminate centric relation and/or maximal intercuspation slides for the treatment of TMJ disorders has little merit.

Physical Therapy

Throughout the history of treating TMJ disorders, physical therapy modalities have been widely used. Virtually all treatment regimens for TMJ disorders involve physical therapy. The primary focus is to treat neuromuscular conditions relating to the TMJ. Physical therapy incorporates many different treatment modalities. They include stretch and/or range of motion exercises, massage, thermal treatments, ultrasonography, and electrical stimulation.

These therapies can be delivered in several manners. Trained dental professionals can carry out the therapy themselves or teach the patient the proper technique, interval, and duration of the treatment. However, physical therapists trained in caring for TMJ disorders are often necessary and highly beneficial. The physical therapists' primary goal is to treat impairments and functional limitations that are related to the patients' disability, which may or may not have a correlation to the medical diagnosis. This does not limit the necessity for an accurate diagnosis so that a proper and complete treatment regimen can be established. Table 39-7 illustrates the functional limitation and the treatment modality that can be used to improve the impairment.

Exercise Therapy

It is well established throughout the orthopedic literature that synovial joints need movement to maintain function. Early mobilization, even during the inflammatory phase after an injury, is widely accepted in the rehabilitation of other joints.[154] These same principles apply to the TMJ.[155] To maintain proper function and joint integrity, full joint motion is necessary. Furthermore, hypomobile TMJs require range of motion exercises. Exercise therapy is best used when hypomobility exists in one or both TMJs or as a result of surrounding soft tissues.[156] Conflicting opinions exist concerning the degree of hypomobility that warrants exercise therapy, but a maximum incisal opening of less than 30 mm is often used as a cutoff. Hypomobility resulting from periarticular tissue tightness and a disc displacement without reduction responds the best to exercise therapy.

The technique of joint mobilization can be done in either an active or passive manner. The active jaw motion technique involves the activation of the mandibular depressor muscles. Passive joint mobilization is a more popular technique where the musculature is relaxed and the jaw is opened manually (finger pressure, tongue blades, mandibular opening devices). Often some degree of distraction technique is necessary for proper passive mobilization. This can include medicinal therapy in extreme cases.

TABLE 39-7 Physical Therapy Treatment Concerns and Treatment Modalities to Consider

Treatment Concerns	Physical Therapy Treatment Modality
Inflammation	Heat, cold, ultrasound, TENS, iontophoresis
Hypermobility	Awareness, yawning, tongue control
Hypomobility	Heat, exercise therapy
Masticatory muscle hyperactivity	Massage, exercise therapy, ultrasound, iontophoresis

Two passive joint mobilization techniques are often used. First is to have the mandible stretched open and the position held for a short period of time (5 to 15 seconds). This is repeated 5 to 10 times in a session and can be repeated several times throughout the day. The second technique uses a low-load prolonged stretch. This technique has been demonstrated effective in laboratory studies to stretch tendinous soft tissues.[157,158] Heat therapy is often coupled with this technique because it produces greater elongation of the treated tissues. Continuous passive motion is often used after surgical procedures to maintain a proper range of motion.[159] The jaw is stretched open for approximately 10 minutes one to three times per day. It is important to not forget lateral excursive and protrusive movements during passive joint mobilization.

Exercise therapy is also often recommended for symptoms associated with masticatory muscle hyperactivity (resulting in myofascial pain). These therapies are often traction of the mandibular depressor muscles will cause the elevator muscles (muscles of mastication) to relax.[160] Care must be taken, however, because excessive exercise and stretching of the masticatory muscles may worsen the myofascial pain.

Exercise therapy used to recapture displaced discs has been found to be minimally effective. Kurita et al found that only 9% of permanently anteriorly displaced discs can be reduced by mandibular manipulation.[161] It is important to remember that exercise therapy is not used to treat the disease process, but to minimize the sequelae. A recent study by Maloney et al concluded that exercise therapy is effective in both joint (intracapsular) and muscle (extracapsular) disorders to relieve pain and increase the range of motion.[162] Exercise therapy may therefore be used to alleviate painful symptoms and maintain functional integrity.

Massage

Minimal research has been done on the effectiveness of massage therapy on symptoms related to TMJ disorders. Massage therapy is only effective in cases involving a muscular component. Techniques, duration, and intervals of massage of the muscles of mastication vary depending on the clinician. Patients can also be instructed at self-massage if they think that it is effective for them. It has been speculated that acupressure techniques are effective at relaxing trigger points within the musculature.[163,164]

Thermal Therapy

Thermal agents are often used in the symptomatic management of TMJ disorders. Patients often express an improvement in symptoms when exercise therapy is incorporated with thermal agents. The use of heat and cold therapy is best used when an inflammatory component is present or with hypomobile TMJs. If marked inflammation is present, heat therapy may be contraindicated.

Superficial heating of the TMJ or surrounding musculature results in an elevation of the pain threshold, increases nerve conduction velocity, and decreases muscle tension.[165-167] No benefit has been cited between moist and dry heat. Heat therapy in the form of a moist washcloth or heating pad is typically applied for approximately 20 minutes to the effected area(s). Application of heat often allows for a greater range of motion with a decrease in pain.

Cold therapy, or cryotherapy, is helpful at decreasing inflammation by causing vasoconstriction and a decrease in tissue metabolism. Furthermore, a *decrease* in nerve conduction velocity has been shown to cause and increase the pain threshold.[168] The "spray and stretch" method has been described to decrease pain while attempting to increase maximal incisal opening.[169] Travell and Simons theorized that stimulation of afferent delta fibers (detecting temperature) produced a decrease in C fiber stimulation (detecting pain).[170] Many clinicians believe that the pain originates from "trigger points" in myofascial pain and the "spray and stretch" technique is effective at decreasing their sensitivity.[171-173]

Ultrasound

Ultrasound has been used widely in various fields of medicine as an additional method of delivering heat to tissues. Unlike superficial heating, however, the tissue interaction is 1 to 5 cm below the skin surface. The deep heat functions similar to superficial heating, intended to decrease pain, increase tissue perfusion, and allow for greater mobility.[174]

In addition to heating the tissues, ultrasound decreases inflammation by increasing cell membrane and vascular wall permeability.[175] Success has been reported in the orthopedic literature when exercise therapy is applied in conjunction with ultrasound.[176] In addition to causing a temperature rise and increased tissue permeability, ultrasound causes an increase in the viscoelastic properties of collagen and hyaluronic acid.[177] This results in greater joint and soft tissue laxity in case of TMJ hypomobility. Care must be taken to perform ultrasound with a proper acoustic conductive gel and use continuous motion so as not to overheat the tissues. Furthermore, ultrasound should not be used over areas of active bone growth; it may cause further aberrant growth.[178]

Electrical Stimulation

The most commonly used method of electrical stimulation is transcutaneous electrical nerve stimulation (TENS). The TENS unit is a small, portable low-voltage electrical device used in an outpatient setting or as a home therapy. The frequency, pulse width, and amplitude of the alternating current can be adjusted. The electrodes are placed over symptomatic areas, areas of inflammation, muscle hyperactivity, or trigger points.[179,180] TENS is most effective

in myofascial pain, resulting in pain relief and muscle relaxation.[181]

The exact mechanism of action of TENS is not known, but it likely involves a counterstimulation of the afferent nerves and controls pain based on the gate control theory.[182] The gate control theory postulates that the pain perception is blocked because the larger proprioceptive afferent fibers are selectively stimulated, inhibiting the smaller nociceptive fibers.[183] TENS has also been shown to produce vasodilation, which increases circulation and lymphatic drainage.[184] Contraindications to TENS treatment include epilepsy, demand-type pacemakers, a history of transient ischemic attacks, or a history of cerebrovascular accidents.[185]

Another method of using electrical stimulation is iontophoresis. Iontophoresis shifts water-soluble ions through the skin to the underlying soft tissue.[186-188] Commonly used ionizing drugs are dexamethasone, methylprednisolone, lidocaine, and salicylates. Medications administered by iontophoresis have been shown to have higher tissue levels than medications taken enterally, but lower tissue levels than achieved by injection.[189] Further research is required on the medication levels achievable in the TMJ. Several studies have shown minimal improvement of pain with the use of iontophoresis, but have shown an improvement in mandibular function.[190,191]

Summary

TMJ disorders are a complex combination of bone disorders, articular problems, inflammatory reactions, connective tissue breakdowns, myalgias, and neural ailments. This can seem quite daunting and has created a stigma against treating TMJ disorders for some clinicians. This has lead to the unfortunate circumstance of specialization of a few clinicians, and the alienation of many others, treating these disorders. As illustrated throughout this chapter, TMJ disorders are quite often multifactorial and require several forms of treatment. This treatment is often best carried out by several members of a team, rather than one individual. Ideally, after an accurate and complete diagnosis has been made, there would be one clinician who is a "team leader" who refers to appropriate specialists (such as orthodontists, oral and maxillofacial surgeons, physical therapists, psychologists, etc.).[192,193]

One method of treatment of TMJ disorders is often ineffective. Common reasons why the treatment of TMJ disorders fails include an inaccurate initial diagnosis and treatment plan, poor patient compliance with treatment, coexisting morbidities, or significant psychosocial problems.[194] It is commonly believed, however, that the treatment should begin with nonsurgical management in the majority of cases. If the initial course of treatment proves to be insufficiently effective, consideration should be made to add additional treatments, surgical or nonsurgical, and to reevaluate the original diagnosis. Nonsurgical management of TMJ disorders, however, has been shown to be quite effective. Okeson reviewed the long-term studies using conservative therapy and found that there was a reported 70% to 95% success rate.[72] The majority of cases have no surgical intervention. Longitudinal studies have shown that patient symptoms fluctuate over time, but the majority improves with a reported remission rate of 31%.[195-197]

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Arthrocentesis of the Temporomandibular Joint

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Introduction

Arthrocentesis is a safe and rapid procedure used to treat a multitude of disorders affecting the temporomandibular joint (TMJ). The popularity of this procedure followed the success of arthroscopic surgical procedures with the initial application for treatment of disc displacement without reduction. Since that time, arthrocentesis has been described for other clinical indications; however, it is not indicated for all temporomandibular joint disorders. This procedure does not change the shape or position of the disc or the anatomic structure of the mandibular condyle and glenoid fossa. Pathology involving bony degeneration, osteophytes and bone spicules, disc perforation or fibro-osseous ankylosis are not amendable to arthrocentesis. Treatment with arthrocentesis is generally indicated when other nonsurgical and pharmacologic methods have failed to alleviate TMJ pain and dysfunction.[1]

The etiology of pain associated with the TMJ is multifaceted. Possible sources of pain include impingement, compression and inflammatory changes in the retrodiscal tissues, inflammatory changes in the synovial membrane with joint effusion, and capsulitis. Biochemical investigations of TMJ synovial fluid obtained through arthroscopic lavage and arthrocentesis have yielded information regarding the pathophysiology of pain in the TMJ. Lysis and lavage of the joint space allows for removal and dilution of inflammatory mediators which may contribute to reduction of pain. Elevated protein levels in synovial fluid parallel the degree of inflammation due to increased permeability of the synovial membrane to plasma proteins. Joint effusion as detected on T2 weighted magnetic resonance images reflects hypertrophic synovial lining and exudation from inflamed joints at a more

ts must undergo appropriate diagnosis and treatment planning. This is based on medical history, visual analogue pain scales if indicated, and clinical and radiographic findings. Clinical examination should include interincisal opening, lateral excursions, deviation on opening, and documentation of any occlusal discrepancies. Auscultation of the joint may be performed to ascertain any clicks or crepitus which may indicate disc displacement or degenerative joint disease, respectively. Radiographic imaging should minimally include a panoramic screening film followed by other imaging modalities including tomography, computed tomography, magnetic resonance imaging or nuclear medicine studies, as indicated based upon the clinical and physical findings for the specific patient.

Nonoperative management for TMJ disorders may include physical therapy, avoidance of traumatic behaviors such as clenching or gum chewing, dietary changes, nonsteroidal anti-inflammatory drugs, muscle relaxants, and occlusal appliances. Patients who fail conservative mea-

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with normal interincisal opening to limited opening lacking translational movement where clicking ceases due to a nonreducible disc. Excessive loading on the joint with a nonreducible, anteriorly displaced disc that restricts the ability of the condyle to translate on the articular surfaces can be treated effectively with arthrocentesis of the superior joint space. When originally described by Nitzan, arthrocentesis was limited to patients with closed locked TMJs. Today, due to its ease and low morbidity, arthrocentesis has found an expanded list of clinical indications including:

1. Acute closed lock due to anteriorly displaced disc
2. Acute open lock due to condyle entrapped anterior to the disc after the more common pathology involving anterior translation past the eminence has been ruled out[4]
3. Palliation of acute episodes of degenerative or inflammatory osteoarthropathies
4. Evacuation of hemarthrosis after traumatic injury[5]
5. Fluid sampling and lavage of septic joints[6]

Contraindications to TMJ arthrocentesis would include those patients who have not undergone appropriate nonsurgical and pharmacologic treatment, demonstrate bony or fibrous ankyloses, or exhibit extracapsular sources of pain such as myofascial or neuropathic pain.[7] Interestingly, some literature has called into question the need for initial conservative therapy, and found better initial pain control and

Pathophysiology of TMJ Dysfunction

There are several sources regarding the development of pain and dysfunction within the TMJ including the musculature, bony structures, synovium, and discal tissues. Past interest has been directed at the changes observed in the shape and position of the articular disc. More recent research has focused on the biomechanical and biochemical processes involved in TMJ dysfunction. Anchored disc phenomenon as described by Nitzan is a sudden onset of limited mouth opening with deviation of the mandible toward the affected side. Forced opening of the mouth may provoke pain. The disc will appear to be stuck to the fossa with the condyle sliding underneath the disc on MRI studies. This is in distinction to disc displacement without reduction where

possibly responsible for maintaining the articular disc adherent to the fossa in anchored disc phenomenon. In an earlier study, greater negative pressures were measured in the upper joint space of patients with anchored disc phenomenon compared to normal joints. The negative pressure was thought to be strong enough to keep the disc from sliding in a normal manner. Insertion of a needle into the superior joint space would reduce the negative pressure; however, other factors may contribute to this condition.[10] Joint overloading may cause collapse of the lubrication system through increased intra-articular pressure and hypoxia that is compensated by re-oxygenation on termination of overloading. The hypoxia-reperfusion cycle can lead to the release and production of reactive oxygen species, which can result in the degradation of hyaluronic acid (HA) and a marked reduction in synovial fluid viscosity.[11] Within the TMJ, surface-active phospholipids function as boundary lubricants and protectors of the articular surfaces. Lysis of these surface-active phospholipids by phospholipase A_2 can result in a significant increase in friction and adhesion between articular surfaces. HA plays a role in joint lubrication through its protection of the surface-active

after surgery so that patients may immediately begin with th [12]

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ity. Proinflammatory cytokines, which are induced by

for destruction of cartilage through degradation of proteoglycans. IL-6 may act to protect cartilage through promotion of the production of tissue inhibitors. It has been suggested that IL-1-β and IL-6 in synovial fluid may be associated with the development of osteoarthritis and the

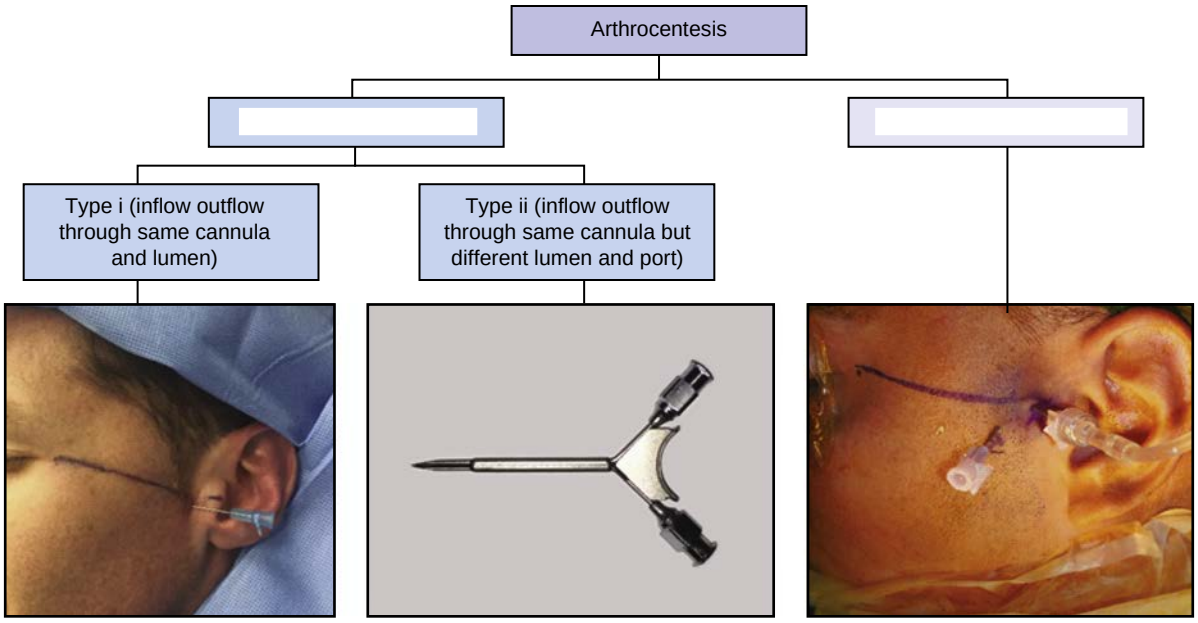
assessment of proinflammatory cytokines. It was determined that the detection of IL-6 and IL-1-β in synovial

function, palliation of pain, and halting the progression of disease should be used. What follows is a summary of current TMJ arthrocentesis techniques described in the literature, indications, contraindications, and adjunctive therapies used to address the pathophysiology and better tailor treatments to each patient using an evidence-based approach.

Technique of Temporomandibular Joint Arthrocentesis

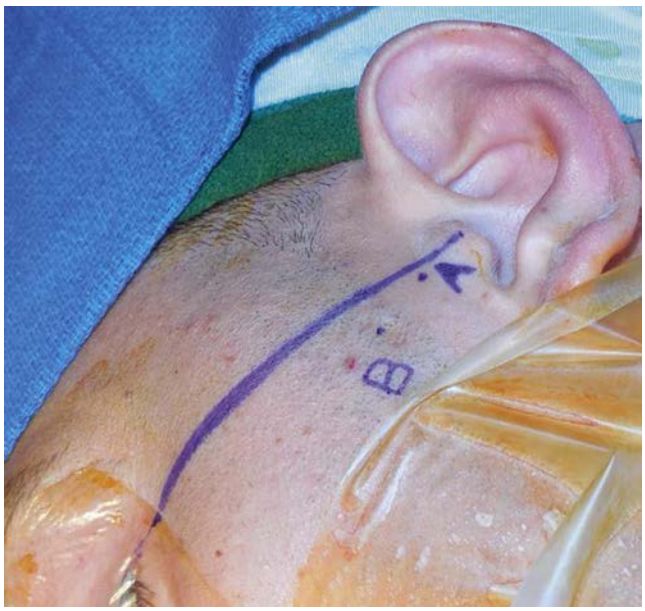
As with any surgical procedure, new techniques and modifications are proposed in the literature, which can cause confusion if there is no universally accepted classification system. Senturk and Cambazoglu created a simple classification system in 2015, taking into account the published

type ii, in which inflow and outflow are through the same cannula but different lumens and ports.[14] Figure 40-1 presents a simplified diagram of this categorization scheme and can be referenced when comparing and contrasting techniques in the following text.



• **Figure 40-1** Classification scheme of arthrocentesis as devised by Senturk and Cambazoglu. (Senturk MF, Cambazoglu M: A new classification for temporomandibular joint arthrocentesis techniques, *Int J Oral Maxillofac Surg* 44(3):417–418, 2015.)

Arthrocentesis of the TMJ may be performed under local anesthesia, sedation, or general anesthesia, depending on the surgeon and patient preferences. It is most conveniently performed with the patient in the office suite in a semi-reclined position. The hair is pulled from the surgical field and retracted using a combination of sterile surgical towels and antibiotic ointment. The external auditory canal should be protected from fluid and blood accumulation using an antibiotic-impregnated cotton pledget. A canthal-tragal line is drawn from the midpoint of the tragus to the lateral canthus of the ipsilateral eye. A point is made 10 mm forward from the tragus and 2 mm inferior to the line. This 10-2 point approximates the posterior extent of the articular fossa. This should be confirmed by palpation with the patient opening and closing the mouth. A second point corresponding to the height of the articular eminence can be marked at 20 mm anterior to the midtragal point and 10 mm below the tragal-canthal plane. This can function as a landmark for the placement of the second portal for the outflow of irrigant (Figure 40-2).



• **Figure 40-2** Canthal-tragal line with entry points marked at 10-2 and 20-10.

An auriculotemporal block and infiltration to the preauricular area for joint penetration are completed with local anesthesia. The superior joint is then entered with an 18-gauge needle directed in an anterior-medial-inferior direction at the 10-2 entry point, aiming for the posterior aspect of the articular eminence or anterior recess. Alternatively, some surgeons prefer to gently touch the zygomatic arch and gently walk the needle into the superior joint space. Once the joint space is entered, it may be insufflated with saline or lactated Ringer's solution. Several milliliters of solution can be injected rather passively into the joint space to the end point where there is rebound of the syringe pressure with jaw movement. With the needle in place, the syringe is removed and either a larger syringe can be attached for irrigation or connection to an intravenous fluid bag may be performed (Figure 40-3). A second needle must be inserted for the outflow portal at either the 20-10 point or slightly anterior to the initial needle placement. The joint is then lavaged, maintaining good outflow to confirm maintenance of the needles in the intra-articular space (Figure 40-4). After the procedure is completed, the joint can be manipulated by the assistant who is not part of the sterile field and has a gloved hand in the patient's mouth, going



• **Figure 40-3** System of IV tubing with syringe attached to provide high flow pressure irrigation.



• **Figure 40-4** Same system in use showing maintenance of outflow to confirm intra-articular positioning of the needle.

through opening, protrusive, and excursive movements. A goal of 30 to 40 mm interincisal opening should be achieved at the completion of the arthrocentesis procedure.

This technique can be used for all indications of arthrocentesis because it allows copious volumes of fluid to be flushed in an expedient manner. In particular, it is helpful for palliation of exacerbations of the inflammatory arthropathies, irrigation of a septic joint, or washing out hematoma after trauma.

As noted previously, arthrocentesis can be carried out with the use of one needle. The landmarks and procedure remain the same as in the two needle technique, however only the 10-2 posterior point of entry is used. The patient is asked to open his or her mouth and the needle is introduced. The patient then closes the mouth and small aliquots of irrigant are introduced with removal of the irrigating device to allow passive efflux of fluid. This increased hydrostatic pressure is postulated to expand the joint space and break up adhesions. The procedure is repeated several times until more passive movement of the jaw is observed.[15,16]

Insertion of only one needle posteriorly reduces the potential complication of penetrating the frontal branch of the facial nerve. In joints with advanced degenerative changes, the single puncture technique avoids the difficulty often seen with insertion of a second needle. This remains a good option if multiple attempts at second needle insertion have failed and avoids the trauma of multiple punctures to not only the joint capsule but also the glenoid fossa. If a steroid or hyaluronic acid solution is being injected postoperatively, the single needle technique theoretically allows more to stay within the joint space because there is no second perforation of the capsule allowing these substances to leak out. These considerations make the single puncture technique a good option for joints with significant hypomobility from adhesions, especially those with advanced degenerative changes. Of interest, a recently conducted randomized clinical trial demonstrated no statistically significant difference between single and double needle techniques when looking at range of motion (ROM), patient perceived improvement in pain, and surgical procedure tolerability.[17]

in the previously described techniques. The disadvantages are related to problems with the device itself such as dulling, rusting after sterilization, and a potentially more difficult access due to the larger gauge of the device. Additionally, some have theorized that these devices may not allow adequate pressure for joint distentsion and lysis of adhesions.[5] However, this could be obviated simply by periodically blocking the outflow port.

Irrigant Volume

Because one of the goals of arthrocentesis is to wash out inflammatory mediators responsible for inflammation within the joint, it would be necessary to provide adequate volume to irrigate the joint space and meet that purpose. Repeatedly injecting solution into the joint will increase pressure to release adhesions, but not necessarily eliminate the inflammatory mediators. It was observed that 200 mL of perfusate was sufficient to achieve a statistically significant reduction in protein, bradykinin, and IL-6 concentrations. An ideal lavage volume between 300 to 400 mL perfusate resulted in no detectable level of protein and bradykinin.[18] Previous recommendations were for 100 mL of perfusate to effectively decrease the concentration of protein in synovial fluid and provide therapeutic lavage. Recommendations should probably be for a minimum of 100 mL of total

arthrocentesis volume to achieve therapeutic lavage of the superior joint space of the human TMJ and, if feasible, up to 300 to 400 mL solution.[19]

In 2009 Alkan and Kilic described use of the irrigation pump on self-irrigating surgical motors to provide higher pressures and reduce treatment time, allowing more infusion. They described the two needle technique, confirming outflow before they attached the pump and then irrigating the joint space in 2 minutes with 300 mL of effluent. They cautioned that if outflow stops or rapid swelling occurs, the procedure should cease immediately and an outflow obstruction should be suspected. No mention of actual pressures achieved in the joint were described.[20]

Irrigant Pressure

Arthrocentesis of the TMJ under low pressure with an elevated infusion bag or syringe has been reported to be effective in treating patients with acute closed lock of the TMJ.[21] Irrigation and lavage under sufficiently high hydraulic pressure has also been postulated to widen the joint space and potentially remove adhesions to improve mandibular mobility. This can be an effective procedure for treating patients with chronic closed lock and adhesions in the superior joint space. High-pressure infusion using the infusion with a maximum pressure of 40 KPa, may offer wider application of arthrocentesis for patients other than those patients with acute closed lock.[22]

Number of Treatment Sessions

In 2012 Manfredini et al. reported an overall positive trend with no statistical significance in clinical outcomes using a protocol of 5 weekly sessions utilizing the two needle technique with HA injection.[23] This was tested in 2015 in a nificant improvement on visual analog scale at 6 months, however, other variables such as patient perceived effectiveness and maximal incisal opening remained unchanged.[24] The issues when evaluating these studies are the confounding col should be attempted to maximize cost/benefit ratio. At this time it does seem that a multitreatment session protocol may be more effective when combined with HA, although the specific number of sessions remains in question.

Adjunctive Substances

Steroids have been the most commonly injected adjunctive agent administered after arthrocentesis. Most protocols make use of betamethasone, dexamethasone, or methylprednisolone. They have been shown either alone or in conjunction with arthrocentesis to decrease pain and provide increased MIO for up to a year, although other studies have found no difference.[25] Steroids remain a good adjunctive treatment, due to their availability and marginal cost.

Hyaluronic acid has been one of the recent focuses of literature because it contributes to joint function by maintaining lubrication, minimizing mechanical wear, and playing a role in the nutritional support of the avascular portion of the disc and condylar cartilage.[26] Most injections consist of 0.5- to 2-mL injections. A Cochrane systematic review steroid injection or oral appliances.[27] Unfortunately, most studies looked at use of HA after arthrocentesis, introducing confounding variables. To further investigate, Triantaffillidou and Venetis performed a randomized clinical trial comparing saline placebo with five sessions of HA alone. They found no statistically significant changes at 1 month, but at 6 months and 1 year, all parameters studied were significantly better, including MIO.[28] Another randomized trial performed in 2014 demonstrated single HA injection performance was statistically significantly superior at 1 and 6 weeks when compared to tenoxicam and betamethasone.[29] No difference has been found in using low molecular weight (600 kDa) and medium molecular weight (1200 kDa) formulations.[30] It seems that hyaluronic acid does have proven superiority to other supplemental joint injections, especially when viewed over longer periods of time, and should be contemplated despite its cost when an adjunctive medication is considered.

Intra-articular injection of opioids holds promise as adjunctive therapy and has been studied in two randomized clinical trials. One study compared use of 5 and 10 mg of morphine versus saline and Marcaine and assessed pain relief at 1 week. Although the levels of pain relief drastically fell off after 48 hours for saline placebo and Marcaine 5 mg, 10 mg of morphine had lasting pain relief at 1 week.[31] Another trial comparing lactated Ringer's placebo, 50 mg tramadol, and 1 mg morphine injected intra-articularly after standard arthrocentesis, found a statistically significant improvement in pain up to 6 months postoperatively with morphine. This pain relief was attributed to more potent agonist at the μ opioid receptor.[32] Of note, neither of these studies demonstrated statistically significant increases in oral opening.

The relationship between muscle activity and TMJ dysfunction is not always precisely defined. Many cases of TMJ dysfunction have a component of muscle hyperactivity which can lead to joint overloading and promotion of inflammation and the potential for development of internal derangements. It has been suggested that injection of Botox-A into the muscles of mastication as an adjunct to TMJ arthrocentesis may be more effective at prolonging the improvement of symptoms compared to arthrocentesis

alone by addressing both the joint and the musculature simultaneously. The positive effect may be attributed to the result of mechanical unloading of the joint or possible anti-inflammatory properties of the Botox-A.[33]

Regenerative medicine using growth factors and stem cell therapy is an area of interest. Many studies have found beneficial properties to the use of growth factors throughout the human body. Hanci et al. conducted a trial comparing the injection of platelet rich plasma (PRP) to arthrocentesis and found that PRP had statistically significant

cell processing units become more popular, these treatments will undoubtedly see increased application.

The literature has clearly shown benefit to all of the described adjunctive treatments in addition to arthrocentesis. Questions remain as to specific formulations, treatment protocols, and superiority of one modality versus another. Selection should be based on the evidence-based findings

may be selected and combined with a high pressure arthrocentesis to lyse adhesions and provide long-lasting gains in function. If pain is the chief complaint in an end stage joint,

Outcome Assessment of Arthrocentesis of the Temporomandibular Joint

Nitzan et al. reported that arthrocentesis is a valuable modification of arthroscopic lavage. They demonstrated that arthrocentesis was very effective in the treatment of closed lock with regard to lack of recurrence of symptoms and significant improvement in pain and jaw function within a year of treatment. Furthermore, the authors recommended that arthrocentesis should be performed without delay in those patients in whom attempts at releasing the closed lock by nonsurgical means have failed. Additionally, it was noted that approximately 30% of the joints presented with no his-

does not always follow disc displacement with reduction.[35]

Carvajal and Laskin[36] reported an overall success rate of 88% in their retrospective review of 26 patients (39 joints) with mean follow-up of 48.7 months after undergoing arthrocentesis. The authors stated that arthrocentesis can reduce pain and dysfunction in patients with anterior disc displacement both long- and short-term. Patients with disc displacement with both reduction and nonreducing discs have interrelated symptoms including pain, which leads to decreased opening, which in turn causes increased dysfunction. Increasing joint mobility may be more important for restoring physiologic function rather than repositioning a disc. Arthrocentesis has been found to be particularly effective in treating patients with disc displacement without reduction, possibly through release of adhesions reducing the obstruction of the displaced disc and by elimination of inflammatory mediators within the joint. For patients with anterior disc displacement with reduction in whom adhesions play a lesser role, the benefits may be derived from the reduction of inflammation and inflammatory mediators.

Kunjur et al.[37] performed a retrospective audit of 298 patients over a 10-year period that had undergone arthrocentesis for refractory TMJ pain. The pain was assessed at 1, 6, and 12 months after the procedure. A significant reduction in their pain score was found and 90% of the patients stated the procedure was beneficial. All patients in this study had failed to respond to conservative therapy including soft diet, physiotherapy, and oral appliances. The joints in these procedures were lavaged with 50 mL of normal saline followed by infusion of 10 mg of morphine and gentle manipulation. These results were reported by the investigators to demonstrate significant improvement in TMJ pain and were recommended as a first-line intervention with patients with TMJ pain refractory to conservative treatment.

Alpaslan[38] reported a 5-year retrospective evaluation of TMJ arthrocentesis patients with a mean follow-up of 22 months. Included patients completed questionnaires as part of the analysis. At long-term follow-up, 26% of the patients were pain free and 88% of patients had decreased pain. There was a significant increase in the maximal mouth opening postoperatively that persisted long-term. Pain and dysfunction levels at follow-up were significantly lower than preoperative levels. A greater reduction in dysfunction with improvement in maximal mouth opening was noted in nonbruxers. Duration of symptoms before undergoing arthrocentesis did not affect outcomes in this study. The

minimal invasiveness.

In a meta-analysis of surgical treatments for patients with TMJ disorders, Reston et al.[39] reported that in

This study reviewed 1,600 journals and included 22 articles that met their criteria of including at least 10 patients, diagnosis of disc displacement with or without reduction, report on the use of a surgical procedure, as well as other factors. In a reappraisal of the study, Ng et al.[40] performed a systematic review of the data using additional inclusion criteria of follow-up duration of 12 months or longer and improvement based on increased maximal mouth opening. The authors discussed the lack of published prospective randomized studies with long-term results to assist the surgeon in selecting a particular surgical option. Their results

indicated that arthrocentesis provided the greatest degree of improvement after intervention compared to the his-

TMJ arthrocentesis and hydraulic distention as related to pain and mandibular range of motion.[42]

Patients with successful outcomes from arthrocentesis were more likely to be associated with a magnetic resonance image finding of osteoarthritis compared to those

Prognostic and Predictive Factors for the Effectiveness of Arthrocentesis

Prognostic factors for successful arthrocentesis have been analyzed. Nishimura[41] reviewed 103 TMJ arthrocentesis procedures performed on 100 patients and evaluated the effectiveness of treatment in terms of maximal mouth opening and degree of pain on a visual analogue scale. Other prognostic factors also were evaluated, including age, gender, duration of symptoms, presence of clicks, and radiographic imaging. There were statistically significant differences noted between successful and unsuccessful cases immediately and 1 week after the procedure in maximal mouth opening and visual analogue pain scales. There were no statistically significant differences noted in age, gender, range of preoperative opening, duration of painful locking, and report of preoperative clicking before locking. The degree of condylar deformity on magnetic resonance imaging was statistically lower in successfully treated cases. Pain on the visual analogue scale was significantly lower in the successful cases, which may be related to increased inflammation reducing the effectiveness of the arthrocentesis procedure. In summary, severe preoperative pain, relapse of maximal mouth opening within 1 week after treatment, and the preoperative presence of condylar deformation may be indicators of potentially unsuccessful outcome following TMJ arthrocentesis.

displacement without reduction had a higher rate of osteoarthritis. The presence of osteoarthritis on magnetic resonance imaging is related to clinical finding of pain and osteoarthritis may be an important prognostic determinant of successful arthrocentesis. Osteoarthritis is significantly involved in the production of TMJ pain and dysfunction, although it is not always associated with TMJ pain and dysfunction. This observation emphasizes the fact that prediction of treatment outcomes is not a matter of simple linearity involving only one risk factor. Treatment plans should be based on identified risk factors to optimize outcomes with successful surgical [43]

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arthritis is a noninflammatory joint disease characterized by

nal derangements described as associated with degenerative changes including surface irregularities, flattening, sclerosis, and osteophyte formation. Arthrocentesis has been demonstrated to be less successful in patients with chronic pain of duration greater than 6 months in regards to outcome of pain reduction. Patients with osteoarthritis were reported

ports the concept that prediction of outcomes is not based on individual factors, but rather a complex interaction among different variables. As duration of pain increases, the condition becomes more refractory to traditional medical treatments.[44]

Successful intervention based on risk factors may have important implications with regards to the management of TMJ disorders. It has been demonstrated through logistic regression analysis that a significant increase in the benefit of successful outcomes occurred with age less than 25 years, visual analogue pain scale of greater than 75 mm, and range

including condylar flattening, sclerosis, and exophyte formation. Comparison of pretreatment versus 2-month

At 2-month follow-up, clinical examination confirmed a

a successful outcome had a higher visual analogue scale pain level and more restricted range of motion compared to those with an unsuccessful outcome. It was hypothesized that these cases may have a more severe inflammatory process

range of motion. It was concluded that although clinical pain may be related to TMJ magnetic resonance imaging

associated with altered constituents in the synovial fluid which was effectively treated with the lavage of arthrocentesis. Predictive modeling may help identify patients who may benefit from arthrocentesis to initiate specific treatments earlier.[45]

Conclusions

Arthrocentesis of the TMJ has been shown to be an effective initial surgical treatment modality for the management of a variety of TMJ disorders in patients who do not respond to affecting the TMJ. The physical action of lysis and lavage is thought to break down adhesions and remove inflammatory mediators, including cytokines and interleukins, which may lead to chronic pain. It allows a port for deposition of therapeutic medicaments, which are backed by a growing body of literature. These attributes lead to relief of pain, resulting in increased opening and decreased dysfunction. Arthrocentesis can be performed effectively as an outpatient procedure with minimal potential morbidity and should be considered as a first-line intervention and when other noninvasive modalities have not been successful. Outcomes have been reported to be very successful for those cases that are appropriate for this surgical intervention and should be considered prior to open arthrotomy surgical procedures except in those cases where open surgery is the only option.[46]

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41

Temporomandibular Joint

A. THOMAS INDRESANO, CHAN M. PARK

History

Tagaki performed the first arthroscopic examination in 1918. He used a cystoscope to look at a cadaver knee.[1] Several further attempts to look into the knee joint were made, but the equipment was problematic. Watanabe then developed several working arthroscopes and described their use in various joints in 1957.[2] Fiberoptic lighting was incorporated in the 1970s, which allowed for reproducible examination. In 1975, Ohnishi used a Watanabe small-joint arthroscope to enter the temporomandibular joint (TMJ).[3]

Sanders brought the Japanese techniques to the United States, and others, like Holmlund in Sweden, developed diagnostic uses for the arthroscope.[4,5] Murakami published descriptions of the arthroscopic [6] ization of instruments that had been developed for the knee.[9] The use of fiberoptic laser delivery in the 1980s by Indresano and Braderick and by Koslin advanced [10,11] and Nitzan showed that a simple procedure known as arthrocentesis, and performing a lysis and lavage without putting the arthroscope into the joint, gave similar results.[13] Today, therefore, arthroscopic lysis and lavage has been all but replaced by arthrocentesis.[14] Operative arthroscopic arthroplasty is used for more advanced tive arthroscopic surgery or open surgery as the next step. This has decreased the volume of arthroscopic procedures that were performed in the 1980s and early 1990s.[15]

Anatomic Considerations

The general anatomy of the TMJ is described in Chapter new terms to those anatomic structures established from dissection.[6]

The volume of fluid in the upper and lower compartments is important to understand. The volume of the normal upper joint space is about 2 mL, but it can increase to as much as 6 mL with pathology. The lower space volume is about 1 mL and can increase to 2 mL. Knowing this is essential to prevent a capsular tear when the initial joint puncture and joint insufflation is attempted.

The joint functions with a complex rotation and sliding motion. The upper compartment is involved in the sliding motion, and most mechanical hindrances and pathologic entities occur here. This is the reason that most arthroscopic artment, one must verify that sufficient joint space exists to establish and maintain fluid flow and to accept arthroscopic portals. The ligamentous and capsular structures are thin in the normal joints and can easily be violated by too many puncture attempts, or from too much fluid distention. Attempts to pass an arthroscope in severely fibrosed or bony ankylosed joints are subject to major complications. With pathologic changes, these structures are much more substantial and can be difficult to traverse.

It is imperative that the anatomy of the region specific to arthroplasty be understood before attempting arthroscopic surgery. The bony roof can be interrupted by a sharp trocar in the deep superior portion of a thin mandibular fossa. The proximity of the external auditory canal must be considered. In a large patient, the mandibular fossa position may be topographically difficult to differentiate from portions

of the external and even the middle ear. The temporal vessels and the facial nerve are also of great concern during the puncture maneuver. Injuries to these structures will be de

Complications

no
occurs or instruments break, it may be necessary to surgically explore the joint. One should always be prepared and have informed consent for that eventuality.

Normal Arthroscopic Anatomy

Superior (Upper) Compartment

Puncture places the arthroscope in the superior space, showing the medial capsule. The synovium is glistening white with a shiny consistency. Posteriorly the synovium folds over the posterior attachment, which is richly vascular, but the vessels are crisp and discrete. When inflammation is present, however, the vascular region is diffuse and blurred. In the normal joint, the posterior band of the disc is raised and glistening but not vascular. The normal disc is white and smooth with no visible vascularity. A folded posterior attachment has been labeled the oblique protuberance and signifies a ligamentous band. The anterior wall is reflected over the pterygoid muscle and is very thin and translucent. Posteriorly and medially the medial capsule is seen. The consistency changes from thin to thick as one moves more posteriorly. The lateral capsule is not easily seen from the inferolateral approach.[17] Figure 41-1 shows a typical posterior recess as viewed arthroscopically, with the corresponding normal MRI appearance.

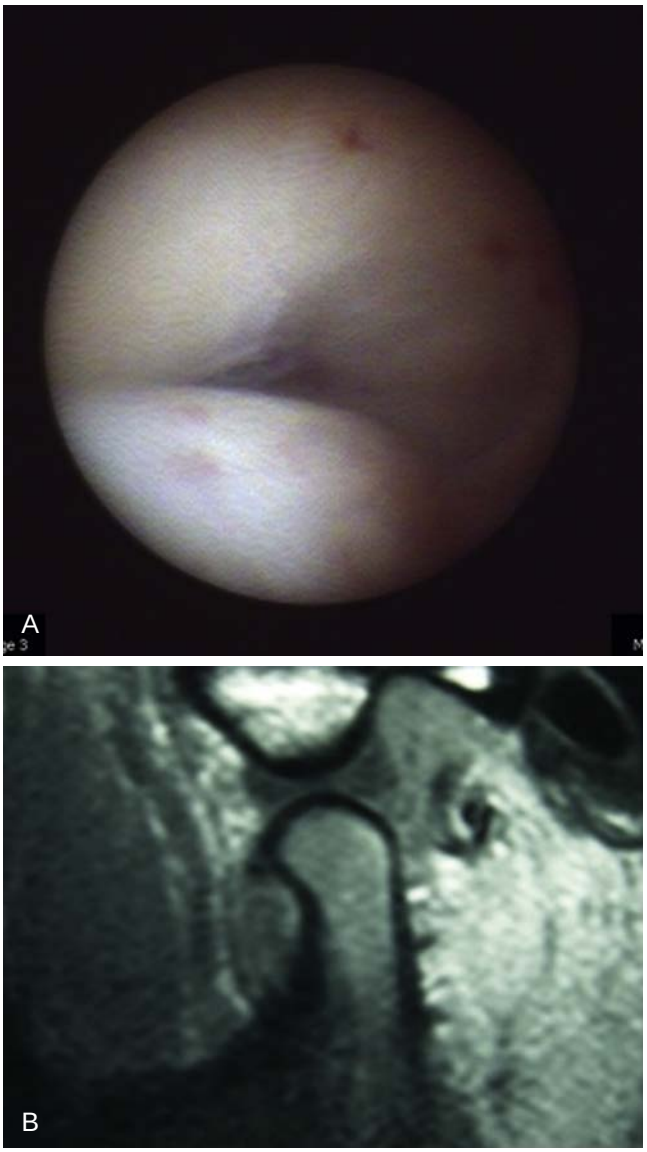
Inferior (Lower) Compartment

Generally, vascularity is not seen in the lower compartment. The surfaces are glistening and smooth, as is the condylar cartilage cap. Because of the small volume and narrow recesses, generally not much is seen and one must be suspect that the scope itself may cause seemingly pathologic changes.

Diagnostic Uses

When temporomandibular joint arthroscopic examination was first performed, its diagnostic usefulness was felt to be the primary benefit. After more than 20 years used as a common tool, direct visualization of the joint is not routinely needed for diagnosis. Although many forms of joint pathology can occur in the TMJ, there may be no correlation with

the TMJ patient.



• **Figure 41-1** Normal joint. **A,** Normal view of upper joint space with

be most useful in staging this disease and determining treatment options.

traumatic conditions may be helped by arthroscopic evaluation. Biopsy is essential if dealing with the very rare tumor that may occur.

Pathology

to inflammation. Increased vascularity in the posterior

attachment, vessels encroaching onto the avascular disc, and blurring of vascular markings may all be seen. Signs of cartilage degeneration in later stages may also be seen. This information may direct the operative therapy when performing arthroscopic surgery, such as the use of laser, anti-inflammatory medications, or lubrication therapy. It might also indicate the need for an open procedure if an undiagnosed perforation of the disc is seen. Figure 41-2

us pathologic conditions as encountered by

Fluid Analysis

joint. Substances such as interleukin-6 (IL-6) and IL-10 have been shown to be markers predicting outcome in lysis and lavage for chronic closed lock.[19] Fluid analysis will be discussed elsewhere.

Equipment

There is much written about arthroscopic equipment, especially at the advent of its use.[20,21] Figure 41-3 shows a typical equipment set-up. Telescopes run from 0.7 to 2.7 mm in diameter. The angle of view can range from zero to 35 degrees. Generally an angled arthroscope is better for visualization of all areas, and a zero-degree arthroscope is better for operative techniques that include triangulation. Various light and camera systems are available. A complex three-chip camera will give the best video reproduction. There has not been much research and development in TMJ arthroscopic equipment recently. Manufacturers have concluded that there is not a large market for this equipment in the United States. With most joint lavage now being accomplished through arthrocentesis, only a few changes in arthroscope design have occurred. These have been accomplished in Japan, and much of the newer equipment is not exported to the United States.

Arthroscopic Puncture—The Inferolateral Technique

forming this procedure effortlessly. Partly, this is due to the process of learning to operate while watching a monitor and making very minor hand movements to achieve objectives, and partly from complications that can occur if not perfor

in

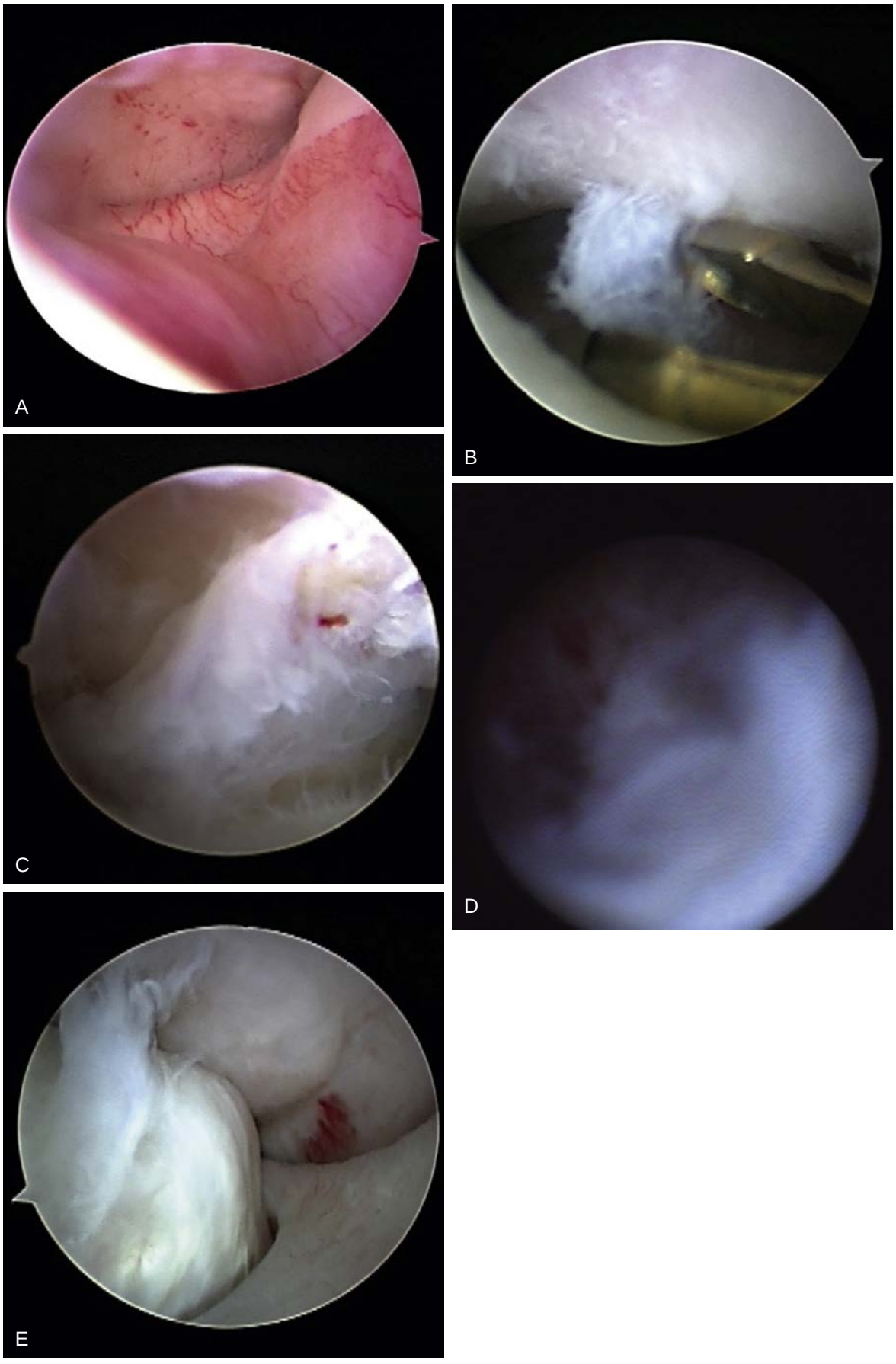
ture observation of the joint, possibly with biopsy. Most often it is performed with the patient receiving a general anesthetic in an operating room, especially if multiple punctures are used and operative equipment such as lasers are required.

Peri-operative antibiotics directed to prevent skin contamination and glucocorticoids for edema management are often used. The patient is placed in the supine position on the operating table and receives nasal endotracheal intubation. Preparation of the skin with povidone iodine or comparable antibacterial solution is performed. After the surgical field is isolated, circular holed aperture (eye) drapes are affixed anteriorly over the ear to provide an isolated field in front of the ear. Neurosurgical drapes may be helpful in keeping the copious irrigating fluid off the floor and shoes.

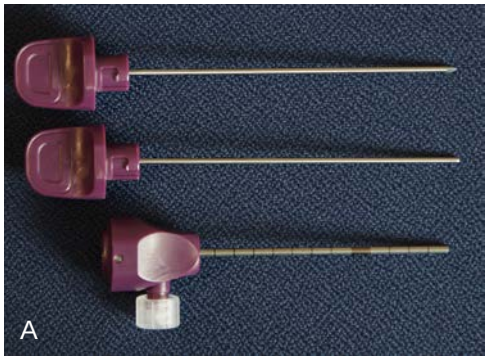
Lidocaine with epinephrine may be injected subcutaneously for hemostasis at the puncture site. It is controversial as to whether epinephrine should be injected directly into the joint space because it may affect visualization of synovial vascularity. The pattern and character of synovial vessels may indicate the level of inflammation present. After the initial evaluation, vasoconstrictor may also be added for hemostasis.

Several different size syringes are needed on the field. Ringer's lactate solution is the preferred irrigant, but normal saline may also be used. It is injected into the superior joint capsule using a 3-mL syringe, so that back-pressure can be felt when the joint space is entered. After a successful circuit is achieved, a large syringe (30 to 60 mL) should be used for irrigation. Some operators suspend a bag of fluid under pressure for this purpose. The drawback to this method may be fluid extravasation.

Puncture using the sharp trocar of a 1.9- to 2.3-mm arthroscope should be along the tragocanthal line approximately 1 cm anterior of the midtragus. As the operator becomes more experienced, the topographic measurement will often give way to palpation to establish the entrance point. The inferolateral approach described by Murakami is standard[8] (Figure 41-4). Moses described an endaural approach that can be used for visualizing the lateral capsule, but it is rarely used.[22] Once the capsule is entered the blunt trocar is used to establish the position inside the joint space. An 18-gauge needle is used as an outflow port temporarily while the arthroscope is inserted and a methodic examination around the superior space is performed. Most diagnoses can be established in this first sweep. Once done, the arthroscope is positioned in the anterior recess, so that a second puncture is performed to provide fluid outflow and triangulation. By measuring the length of the first trocar, the second puncture point can be established. If the lights are dimmed the arthroscope light will transilluminate the position in a thin patient. The second puncture is performed at 90 degrees to the first. The operator should be able to see the entrance of the second trocar in the field in the anterior recess. Now, the operator is prepared to perform any surgical maneuver necessary. Operators who do not instrument the joint, but only observe and lavage the joint, may be able to use only an outflow needle, which simplifies the procedure greatly.

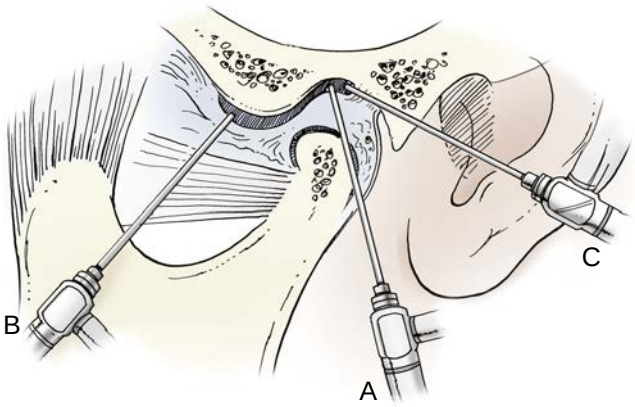


• **Figure 41-2** Upper compartment of the left joint showing various pathologic conditions. **A,** Loss of well-defined boundary between the posterior band of the disc and the posterior disc attachment. The area shows capillary hyperemia. **B,** Biopsy of fibrillation of the fibrocartilage on the posterior slope of the eminence. The disc, below, is unaffected. **C,** Pronounced fibrillation of the central part of the disc. **D,** Close view of the fibrocartilage in the glenoid fossa, showing arthritic lesions and remodeling. **E,** Joint perforation.





• **Figure 41-3** **A,** Sharp and blunt trocars and arthroscopic cannula. **B,** Standard arthroscopic equipment tower with monitor, camera, light



• **Figure 41-4** Puncture direction for the upper compartment of the temporomandibular joint. **A,** Inferolateral approach. **B,** Anterolateral approach. **C,** Endaural approach.



• **Figure 41-5** A zero-degree telescope suitable for arthroscopic surgery. Small-diameter scissors and forceps must be of high quality.

The goals of arthroscopic surgery vary with the diagnosis, but generally follow several paths.

Various arthritides may require diagnostic observation and biopsy. Anti-inflammatory medications can be directly applied by lavage, or by direct needle placement for injection into the pathologic tissues. Laser energy can be used to remove pathologic tissue or to contract redundant or hyperm

oft
diagnostic stage. Usually the surgery is directed to increasing motion and function. These goals can be obtained by stretching the capsular tissues with probes, cutting the restrictive capsular elements with knives or laser, removing scarred or hyperplastic tissues with shavers or laser, removing adhesions, or placing anti-inflammatory agents with direct needle injection.

More severe degenerative joint disease may require the ablation and resurfacing of the joint surfaces. This can be attained with mechanical shavers or laser, and application of medications (Figure 41-5).

Arthroscopic Lysis and Lavage

Joints with surface breakdown caused by mechanical injury or arthritides may benefit from lavage with a suitable fluid.[4-9] Lavage is a normal part of all arthroscopic procedures. The fluid can be used as a mechanical dilator in the joint space, releasing some adhesions through distention or breaking the "suction cup" effect described by Nitzan.[25] Fluid is also used to wash out cytokines, interleukins, and other pain mediators and breakdown products of cartilage damage and arthritic destruction. Milam has also determined that the greater volume of lavage fluid removes the larger molecules more effectively.[28]

Lysis of adhesions may be performed with the arthroscopic "sweep" described by Sanders,[4] with surgical instruments or



• **Figure 41-6** Lysis of fibrotic bands using the blunt trocar in sweeping movements from anterior to posterior.

with laser[10] (Figure 41-6). This technique is usually part of all arthroscopic surgery, and is used to free the superior joint space to gain increased motion. Lysis and lavage was the first

90%.[15,27] Since the procedure included several components, it was difficult to ascribe success to any specific part of the proce-

Arthroscopic Arthroplasty

The addition of miniaturized hand instruments, mechanical shavers, and lasers to the armamentarium created arthroscopic arthroplasty of the TMJ. Procedures performed previously only in open arthroplasty could now be performed arthroscopically. These techniques increased the difficulty of the procedure, requiring increased technical ability. Consequently, the pool of surgeons performing arthroscopic arthroplasty decreased, with the majority performing arthrocentesis.

Arthroscopic Removal of Adhesions

Superior joint space adhesions can be released with the sweep of a surgical probe. More definite and thick bands require sharp or laser dissection. Multiple severe adhesive bands may require a mechanical shaver, but can also be lysed using a holmium laser fiber.

Capsular Releases

Anterior Capsular Release

The arthroscope is placed into the anterior recess and the anterior wall may be stretched using a probe or released using sharp dissection or laser (Figure 41-7). Immediate widening of the anterior wall is achieved. This may have a profound effect on joint translation.

Lateral Release

Lateral capsular release, described by Moses,[29] increases translation and lateral excursion. The release is performed by stretching with probes or sharp laser dissection. The Moses elevator was designed for this procedure.

Disc Repositioning

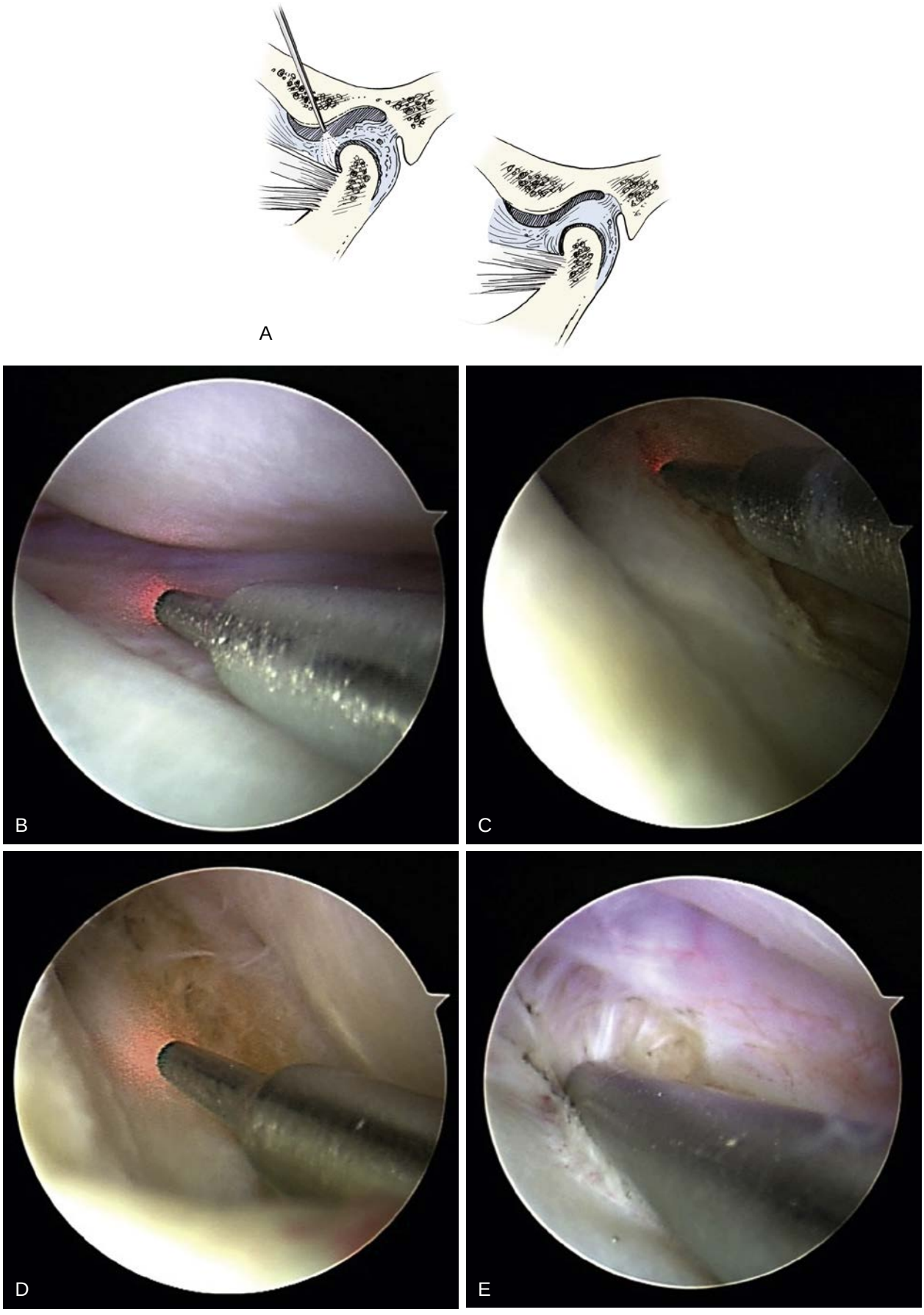
cal treatment with success rates of about 85%.[31] Arthroscopic repositioning can be achieved by performing anterior release and contracting the posterior attachment by either using laser, injecting sclerosing agent, or performing a suturing maneuver as described by McCain[33] (Figures 41-8 through 41-11). There does not seem to be any difference when compared with open arthroplasty with suturing. Successful disc repositioning that has been maintained over time has not been reported. When using laser, there is no pretense of repositioning the disc to normal position, but this combination technique has been shown to be successful in a prospective study.[15] It should be recalled that success is based on return to normal function with minimal pain, not based on the preconceived notion of restoring normal anatomic position. Arthroscopic suturing is technically difficult and requires a high level of expertise. It is, therefore, employed by very few surgeons.[34]

The holmium:YAG laser is most often used, although any laser with fiberoptic delivery can be potentially used. Holmium has the advantage of being precise and safe. With a small amount of energy, the laser can perform pinpoint cutting or the beam can be defocused to contract tissues and ablate blood vessels (Figures 41-12 through 41-14). The laser is of little use on bony surfaces, where it is inefficient at cutting and may char the surface. Electric cautery can be used for contraction of tissues, but it has been replaced by the laser for ease of use and safety.[35]

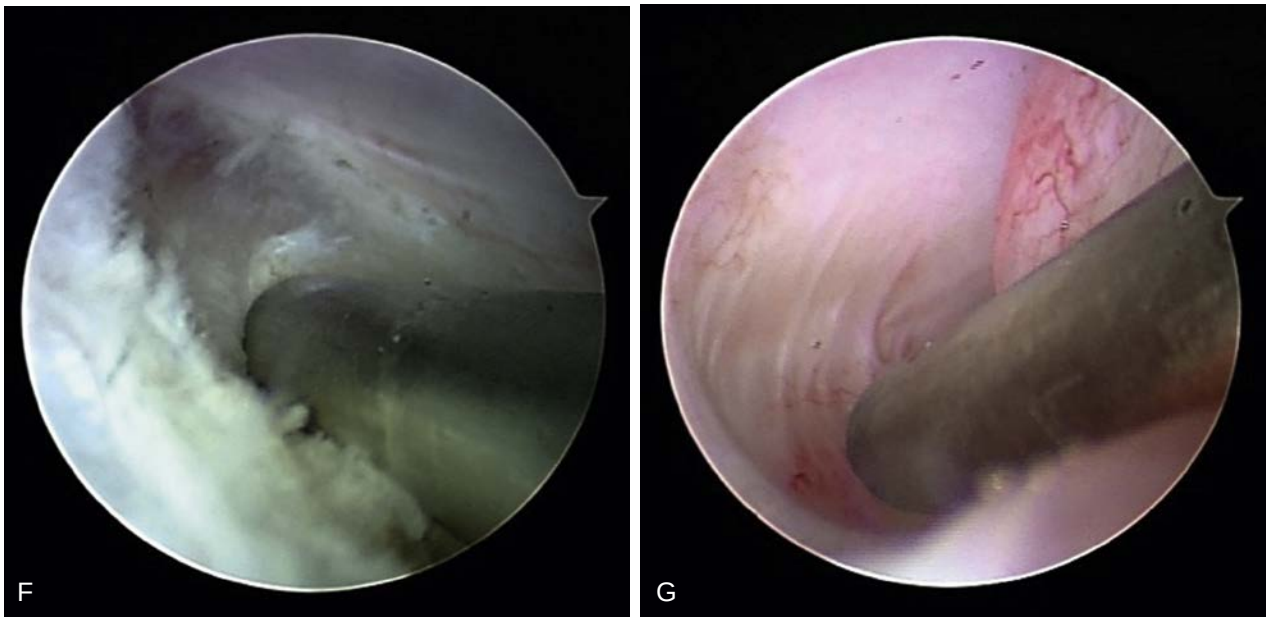
Both Ohnishi and Merrill studied the use of chemical sclerosants as a means of limiting motion in a hypermobile joint.[36,37] Several agents (Sotradeccol, sodium morrhuate) have been injected into the posterior attachment under direct vision. The technique is underutilized, but is successful at stabilizing loose joint tissues.

Complications

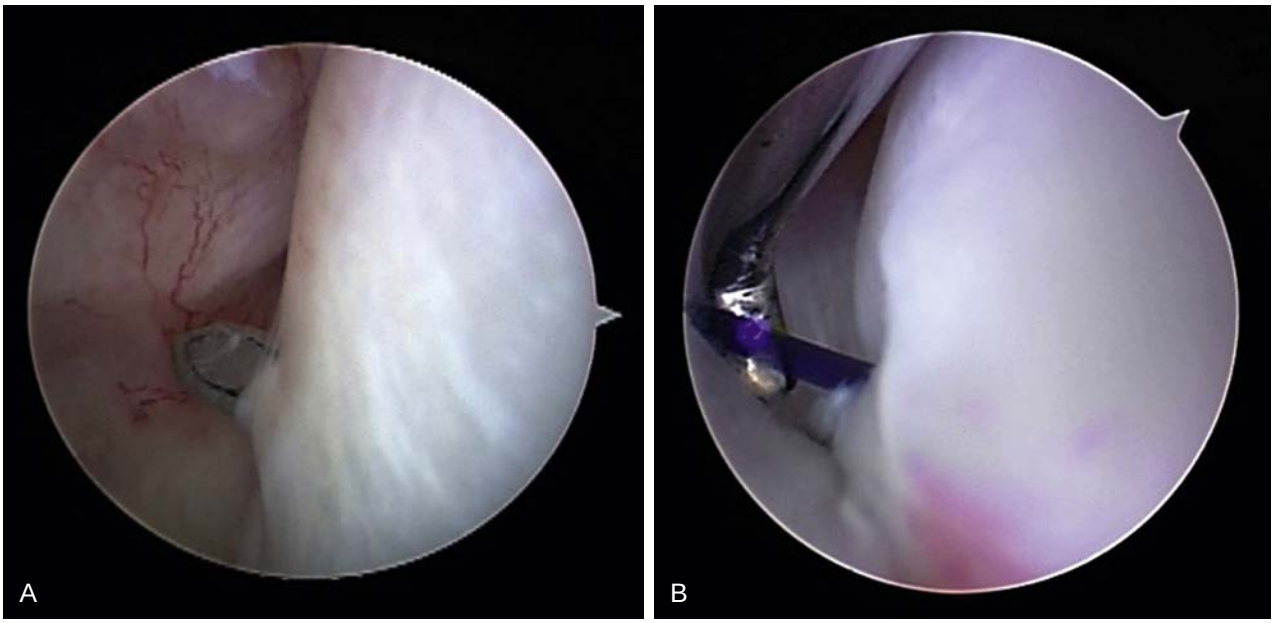
The complication rate for arthroscopic temporomandibular joint surgery is small,[38,45] but the arthroscopist must be able to perform all open procedures in order to assure safety. Extravasations of fluid are possible with extensive procedure time, multiple failed punctures, or excessive pressures. The swelling can usually be controlled with pressure dressings, but possible airway compromise must be considered when large volumes of fluid extravasate.



• **Figure 41-7** Anterior release and repositioning of the disc using laser technique. **A,** Diagram demonstrating effect of anterior capsule release. **B,** Anterior recess with laser probe. **C,** HoYAG laser incision. **D,** After incision, pterygoid muscle is visualized. **E,** Followed by blunt probe to expand incision.



• **Figure 41-7, cont'd** **F,** Anterior disc attachment is freed. **G,** Lastly, probe distracts disc posteriorly.



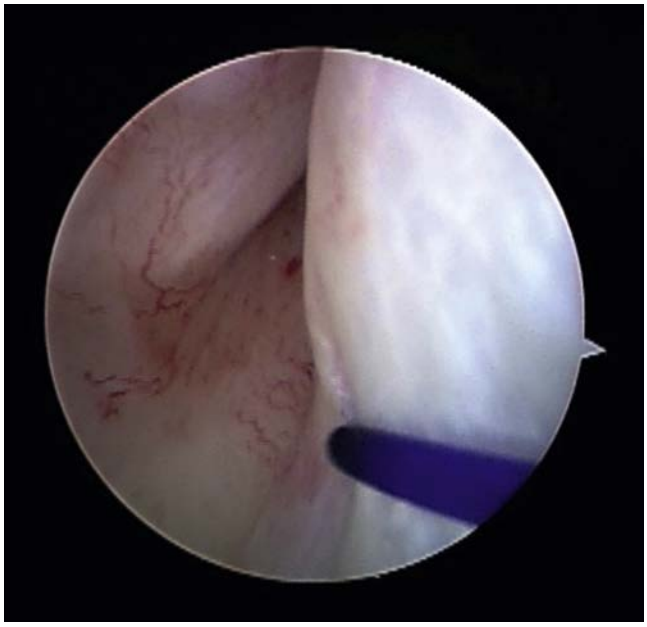
• **Figure 41-8** **A,** Spinal needle through posterior aspect of the disc. **B,** Hook probe used to manipulate suture.



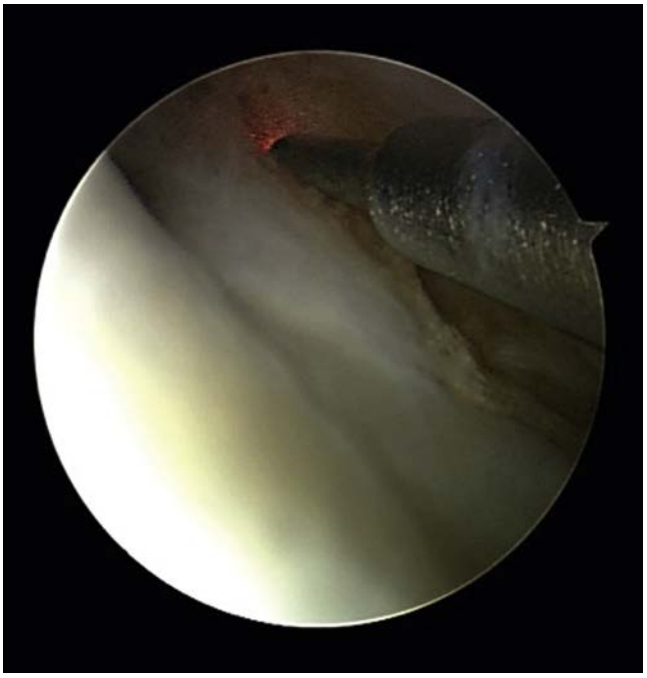
• **Figure 41-9** Alligator forceps used for suture retrieval.



• **Figure 41-11** Laser energy directed at oblique protuberance.



• **Figure 41-10** Suture has been passed to the outside of joint for disc stabilization.



• **Figure 41-12** Anterior release through disc to the underlying pterygoid muscle.

Vascular damage was seen in about 2% of patients in a study by Carter.[16] Hemorrhage can be controlled in the superficial vessels with pressure or with ligation. Intraoperatively, deep hemorrhage from within the posterior attachment can usually be treated by retruding the condyle to put direct pressure on the posterior attachment for at least 5 minutes. In the rare instance that bleeding cannot be controlled, arthrotomy must be performed. Rarely, an arteriovenous fistula may occur, in which case the patient will be bothered by a whooshing sound that occurs several days post surgery. Arthrotomy with direct ligation of the vessel or endovascular treatment may then be required. [44]

Broken instruments are rare and can often be removed with a magnetic probe or with a biopsy forceps.[39] It is imperative that visualization of the instrument be maintained from the time it is broken. If it cannot be removed, then fluoroscopically guided open surgery may be necessary.

Otic injuries are the result of instrument positioning errors and can result in external, middle ear complications or intracranial injuries, all of which are quite rare. Infection occurs in less than 0.5% of cases.[12]



• **Figure 41-13** Posterior tissue after laser treatment.



• **Figure 41-14** Posterior synovial hyperplasia with pain.

Postoperative Care

Immediate postoperative care is directed to controlling swelling and pain. A pressure dressing is usually applied short term, and may be removed in the recovery room before discharge. Peri-operative antibiotics may be given during surgery with a second dose before discharge. Dexamethasone is also administered at the beginning of the case and before discharge. Other medication schedules exist, but there is generally no rationale for long-term antibiotics or steroids. Moderate pain medication is prescribed for home use.

Postoperative Physical Therapy

Postoperative physical therapy is often the most important part of the overall treatment plan, especially if joint restriction is present. A regimen of 1 hour 3 times a week with a therapist is necessary until goals are met, which usually occurs in 2 to 4 weeks. Specific goals of maximum incisal opening, protrusion, and excursions are established by the surgeon as they apply to each patient. A decrease in pain to a level that the patient can tolerate with nonnarcotic pain medicine and a return to a normal diet are also therapeutic goals.

Evidence

Published arthroscopic results have been mostly retrospective case series, with varying techniques and populations. They are difficult to compare and many have no controls. Retrospective studies that report results as "excellent" or "successful" provide the preponderance of these results. [46] Success is usually defined as increased mobility and function and decreased pain and disability. Authors often mix the use of lysis and lavage with other operative techniques, and the results. When most reports agree that "success" rates are 80% to 90%, one has to conclude that the technique is achieving the results indicated. It is difficult to design prospective, controlled studies with surgical options that might have to be withheld to satisfy the design.

In 1993 Sanders and Buonchristiani reported 86% excellent results and 9% good results for 306 patients who had undergone lysis and lavage and were followed for 5 years.[39] McCain and colleagues reported a multicenter study in 1992, the largest study to date; this study had a 6-year follow-up on 1114 patients, with an overall success rate of 91% using multiple techniques.[12] The study by White[40] in 2001 reported on 100 patients who had received lysis and lavage and were followed for 13 years; 94% of these patients were greatly or moderately improved.[41] Indresano reported placement of medications is more difficult to track since many surgeons use medicinal adjuncts to arthroscopic surgery. It may be impossible do distinguish the effects of these agents without specific studies such as that published by Kopp.[42]

More research must be done in the area of therapy directed to joint lubricaton.[43] The advent of high molecular weight hyaluronate compounds has only added to the need for research into the loss of lubrication and how replacement may contribute to joint health. Arthroscopic lysis and lavage has been shown to provide most of the benefits of more complex operative arthroscopic surgery in many TMJ patients. However, arthrocentesis may often achieve these

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42

the Temporomandibular Joint

WILLIAM CHUNG, ALEJANDRO J. ALMARZA

The term temporomandibular joint disorder (TMD) describes a condition that involves temporomandibular joint (TMJ) pain and dysfunction. TMD may arise from a muscular disorder or may involve the joint itself or any of its associated structures. Effective management of TMD becomes more critical, and potentially complex, when a patient presents with both myofascial pain and articular disease. DeBont et al created a detailed classification system for the articular disorders of the TMJ[1] (Box 42-1).

The earliest recognized and reported dysfunction of abnormality of the disc-fossa relationship resulting in a mechanical disorder that creates irregular joint noises and prohibits normal, smooth condylar movements. A staging system for ID was created by Wilkes, which describes the clinical and radiographic characteristics of this disorder (Box 42-2).[3] Stage I is clinically consistent with painless clicking but no limitation of jaw opening. In Stage II the patient experiences occasional painful clicking and intermittent joint locking. As the patient progresses to Stage III, more significant joint pain on function occurs along with restricted jaw opening. In Stage V, the patient's exam is positive for crepitus, episodic and variable joint pain, and restriction of opening.

The presence of parafunctional oral habits, concomitant medical and/or psychological conditions, and other past and present treatment need to be carefully identified and considered prior to pursuing surgery. Proper patient selection is also a fundamental and essential aspect of TMJ surgery. Although nonsurgical, conservative therapies should be undertaken, and often exhausted, before pursuing surgery, certain pathologic disorders of an articular origin are best treated by surgery, specifically TMJ dislocation, ankylosis, certain condylar fractures, neoplasms, and degenerative joint disease.

The evolution of surgery for ID is well documented in the literature. In 1887 Annandale reported the first intracapsular procedure for ID,[4] while in 1909 Lanz reported the first use of a discectomy for painful joint dysfunction.[5] An array of procedures ranging from minimally invasive techniques to arthrotomy have been used to treat ID, and the benefits of each have been clearly documented.[6-14] The use of TMJ arthrography was instrumental in establishing disc pathology as a factor in TMD,[15,16] and studies by Dolwick elaborated on the role of various disc surgeries, such as repositioning and repair, in the treatment of ID.[17-19] Yet the exact role of surgery for the management of ID remains controversial. Detractors of surgery for ID are quick to point out that amidst progressive anatomic degenerative changes, TMJ pain and dysfunction can still decrease in the absence of any treatment.[20,21]

This chapter discusses key elements in a patient's history and physical exam that assist the surgeon in selecting the proper surgical candidate. The chapter also lists the goals of surgery for ID and the role of diagnostic imaging in treatment planning. Only open arthrotomy techniques are reviewed, as other minimally invasive procedures used to treat ID and TMD are covered elsewhere in this text. Lastly, complications of surgery and the importance of postoperative physical therapy will be discussed.

History and Physical Examination

The diagnosis of ID is achieved through a thorough history and detailed clinical examination, and an accurate diagnosis is paramount in determining either the most appropriate surgical technique or the need for surgery altogether. However, establishing the patient's diagnosis can be an obstacle for the surgeon because each patient's symptoms are highly individualized. Additionally, the patient may not always accurately report or describe his or her symptoms. Focused questionnaires regarding TMJ pain

• BOX 42-1 Classification of Temporomandibular Joint Disorders

Articular Disorders

Non-inflammatory arthropathies
Osteoarthrosis

Primary
Chondromalacia

Secondary

Condyle-eminence mobility disturbances
Trauma
Avascular necrosis

Bone and Cartilage Disorders with Articular Manifestations

Inflammatory arthropathies

Primary
Rheumatoid arthritis
Juvenile rheumatoid arthritis
Psoriatic arthritis
Ankylosing spondylitis
Seronegative polyarthritis

Secondary
Synovitis
Traumatic arthritis
Osteoarthritis
Crystal-induced arthropathy

Growth Disorders

Neoplasms
Developmental or acquired
Diffuse connective tissue disorders
Miscellaneous articular disorders

Adapted from deBont L, Dijkgraaf L, Stegenga B: Epidemiology and natural progression of articular temporomandibular disorders, *Oral Surg Oral Med Oral Path Oral Rad Endo* 83:72-76, 1997.

Derangement of TMJ

Stage I Early

Clinical—Painless clicking
No limitation of opening
Radiographic—Mild disc displacement with early reduction
Normal disc morphology

Stage II Early/Intermediate

Clinical—Occasional painful clicking
Intermittent locking
Radiographic—Mild to moderate disc displacement with late reduction
Mild disc deformity

Stage III Intermediate

Clinical—Joint tenderness
Limited opening
Frequent pain
Radiographic—Displaced, *nonreducing* disc
Disc deformity

Stage IV Intermediate/Late

Clinical—Chronic pain
Limited opening
Radiographic—Severe displacement, without reduction
Deformity of disc
Degenerative osseous changes

Stage V Late

Clinical—Variable joint pain
Joint crepitus
Radiographic—Nonreduction of disc with perforation of disc attachment or disc
Degenerative osseous changes

and dysfunction can be completed by the patient to help the surgeon rule out certain subtypes of TMDs that may not be amenable to surgery. If the patient reports a history of painful joint noises and pain on mandibular function, a diagnosis of ID is likely and surgery may be indicated. One scenario that should cause concern for the surgeon is a recent resolution of a patient's history of painful joint noises in lieu of continued joint pain. This clinical picture may indicate acute disc perforation. Physical exam findings consistent with ID include:

1. Pain on palpation directly over the TMJ, particularly during joint loading
2. Limitation in joint range of motion
3. Deviation on opening, if unilateral
4. Joint noises consistently associated with pain
5. Joint crepitus

If concomitant myofascial pain or dysfunction exists, it must be specifically addressed in the comprehensive treatment of the patient. Myofascial pain may develop secondarily in patients with ID, and ID may develop secondarily in patients with myofascial pain. In cases of disc dislocation with reduction, a patient may experience significant pain while trying to move past the obstructing portion of the disc. When a patient has a unilaterally dislocated disc, the mandible will deviate to the affected side during rotation and then correct its path toward the midline once the condyle has moved past the obstruction and has reduced itself into the disc. In bilateral disc dislocation with reduction, the mandible will deviate to one side and then click. The mandible may deviate to the contralateral side and then click again.

Pathogenesis

Recent studies have related the molecular biology of the joint to the pathogenesis of ID. An imbalance favoring catabolic over anabolic processes has been implicated in the development of degenerative disease. Milam proposed that mechanical stresses in the joint make the TMJ susceptible to formation of free radicals that are thought to contribute to the production of other metabolites and enzymes that promote degenerative changes.[22] One specific free radical, nitric oxide, has been formed in increased levels in

arthritic joints. Nitric oxide also promotes the formation of enzymes and prostaglandins that lead to inflammation and tissue breakdown within the joint.[23] Nitzan hypothesized that free radical formation leads to oxidative stress, which subsequently may impair the lubrication system of the joint.[24] The ultimate disruption of joint lubrication leads to increased friction within the joint space. Nitzan and Etsion suggested that this increased friction due to a lack of disc lubrication is what causes disc dislocation as the disc is repetitively pressed against the articular surfaces.[25]

Synovial fluid analysis of the TMJ has shed light on the role of cytokines, proteinases, and other substances in the development of ID. Interleukins are specific cytokines that mediate inflammation and have been detected in both ID and osteoarthritis (OA) of the TMJ.[26] Cytokines appear to contribute to tissue damage by inducing the release of proteinases and collagenases. Gruber et al[27] reported on the possible role of one such marker, matrix metalloproteins (MMPs) produced by synoviocytes and articular chondrocytes, as mediators of cartilage degradation. Kubota et al[28] compared the TMJ synovial fluid between asymptomatic patients and those with established ID or OA for differences in interleukin-1 (IL-1β) and IL-6 levels to determine whether the IL levels would reflect the pathogenesis of ID. Results indicated higher levels

lavage of inflammatory mediators and lysis of adhesions can be accomplished by either technique. Other past and more recent studies continue in their attempts to establish the role of molecular biology of the TMJ with ID.[29-33]

Goals and Criteria for Surgery

Surgery is reserved for patients whose TMJ pain and dysfunction are refractory to conservative nonsurgical modalities and when symptoms result in significant impairment.[34,35] The goal of surgery is to preserve the articular tissues while returning the patient to a more regular diet and reestablishing a normal range of motion to the jaw. Individualized goals of surgery are discussed with each patient before undertaking any form of surgery. The American Association of Oral & Maxillofacial Surgeons (AAOMS) published the first guidelines for disc surgery in 1984 based on a literature review and the general consensus of surgeons.[36] This document was succeeded by another in 1990 stating the standards and criteria for TMJ surgery.[37] TMJ arthrotomy is performed for TMJ ankylosis, trauma, previous surgery, severe degenerative disease, growth disturbances, and neoplasms.[38-44] As recently as 2005, a study by Hall et al compared the outcomes of four commonly used techniques in treating ID.[6]

Two reports by Holmlund and The Second International Consensus Meeting in 1992 have stated criteria for successful TMJ disc surgery.[45,46] These criteria include:

1. Mild, brief, or infrequent pain of no concern to the patient
2. A vertical range of motion greater than 35 mm and lateral range of motion greater than 6 mm
3. Ability of patient to eat a regular diet, at worst avoiding tough or hard foods
4. Stabilization of possible degenerative imaging changes
5. Absence of symptoms for at least 2 years
6. Absence of significant complications

A common form of ID is closed lock. This condition

in the superior joint space. These adhesions can subsequently be removed by arthroscopic techniques. Adhesions

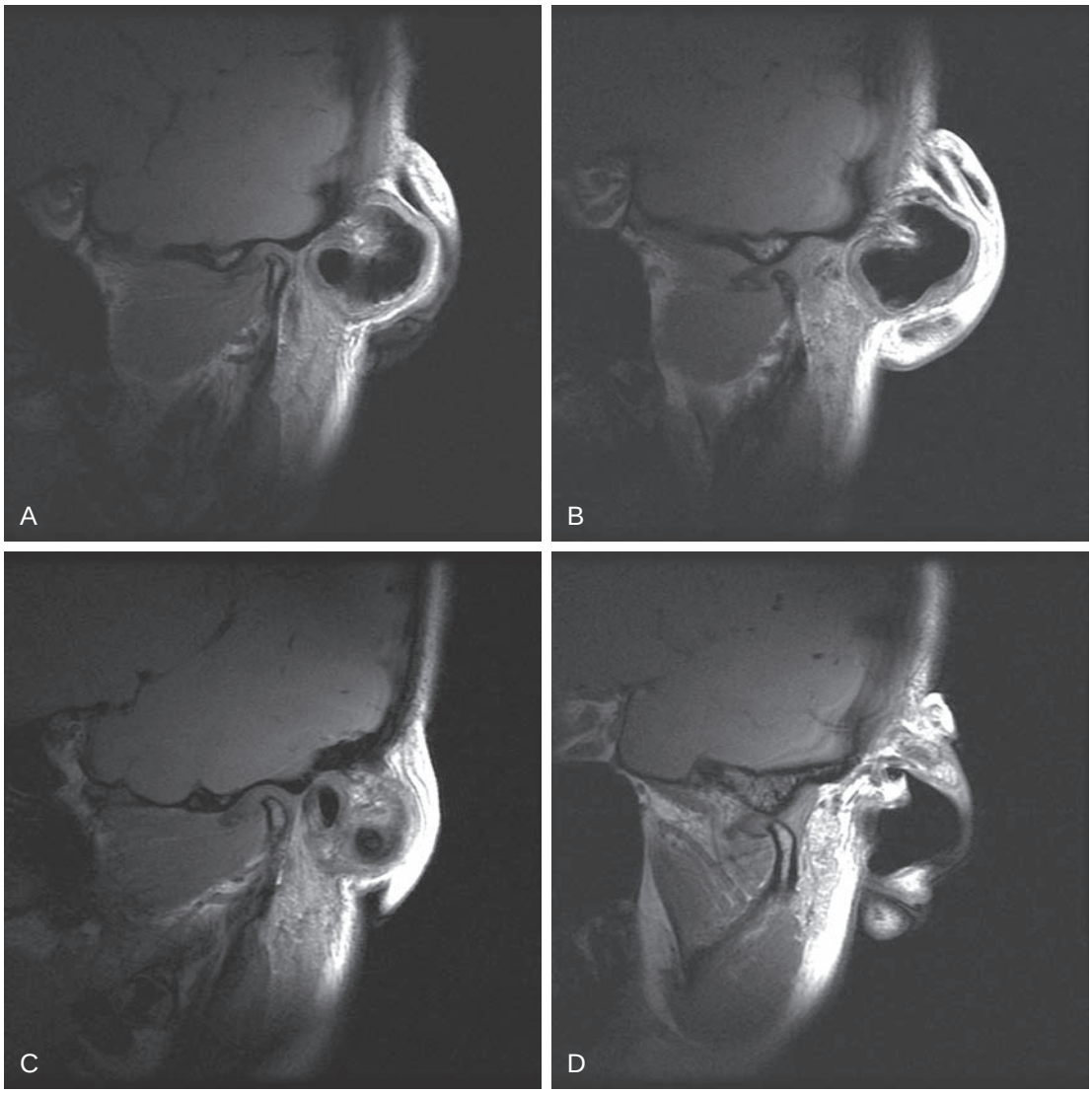
closed lock if arthroscopic techniques fail to correct the mechanical disturbance.

Diagnostic Imaging

Hard tissue abnormalities of the TMJ are most readily identifiable by plain films and computed tomography (CT) scans.[52-54] Panoramic radiographs best serve as a screening tool to identify any gross bony abnormalities, while CT scans are superior to plain tomography in evaluating hard tissues. CT scans provide only limited evaluation of the soft tissues surrounding the TMJ, particularly the disc. Soft tissue disorders of the joint can be determined by arthrography.[54,55] However, an MRI is the study of choice to evaluate ID. MRI studies differentiate the variable proton density within a given tissue volume and then use variable pulse sequences to configure images. The TMJ disc has a low signal pattern and appears black due to its low proton density. Tissues that are higher in either water or proteins appear white on an MRI, which may be indicative of tissue edema. No direct correlation has been definitively reported linking higher signal intensities of TMJ discs with perforations or other surface damage.

Studies of disc displacement or degenerative changes of the condyle have been clearly demonstrated in asymptomatic patients.[56-58] Thus, one must avoid over-emphasizing radiographic findings so as to prevent unnecessary or overly aggressive treatment. Figure 42-1, *A* and *B* show an MRI that displays anterior disc displacement without reduction. This patient was involved in a motor vehicle accident and sustained a whiplash-type injury and developed a unilateral TMD. Figures 42-1, *C* and *D* illustrate how the same patient can manifest the identical anatomic abnormality on the contralateral side. However, this patient reported no symptoms from the contralateral side.

When ordering an MRI for ID, the surgeon should request both sagittal and coronal views to accurately depict



• **Figure 42-1** **A,** Direct sagittal magnetic resonance image (MRI) of an anteriorly dislocated disc in the closed mouth position. The disc is located anterior to its normal position relative to the condyle and articular eminence. **B,** Direct sagittal MRI of patient in part **A** in the open mouth position. The nonreducing dislocated disc is situated at the bottom of the articular eminence with the condyle articulating against the posterior attachment of the disc. **C,** Direct sagittal MRI of contralateral disc in the closed mouth position in the same patient. The disc is anteriorly dislocated. **D,** Direct sagittal MRI of the same disc in the open mouth position. The disc is severely dislocated without reduction.

the three-dimensional aspect of ID. Sagittal views alone may not depict medial or lateral disc displacement. Liedberg and Katzberg have reported the diagnostic value of coronal MRI views in verifying disc displacement.[59,60] An MRI should also be ordered in both T1- and T2-weighted images. T1-weighted images best depict the anatomy of the TMJ, while T2-weighted images allow for visualization of joint effusions. No studies have been able to consistently or accurately determine disc perforations.

Preoperative Therapies

Nonsurgical, conservative therapies used in the treatment of TMD are covered in greater detail in other chapters of this text. Non-steroidal anti-inflammatory drugs, a soft diet, physical therapy, splint therapy, and behavioral therapy when indicated are among the various nonsurgical, conservative therapies that are typically implemented, and sometimes exhausted, before surgery is considered in the treatment of ID. When myofascial pain exists concurrently with ID, splint therapy may relieve one pain but aggravate another. If an anterior repositioning splint is implemented because of the presence of the ID, the patient's myofascial pain may be aggravated. If the more common maxillary stabilization splint is fabricated, the myofascial pain may be improved, but joint pain may still exist, especially if the patient is functioning on the posterior attachment of the disc.

Surgical Approaches

A variety of open surgical techniques exist for the treatment of ID. These include the following:

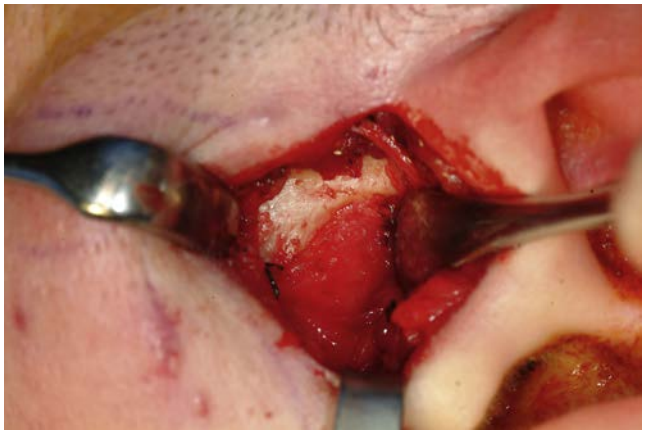
1. Disc repositioning
2. Disc repair
3. Discectomy alone
4. Discectomy with autologous graft replacement
5. Condylotomy

The above-mentioned procedures are all performed through either a preauricular, endaural, or postauricular skin incision. Regarding grafting procedures, this chapter will discuss only those techniques that use autologous tissue sources, as numerous studies have concluded that the use of alloplastic graft materials in TMJ surgery is unsupported.[61-66] The specific arthrotomy technique chosen is usually dependent on the surgeon's skills and experiences. The procedure should also result in the fewest complications, such as facial nerve injury, permanent occlusal changes, and relapse of joint pain and dysfunction. Another consideration is if a second surgical site is required for procurement of an autologous graft.

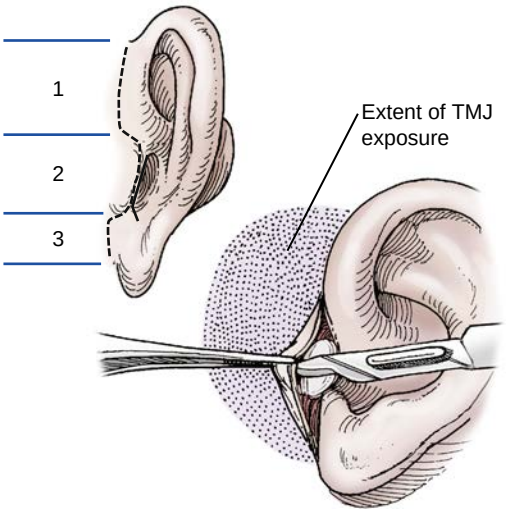
Preauricular Incision

The preauricular incision is commonly used and a modification of an incision designed by Blair.[67] The incision provides maximal lateral and anterior access to the joint space. The preauricular incision is approximately 3 cm long and has a superior and inferior component, which meet at a point level with the superior aspect of the tragus. The incision is placed within a preauricular skin crease that lies posterior to the superficial temporal vessels and the auriculotemporal nerve. The vessels can be avoided by following the preauricular cartilage during the dissection. Sufficient surgical access in the inferior portion of the incision can be easily achieved by carrying the incision to a point just below the tragus, but the incision can be extended inferiorly to the level of the lobule.

The skin and subcuticular tissues are sharply incised with a No. 15 blade. The superior portion of the incision is progressively dissected with mosquito hemostats down to the intensely white temporalis fascia. The inferior portion of the incision is dissected down to the lateral TMJ ligament. Since the external auditory canal is angled nearly 45 degrees anteromedially to the skin surface, the inferior portion of the dissection follows the pretragal pocket to avoid perforating into the external auditory canal. Small retractors are placed into the superior and inferior pockets. A sharp, curved Metzenbaum scissors is placed on top of the temporalis fascia and used to connect the superior and inferior pockets, and the overlying tissues are sharply incised. A flap is reflected anteriorly and superiorly, clearly exposing the temporalis fascia. This flap is then retracted anteriorly away from the tragus. A No. 15 blade is used to make a vertical incision through the temporalis fascia, then the dissection proceeds down to the root of the zygomatic arch. A full-thickness flap is then elevated anteriorly off of the arch until the articular eminence is visualized.



• **Figure 42-2** Preauricular incision with exposure of the articular eminence and TMJ capsule.

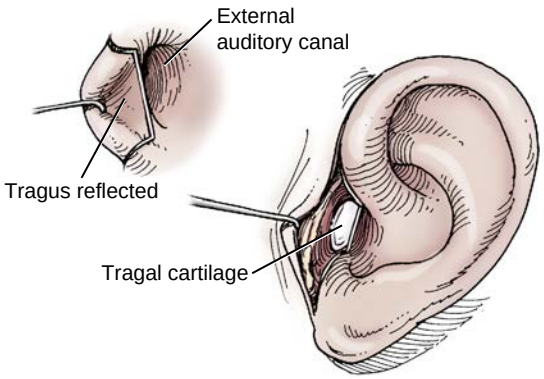


• **Figure 42-3** Endaural incision. Although the skin incisions are made in creases to hide them, the deeper dissection hugs the cartilage of the pinna or external auditory canal cartilage. The shaded area is that which is eventually exposed.

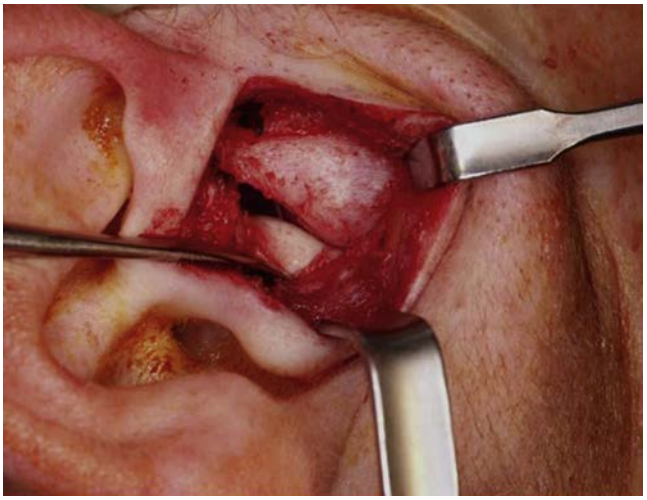
The mandible can be manipulated through a sterile drape, allowing the surgeon to become oriented and possibly identify the lateral pole of the condyle. The overlying tissues are bluntly dissected with Metzenbaum scissors until the lateral capsule is identified (Figure 42-2). Small Obwegeser right angle retractors can be used inferiorly and anteriorly to expose the articular eminence and the lateral capsule. A superior extension of the preauricular incision allows access to the temporalis muscle if a temporalis muscle flap must be harvested for reconstructive purposes. The primary disadvantage of the preauricular incision is the risk of injury to the superficial temporal vessels.

Endaural Incision

The endaural incision described by Rongetti is a modification of an endaural approach first reported by Lempert for treatment of otosclerosis.[68] The endaural incision is more esthetic because the incision is made in the external auditory



• **Figure 42-4** The skin incision inside the tragus connects the superior and inferior portions of the endaural incision at right angles to facilitate reapproximation and closure. A supraperichondrial dissection is continued on the anterior aspect of the tragal cartilage deep into the wound following the contour of the cartilage.



• **Figure 42-5** Lateral capsule incised and an intact, shiny, white, and firm disc is visualized.

canal (Figure 42-3). However, this incision does carry the disadvantage of possible perichondritis. The superior portion of this incision begins at the junction of the face and pinna and extends to the top of the tragus. The incision is made at a 90-degree angle to the skin surface just anterior to the pinna, following the cartilage of the pinna. The inferior portion of the incision begins at the base of the tragus and extends to the junction of the lobe and the face. The tragus is retracted anteriorly and an incision is made 2 to 3 mm inside the crest of the tragus, connecting the superior and inferior incisions (Figure 42-4). The skin is dissected off of the tragal cartilage without creating a perforation of the skin while it is being reflected over the cartilage.

Metzenbaum scissors are used at the superior extent of the incision to bluntly dissect down to the temporalis fascia. The superficial temporal vessels can be avoided by closely following the cartilage of the pinna. The dissection anterior to the tragus follows a supraperichondrial plane, over the cartilage that forms the anterior wall of the external auditory canal. An important landmark during this dissection is the bony postglenoid tubercle, which is located anterior to the cartilage of the external auditory canal. The dissection along the anterior portion of the cartilaginous canal must stop at the postglenoid tubercle because the tympanic membrane is attached to the cartilaginous canal near the junction of the cartilaginous and bony canal. If the bony canal is perforated, the tympanic membrane can be injured. The plane of dissection follows that of the cartilage of the canal rather than the skin surface, or the parotid gland may be violated. Inferiorly, the dissection proceeds down to the skin just beneath the lobe. Sutures can be placed through the tragal cartilage and the superior flap to assist in retraction.

Other Skin Incisions

Alexander wrote on the postauricular approach for TMJ surgery.[69] More recently, Politi described a deep subfascial approach to the TMJ or zygomatic arch.[70] The incision is a modification of the preauricular incision that follows a deep subfascial dissection, passing deep to both layers of the temporalis fascia. No injuries to the facial nerve were reported with this incision and it was not necessary to ligate any superficial temporal vessels except an occasional posterior branch of the superficial temporal artery. The deep subfascial approach was recommended in second procedures of the TMJ or in delayed surgery. The specific incision used is ultimately determined by the surgeon's experience, as no studies have indicated that the incision affects the intended goals of the surgery.

Capsular Incisions

Once the lateral capsule is identified, the mandible can be distracted through a sterile drape, enabling the lateral pole of the condyle to be palpated through the capsule. The capsule can be incised through any number of different incision designs to gain access to the superior joint space. The most commonly used incisions involve making an incision either over the lateral rim or just below the lateral rim of the glenoid fossa (Figure 42-5). The superior joint space is insufflated with 2% lidocaine with 1:100,000 of epinephrine-impregnated local anesthesia through the lateral capsule. The local anesthesia will rapidly escape once the capsule is either dissected off of the rim with a periosteal elevator or incised with a No. 15 blade. In the case of the latter design, the incision is extended anteriorly and posteriorly with a pair of sharp scissors. The surgeon should excise any adhesions within the superior joint space, but should not be overly aggressive with removing tissue from the undersurface of the fossa, as the synovial lining may be inadvertently removed.

Care must be taken not to damage the posterior attachment of the disc while dissecting the capsule. If the surgeon must access the inferior joint space, the capsule can be incised off of the disc and the periosteal elevator can reflect a flap to expose the condyle. Vertical reduction of the articular eminence can be performed to maximize the surgeon's view of the superior joint space. Reduction typically involves removal of 4 to 5 mm of bone on the most lateral aspect of the eminence along the lateral tubercle. If necessary, an



• **Figure 42-6** The endaural incision is closed in layers. The skin immediately anterior to the tragal cartilage is sutured before skin closure to prevent tenting of the skin over the tragus, obliterating the natural depression in the face anterior to the tragus. The skin is closed with interrupted sutures at the corners of the endaural incision with 5-0 monofilament sutures. The inferior portion is closed with interrupted sutures, while the superior portion is closed with a continuous subcuticular 5-0 monofilament "pullout" suture.

additional 1 to 3 mm of bone can be removed from the medial aspect of the eminence to optimize movement of the condyle within the fossa during the arthroplasty.

Wound Closure

Regardless of the specific incision design used, the wound is closed in layers. If the capsule is incised below the lateral aspect of the zygomatic arch, the capsule can be reapproximated and closed with interrupted 4.0 vicryl sutures. The deeper tissues that lie over the capsule and the subcuticular layer are also closed with interrupted 4.0 vicryl sutures. In a preauricular incision, the skin is closed with a running 5.0 monofilament suture. Closure of an endaural incision begins by suturing the corners of the tragal portion of the incision with interrupted sutures (Figure 42-6). Then interrupted sutures are placed to close the inferior portion of the incision by the lobe. The superior portion of the incision is closed with a continuous subcuticular suture.

Arthrotomy Procedures

Disc Repositioning

In 1979 McCarty and Farrar first reported surgery to reposition the disc into its normal anatomic relationship relative to the condyle and fossa.[71] Disc integrity, or deformity, must be carefully assessed if repositioning is to be contemplated. The chances of successful repositioning increase if the disc has maintained its normal appearance (white, shiny, firm) and length, and is minimally displaced. The posterior aspect of the disc is positioned over the superior portion of the condyle in a normal, healthy joint. If the disc is severely displaced and does not reduce, loading by the condyle increases on the retrodiscal tissues, making them hypovascular. Both the condyle and articular eminence can undergo remodeling, and a "pseudodisc" may eventually form. However, an MRI may not be able to distinguish the pseudodisc from remnants of the true disc.

One must closely inspect the disc before proceeding with its repositioning. The disc should not be distorted or placed under tension during posterior repositioning. Dense adhesions that result from longstanding disc displacement often require releasing incisions in the anterior and/or medial regions of the disc. If a releasing incision must be performed on the medial aspect of the disc, it must be made with caution because of the risk of significant hemorrhage.

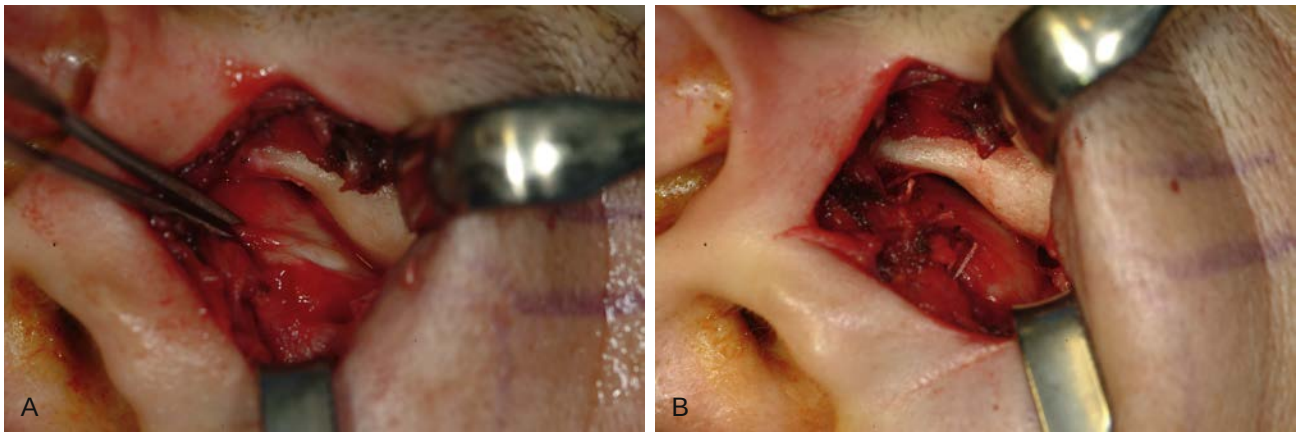
repositioning, it is plicated posteriorly or posterolaterally to return the anteromedially displaced disc to its more normal anatomic location.

Hall described a partial-thickness plication of the disc if the disc can be repositioned without entering the lower joint space.[72] If a situation exists where the inferior joint space must be entered, such as osseous recontouring of the condyle, then a full-thickness plication should be performed as described by Dolwick and Sanders.[73] Numerous studies have reported disc repositioning success rates based on the reduction of TMJ pain and an increased range of motion, of 80% or more[19,71,74-76] (Figure 42-7). Weinberg and others have reported how an eminectomy or condyloplasty may also facilitate improved disc repositioning.[77-79]

After disc repositioning is completed, the patient should be educated on the possibility of recurrent joint noises. The patient should not worry about either continued joint dysfunction or progression of the ID as long as the joint noises are not accompanied by pain. Further surgery is not recommended for the treatment of unremitting postoperative pain.[46]

Disc Repair

When indicated, perforations of the disc can be managed by reparative techniques.[17,80] For smaller perforations, the disc can be undermined from the surrounding soft tissue for a tension-free primary closure with a non-resorbable suture. Osteophytes and bony overgrowths are commonly found under disc perforations. Any necessary arthroplasty of the condyle can be conveniently performed during disc repair procedures through the perforation. Larger perforations of a dislocated disc require a more extensive repair, because the disc is unlikely to reduce after the margins of the perforation are excised due to more dense adhesion formation and scarring. If the disc cannot be adequately repaired, then the surgeon must make the decision to replace the disc with either an autologous or homologous graft, or perform a discectomy.



• **Figure 42-7** **A,** Disc repositioning through a preauricular incision. Adhesions have been removed from the undersurface of the fossa. The disc is without perforations and is white, shiny, and firm. The disc is being repositioned with Adson tissue forceps. **B,** Disc from part **A** has been plicated posteriorly.

Discectomy

Intraoperatively, if a surgeon believes that a deformed disc is not beyond repair, a discoplasty can be performed. However, if a deformed disc is determined to be unsalvageable, a discectomy is considered. Additionally, if the disc is anatomically amenable to repositioning and/or repair but prohibits the fluid, smooth movement of the condyle, the disc should be excised. First described by Lanz in 1909,[5] discectomy is indicated in several instances: irreparable disc perforation; complete loss of elasticity of the disc; or persistent pain and dysfunction even after disc repositioning. Excising the irreparable disc allows the jaw to move without an impediment. Both partial and total discectomies have been described.[81,82] Kondoh described a procedure referred to as disc reshaping, which is a modification of a partial discectomy.[80] Only that portion of the disc and posterior attachment deemed unsalvageable is excised to eliminate diseased tissue and remove any obstacle for smooth condylar movement.

During a discectomy, all remnants of the disc do not need to be removed to avoid unnecessary, significant hemorrhage, particularly in the highly vascular retrodiscal or medial regions of the joint space. After the disc and posterior attachment are excised and a smooth motion of the condyle can be consistently repeated intraoperatively, the condyle can be conservatively recontoured to remove any irregularities or osteophytes (Figure 42-8). Intact articular cartilage should not be removed from either the condylar head or the fossa. Excessive removal of articular cartilage may predispose the joint to heterotopic bone formation and subsequent ankylosis.

Both short-term[83,84] and long-term[85,86] favorable results from discectomy have been documented. Most patients from these studies were pain-free and had little in the way of dietary restrictions. Takaku and Toyoda's study followed 39 discectomy patients over an average of 20 years after surgery.[87] All but two of their patients had no pain and none experienced masticatory disorders. Mouth opening of 35 mm was attained by 38 of the patients. Eriksson and Westesson's long-term evaluation of 15 discectomy patients with a mean follow-up of 29 years also revealed successful results.[85] All patients were free of pain and none had reported mandibular dysfunction. Only one of the patients could not open beyond 39 mm.

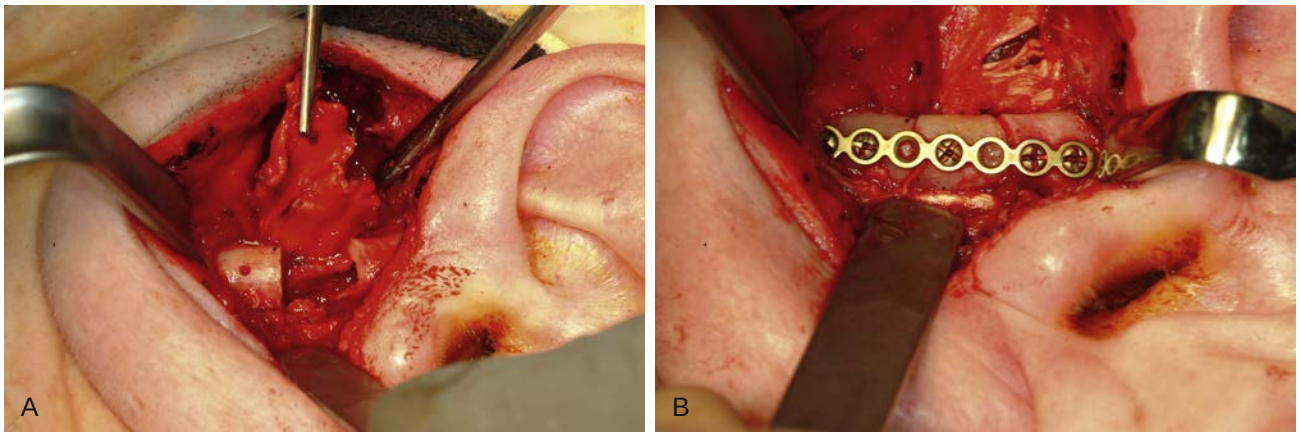


• **Figure 42-8** Large perforation through the disc. The top of the condylar head can be seen through the perforation.

Of interest is the significant bony remodeling as evident by the flattening of the fossa and condyle that has been reported with discectomy.[88,89] These changes were noted to stabilize after just 2 years and were not viewed as degenerative due to a lack of symptomatology.[90-92] Post-discectomy physical therapy is essential because the therapy helps the patient reestablish an adequate range of motion. Additionally, in unilateral cases, it assists the patient in compensating for the expected deviation of the mandible to the operated side. When bilateral discectomies are performed, an anterior open bite may occur because of posterior displacement of the condyles. Use of "light" elastics for a period of 6 weeks may prevent this.

Discectomy with Replacement

Intuitively, a surgeon may feel compelled to replace a disc to avoid a scenario where a patient's TMJ is allowed to



• **Figure 42-9** **A,** Partial-thickness temporalis muscle flap. The patient's zygomatic arch was preplated with a 1.2-mm miniplate. The miniplate and screws were removed and the osteotomies completed. The zygomatic arch was removed to gain access to the temporalis muscle. **B,** Temporalis muscle flap inset into the fossa and secured with sutures. The arch is placed back with the miniplate and screws.

function against the bony fossa without any intermediary tissue. The rationale behind disc replacement with a graft was to protect the articular surfaces from further degenerative changes and to deter joint adhesion formation. The graft material was to create a scaffold for synovial tissue in-growth, and some studies have reported this process to partially occur.[93,94] Yet clinical uncertainty still surrounds performing a discectomy without replacement versus disc replacement.

Animal studies have suggested that autogenous graft placement after discectomy is beneficial.[93] Thyne et al investigated the changes that occur to the joint tissues following the use of temporalis muscle as an interpositional graft following discectomy in sheep.[95] The results revealed that although the temporalis muscle in sheep underwent avascular necrosis and subsequent displacement, the condyle and fossa could still remodel. A study by Tucker et al evaluated the histologic changes in primate TMJs after autogenous auricular cartilage grafts were placed following discectomy.[93] Viable auricular cartilage was found in each of the sacrificed monkeys. A variable amount of fibrous connective tissue was found in all grafts, and one graft was fused to the glenoid fossa, while a second graft was fused to the condyle. Regardless of the positive results reported by these and other animal studies, Takaku et al[89] and McKenna[96] have reported long-term evaluations in humans with discectomy alone that surpass those short-term results of discectomy with grafts.

Reports by Wagner, Westesson, Ryan, Heffez, Dolwick, and others have clearly documented the poor clinical outcomes of alloplastic materials such as silastic, silicone, and Proplast-Teflon for disc replacement.[61-66] Autogenous tissues have been used as both disc replacement material following discectomy and as an interpositional material in the treatment of joint ankylosis. Autogenous sources such as temporalis muscle flaps, auricular cartilage, and dermal grafts have proven far better options for disc replacement than their alloplastic counterparts.[97-100]

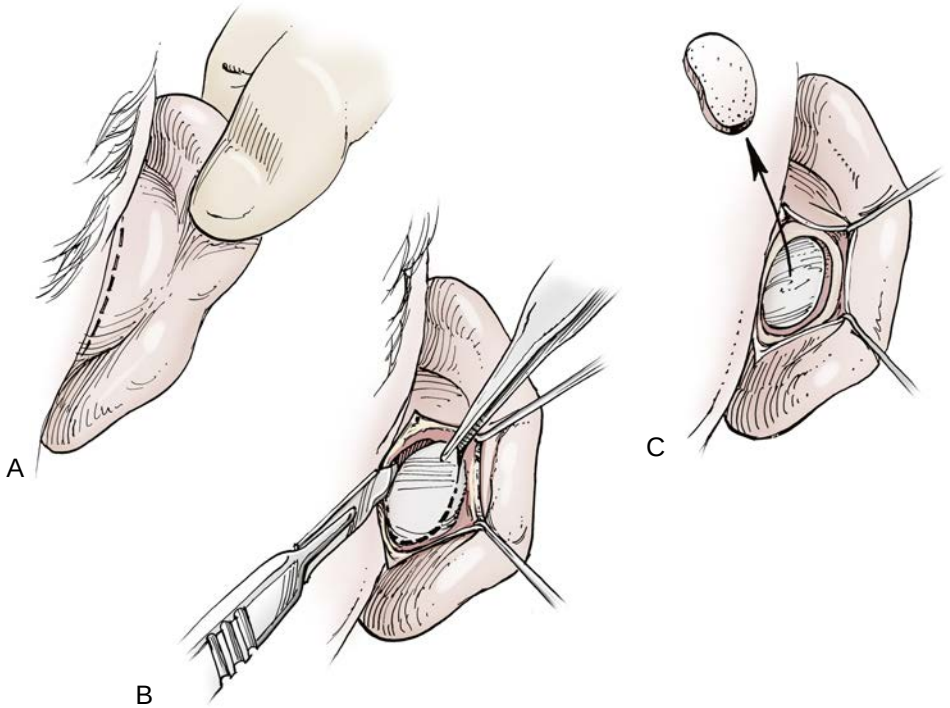
Temporalis Myofascial Flaps

The primary uses for a temporalis myofascial flap are as an interpositional graft in the TMJ to avoid ankylosis and to reconstruct a joint with significant degenerative remodeling. Temporalis myofascial flaps can also be used as a replacement material after discectomy. In choosing the type of autogenous tissue material, remote or adjacent donor site morbidity is a consideration. Avoiding a separate, remote donor site is one advantage of the temporalis flap. It also has the distinct advantage over other autogenous sources of being a vascularized flap, maintaining a viable blood supply. Umeda et al reported that the muscle tissue in the flap maintained its viability with only some fibrosis for 15 months.[101]

The temporalis myofascial flap owes its versatility to its ability to be harvested in variable thicknesses to allow for reconstruction of defects of variable sizes. A flap 3 to 4 cm wide is usually sufficient to adequately cover the fossa. The zygomatic arch can be preplated prior to it being osteotomized if the surgeon desires to place the myofascial flap under the arch and over the eminence (Figure 42-9). The procedure has also been described by placement of the flap over the arch.[102] In unilateral cases of ID where the disc is determined intraoperatively to be unrepairable, a temporalis flap can minimize or avoid a posterior open bite that can occur on the non-operated side. Disadvantages of this flap include possible flap necrosis and fibrosis or adhesion formation within the joint space. The temporalis muscle flap is similar to other arthrotomy techniques in its risk of postoperative decreased interincisal opening.

Auricular Cartilage Grafts

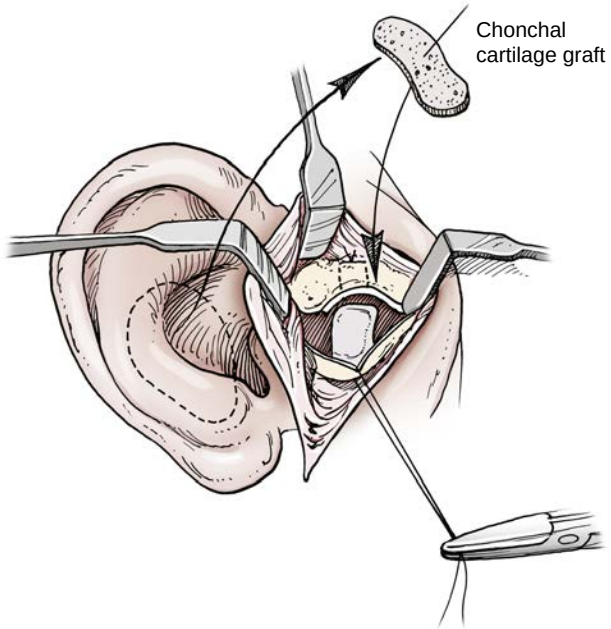
The auricular cartilage graft is procured with the intent to use it as an interpositional material after discectomy and occasionally in the treatment of ankylosis. It is most commonly harvested through a posterior approach to the ear (Figure 42-10). A vertical incision is made on the posterior side of the conchal bowl. A supraperichondrial dissection is performed on the convex side of the cartilage. The cartilage



• **Figure 42-10** **A,** Auricular cartilage is harvested via a vertical incision on the posterior aspect of the concha. **B,** The cartilage is exposed, and the desired size of the graft is outlined. The perichondrium is left on the convex surface of the cartilage. **C,** The outlined portion is excised so the perichondrium is not removed with the graft. The graft should only have perichondrium on the convex side and none on the concave side.

is incised parallel to the helix. A subperichondrial dissection is created on the concave side of the cartilage. Sufficient cartilage must remain to support the ear. The skin is then closed primarily. The graft is sutured with several horizontal mattress sutures to the surrounding tissues (Figure 42-11).

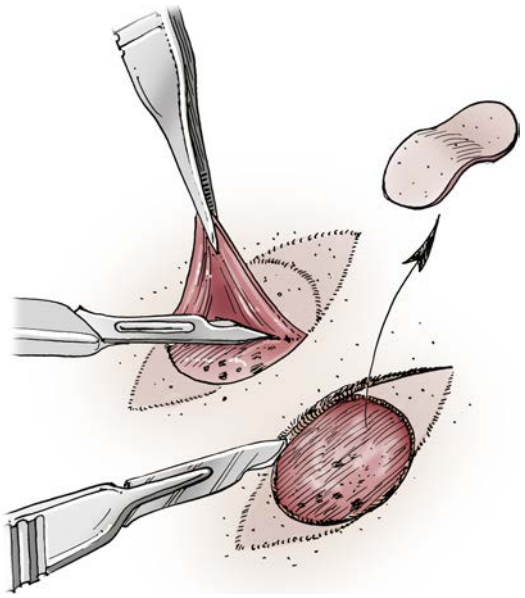
Although not commonly used at the present time, the auricular cartilage graft was previously used to replace a failed alloplastic graft when alloplasts were still widely used. It is important to recall that if an auricular cartilage graft is being considered, the perichondrium is left intact on the convex side of the graft, which opposes the glenoid fossa. Auricular cartilage grafts do not induce a foreign-body reaction and appear to resist most occlusal loading forces. However, histologic analysis in both animal and human studies has shown that dense adhesions or a fibrous fusion occurs between the graft and either the fossa or condyle.[94,95,104] A disadvantage of the auricular cartilage graft is that it requires a second donor site, although it is in close proximity to the primary surgical field. Reported complications related to auricular cartilage grafts include the graft becoming prematurely displaced and infections of the graft.



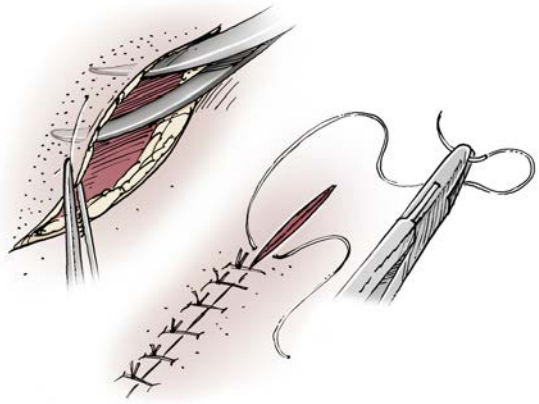
• **Figure 42-11** The graft is sutured to the fossa and the posterior slope of the eminence with either wires or heavy sutures.

Dermal Grafts

Dermal grafts have been used for disc replacement but are more commonly used for repair of disc perforations and as an interpositional material in cases of TMJ ankylosis. The most common sites from which to harvest dermal grafts for TMJ surgery include the upper lateral thigh, buttock, and groin. Dermal grafts are harvested as either partial-thickness or full-thickness grafts. A dermatome is used to obtain a partial-thickness graft. Complete removal of the epidermis from the graft is preferable to avoid leaving epithelial remnants on the graft, which may lead to epithelial cyst formation on the condyle from the undersurface of the graft. A



• **Figure 42-12** Dermal harvest includes removal of epidermis over an ovoid area of skin. The epidermis is discarded.



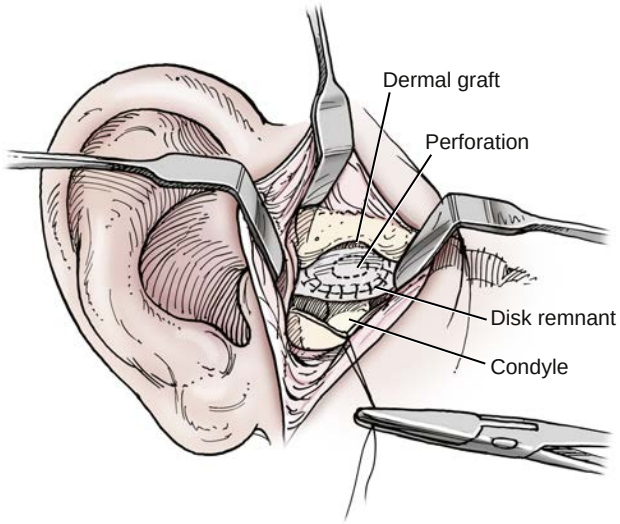
• **Figure 42-13** The oval is converted to a full-thickness fusiform shape, three times longer than wide. The split-thickness oval, along with the remainder of the fusiform, is excised down to the subcutaneous fat. The full-thickness ends are excised. The wound is then undermined and closed primarily.

thin film of antibiotic ointment is coated over the donor site, and a transparent, occlusive wound dressing is placed over the area.

Full-thickness grafts begin by drawing a fusiform outline of the desired graft on the skin (Figure 42-12). A circular area of epidermis is removed from the center of the fusiform outline. Next, the entire outlined area is excised down to the subcutaneous fat. The graft site is undermined and closed primarily (Figure 42-13). The dermis alone is excised from the central portion of the fusiform-shaped graft, and then defatted by hand with either a No. 15 blade or scissors (Figure 42-14). Removal of fat from the dermal graft assists in revascularization of the graft by capillary in-growth from the tissues in the recipient bed. An animal study by Tucker et al indicated that vascular perfusion of dermal grafts placed



• **Figure 42-14** The dermal graft being defatted by hand.



• **Figure 42-15** The dermal graft sutured in place.

in the TMJ occurred soon after its placement.[105] The graft appears to remain viable as a free graft.

When dermal grafts are harvested for disc repair, the margins of the perforation should be freshened. The harvested graft should be approximately twice the diameter of the measured defect to allow for anticipated contraction of the graft (Figure 42-15). The dermal graft should also extend well beyond the extent of the perforation to avoid exposure of the condylar head if the dermal graft were to migrate. Postoperative physical therapy will help to prevent possible fibrous adhesion formation within the joint space. One disadvantage of the dermal graft is that it requires a remote donor site. Additionally, dermal grafts, much like auricular cartilage grafts, can result in fibrous tissue formation with subsequent fibrous ankylosis.

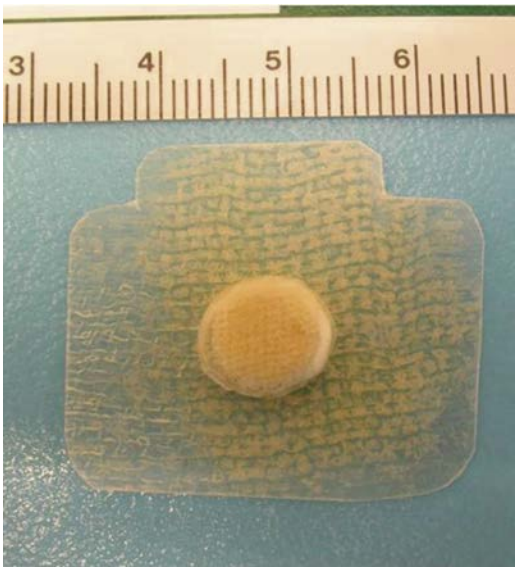
Regenerative Medicine Alternatives for Future Treatment of Disc Perforation

Epidemiologic surveys report that 20% to 25% of the population has TMD symptoms,[106] while patient studies show that 3% to 4% of the population seeks treatment.[107] The TMJ disc is relatively avascular and does not spontaneously regenerate or repair itself in vivo.[108] It has been shown that almost 70% of patients with TMDs suffer from disc displacement,[109] a finding that identifies the TMJ disc as a key structure in the cascade of events that lead to progressive

pathology and morbidity. A novel, effective treatment for disc regeneration may signal a paradigm shift in the treatment of perforated TMJ discs and prevent the inevitable consequence of degenerative articular surface damage with subsequent total joint replacement.

Tissue Engineering Strategies

From 2004 through 2008, Almarza et al[110,111] published 13 articles describing the use of porcine TMJ disc cells for creating a tissue-engineered TMJ disc in vitro. These studies optimized monolayer culture conditions, scaffold selection, seeding density and technique, growth factor regimens, and biomechanical stimulation regimens, but the ability to create a TMJ disc with properties that matched the native disc was limited. More recently, a series of studies has been published in which costal cartilage was evaluated as an autologous cell source for a tissue-engineered disc.[112-114] This autologous tissue would be appealing as many craniofacial surgeons also have experience replacing the mandibular condyle with a rib graft. However, this procedure has variable results and significant questions remain regarding cell source, scaffold choice, and stimulation regimen.



• **Figure 42-16** Macroscopic image of the pre-implantation UBM-ECM device. The central "pillow" consists of a fine particulate form of the same ECM that encases the deformable pillow. The encasing sheets serve as the brim for attachment to the joint capsule.

approach for TMJ disc replacement and a departure from purely in vitro strategies. The approach involves recruitment of progenitor cells with local modulation of the host innate immune response by promoting an M2 versus M1 macrophage phenotype. These processes are centered on the use of a biologic scaffold material composed of xenogeneic ECM.

Macrophage Phenotype as a Predictor of Constructive Remodeling

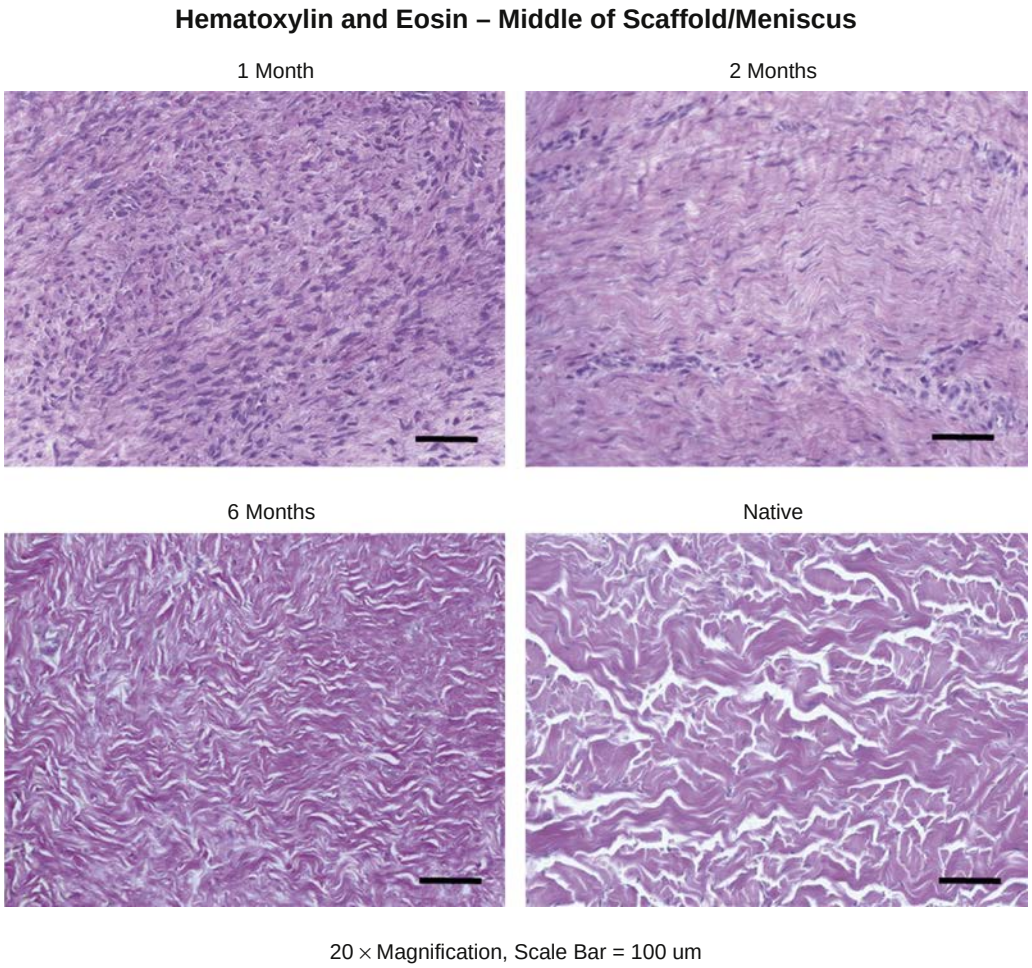
Badylak and co-workers have shown that the phenotype of macrophages that participate in the remodeling of ECM scaffolds plays a critical role in determining whether the events follow a pro-inflammatory course leading to fibrosis and scarring, or a constructive remodeling course resulting in [120] The causes and effects of this macrophage dichotomy toward a given phenotype have been studied in the context of tissue engineering. It was shown that M1 and M2 macrophages have distinct effects on the recruitment of progenitor stem cells, a cell population believed to play a critical role in repopulating the ECM scaffold material.[121] M2 macrophages promote the chemotaxis/recruitment of these cells, while M1 cells inhibit the chemotaxis of these stem cells.

Canine Unilateral Discectomy Model

A prototype ECM derived from porcine urinary bladder mucosa (UBM) was first evaluated as a scaffold for TMJ disc reconstruction in a canine model.[115] Five dogs were subjected to unilateral resection of the native disc and subsequent replacement with the UBM-ECM (Figure 42-16). Analyses were performed at 3, 4, 8, 12, and 24 weeks in this pilot study. Macroscopically, the scaffold remodeled rapidly, and it was indistinguishable from newly deposited host tissue at all time points, including the 3-week time point. Microscopically, remodeling was characterized by intense vascularization during the first 2 months, and a dense infiltration of predominantly CD68+ mononuclear cells (i.e., macrophages) and smooth muscle actin (SMA)+ large, round cells at early time points. The cell population changed over time to a sparse population of SMA spindle-shaped cells resembling those of the native TMJ disc (i.e., fibrochondrocytes) (Figure 42-17). Furthermore, the remodeling process showed deposition of predominantly collagen type I (as determined by Herovici staining),[122] the density and organization of which resembled that of the native disc by the 6-month time point. In-growth of skeletal muscle tissue was observed at the interface of the remodeled UBM with the host periarticular musculature. No adverse changes in the articulating surfaces of the condyle or fossa were observed, thus confirming the protective function of the remodeled scaffold. Results of this pilot study suggest that the xenogeneic ECM scaffolds have the potential to provide an effective interpositional material while serving as

Canine Bilateral Discectomy Model

In light of the promising findings in the pilot study described above, a more definitive study was conducted in which 10 dogs were allowed to survive for 6 months following UBM implantation.[116] It was decided that confirmation of the long-term (6 month) remodeling events was needed.



• **Figure 42-17** Histologic appearance of the remodeling process at 1, 2, and 6 months. The dense cell infiltrate at 1 month transforms into a fibrocartilaginous tissue very similar to the native TMJ disc *(lower right)*. Recall that the original implant is totally acellular.

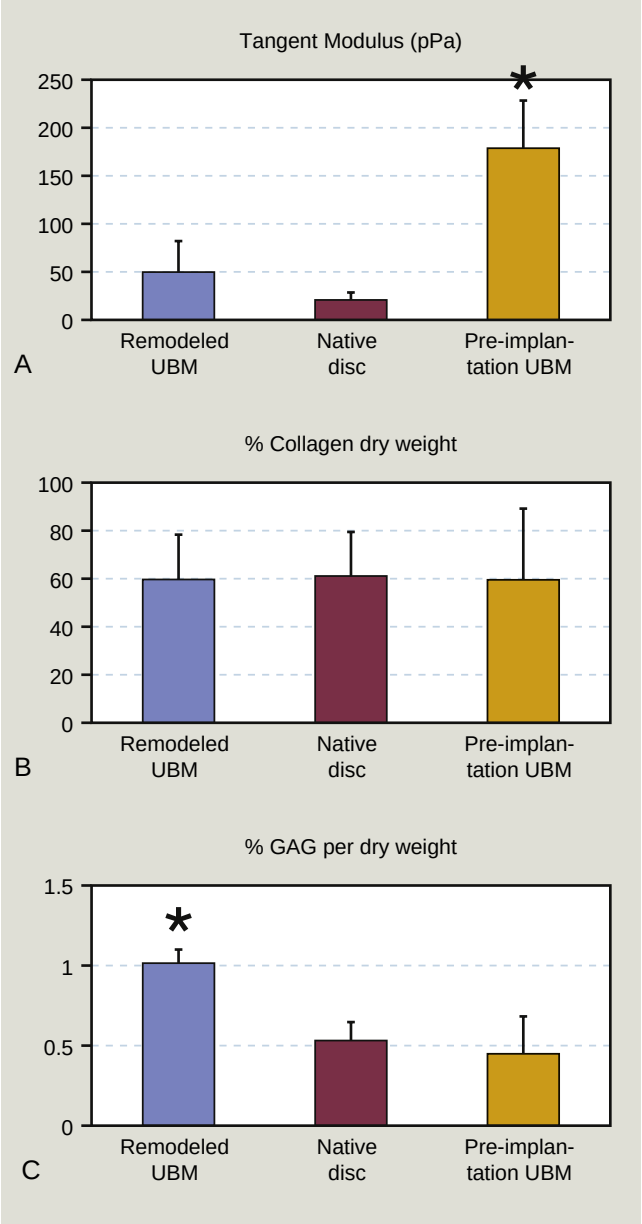
The goal of this study was to examine the 6-month gross morphologic and histologic outcome in a more comprehensive manner than the initial pilot study and to evaluate the biomechanical properties and biochemical content of the remodeled tissues at 6 months post-implantation.

Unlike the pilot study, a bilateral discectomy was performed in this trial with one side being treated with the xenogeneic UBM and the opposite side serving as a control and left empty. The results in 9 out of the 10 dogs showed excellent remodeling of the scaffold with articular surface protection while the contralateral, untreated control side clearly displayed pitted articular surface irregularities within 6 months and no regrowth of the TMJ disc tissue.

Gross morphologic findings showed little to no change in the articulating surfaces of the temporal fossa or the mandibular condyle following placement with the UBM device, again confirming the protective effect of the ECM device even during the remodeling process. Consistent with the pilot study results, the UBM in the second study was replaced with a dense collagen fiber structure that resembled the native TMJ disc by the 6-month post-surgery time point in 9 of 10 animals. The one animal in which the ECM scaffold did not remodel in a constructive manner showed degeneration and scar tissue deposition at the site of UBM, the cause of which is unknown.

Immunolabeling for CD31 showed that the number and size of blood vessels within the remodeled device at 6 months were similar to those of the native disc. Immunolabeling for CD68 was negative, indicating that the macrophages present at early time points were replaced with a population of cells that resembled those of the native disc.

Biomechanical testing showed that the pre-implantation ECM device had a higher maximum stress, equilibrium stress, and tangent modulus than did the native TMJ disc tissue and a lower percentage of relaxation. By 6 months post-implantation, however, the mechanical properties values of the remodeled UBM and the native disc were indistinguishable (Figure 42-18). Biochemical testing showed that both the pre-implantation UBM device and the remodeled UBM had collagen and water contents that were similar to those of the native disc tissue (see Figure 42-18, *B*). The remodeled UBM had higher glycosamino glycans (GAG) content than both the pre-implantation device and the native tissue (see Figure 42-18, *C*).

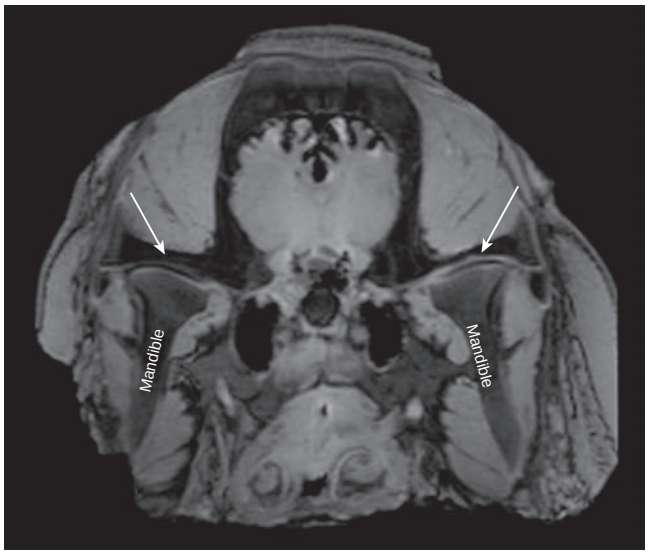


• **Figure 42-18** Biomechanical and biochemical results of the scaffold (N=6). **A,** Tangent modulus in kPa from stress-strain behavior, with pre-implantation ECM scaffold significantly higher than the other differences found. **C,** GAG content per dry weight basis, with remodeled

In summary, the tissue into which the UBM scaffold material had remodeled showed remarkable morphologic, biochemical, and mechanical similarity to the native TMJ disc tissue.

Porcine Bilateral Discectomy Model

Current efforts are being shifted to adapt the bilateral meniscectomy procedure to a porcine model (Figure 42-19), a species in which the structure and function of the TMJ disc is more like human than other species.[123-125]



• **Figure 42-19** MRI of adult porcine skull from a recent study showing bilateral TMJ discs *(arrows)*.

The pig is thought to be the most suitable non-primate model of human TMJ anatomy and function.[123-125] Berg[123] examined pigs, sheep, calves and dogs, and noted that the pig was best suited for experiments in replacing the TMJ disc. Bermejo et al[124] also concluded that the pig was the only suitable experimental animal model after comparison to dogs, cats, rabbits, rats, cows, sheep, and goats. Similarities of the pig to human include the size of the articular structures, shape of the disc, and the omnivorous diet. Ström et al[125] recommended the domestic pig as a useful model in the investigation of masticatory system function. Thus, it has been established that pig and human TMJs have similar gross morphology, size, and structure of each TMJ component, including the disc, which will prompt further studies in this model.

Data from these two novel studies show a dramatic and rapid change from an acellular ECM scaffold to a fibrocartilaginous tissue in the dog discectomy model. Additional work shows that ECM remodeling includes a process of cellular infiltration that involves M2 macrophages, multipotential stem cells, and transient vascularization. Chemical crosslinking of ECM scaffolds shifts the macrophage response to a proinflammatory M1 phenotype in soft tissue applications[126] and markedly inhibits degradation and release of bioactive peptides.[118] The temporospatial pattern of remodeling is largely unexplored and the relative contribution and importance of factors such as scaffold degradability, the innate immune response, and the mechanical loading are unknown, especially in an intra-articular environment. Therefore, in the future these different aspects of ECM remodeling will be studied in the porcine model.

Condylotomy

The principal indication for condylotomy is reduction of pain in disc displacement with reduction, but it can be

used for any Wilkes stages I-III. Studies have reported favorable outcomes with a condylotomy for painful ID but no restricted range of motion.[127,128] The condylar sag that results from the condylotomy creates increased joint space and decreased articular pressure. This procedure has also been used for treatment of recurrent TMJ dislocation. Campbell described the first condylotomy, a closed procedure, which was performed with a Gigli saw.[129] Nickerson modified the procedure in 1983 by changing the osteotomy to one that resembles an intraoral vertical osteotomy.[130]

Several technical aspects of importance exist when performing the condylotomy for ID. The first important technical aspect is the location of the osteotomy. The vertical ramal osteotomy must be performed just posterior to the antelingular prominence to avoid the mandibular canal and unnecessary injury to the inferior alveolar nerve and vessels. The surgeon also needs to avoid placement of the inferior portion of the vertical osteotomy through the posterior border. The osteotomy should be carried through the inferior border of the mandible to allow for the desired condylar sag and better control of the condylar (proximal) segment.[132,133] Additionally, if the inferior portion of the osteotomy is made too far posteriorly along the ramus, the tip of the proximal segment may be either palpable or visible after resolution of the surgical edema. This result can be avoided by removing the tip of the proximal segment at the time of surgery with a rongeur.[134]

The amount of condylar sag is estimated by the distance created between the tip of the proximal segment and the inferior border. Factors such as the amount of medial pterygoid muscle attachment on the proximal segment and joint laxity determine the amount of condylar sag and proximal segment mobility. Proximal segment mobility can be appreciated by pushing up on the inferior portion of the proximal segment with a gauze director. A 3- to 4-mm step at the inferior border implies adequate condylar sag.

A second technical aspect of importance is the amount of bone removed along the osteotomy site. Nickerson and Veaco first described the modified condylotomy with a forward position of the proximal segment.[130] The proximal segment is placed slightly anterior and lateral to the distal segment by creating a step in the medial edge of the proximal segment. Hall later stated that forward positioning of the proximal segment was not necessary.[132] He advocated creation of a butt joint between the proximal and distal segments and encouraged creation of a medial step on the proximal segment only if a greater anterior positioning of the proximal segment was necessary.

The primary proposed advantage of the condylotomy over other arthrotomy procedures is less intra-articular scarring because the condylotomy is an extra-articular procedure. Less scarring in the joint space results in an increased range of motion, and the disc and posterior attachment remain unaltered. Maxillo-mandibular fixation (MMF) via Erich arch bars is used for 1 week in a unilateral condylotomy and for 2 weeks for bilateral condylotomy followed by application of light training elastics for an additional 4 to 5 weeks in either case to avoid an anterior open bite.[132] Active range of motion exercises are initiated 4 weeks after surgery to restore a normal range of motion. A regular diet can be reinstituted in 6 to 8 weeks.

The most significant complication associated with condylotomy is malocclusion as a result of condylar sag and changes in ramal segment position. Hemorrhage; injury to the inferior alveolar, lingual, or long buccal nerves; infection; and condylar dislocation are among the other complications.[131]

Controversy still surrounds the use of the condylotomy in the treatment of ID, and the procedure has both its strong advocates as well as opponents.[131,132,134] Proponents of the condylotomy are quick to point out how the normal disc-condyle relationship is restored and pain relief is achieved to a greater degree and more quickly than with other arthrotomy procedures. Various studies by Nickerson and Veaco,[130] Upton,[134] and McKenna[135] all showed significant decreases in pain after modified condylotomies for ID.

Complications

The common complications associated with all arthrotomy procedures include hemorrhage, auriculotemporal nerve and facial nerve injury (particularly of the temporal branch), fibrous adhesion formation, persistent pain, and occlusal changes.[136] The inferior alveolar, lingual, and long buccal nerves can also be at risk for injury from surgical retraction or manipulation of the condyle. Complications more likely with a discectomy involve heterotopic bone formation and joint ankylosis. Infection rarely occurs with TMJ arthrotomy.

Postoperative Therapies

The 1990 AAOMS standards and criteria of surgical procedures (for TMJ surgery) list a number of factors that impact a patient's postoperative course.[37] Several of these factors are issues remote from the intrinsic joint pathology, such as concomitant facial pain from other sources, poorly controlled parafunctional habits, psychological disorders, and systemic disease affecting the muscles, ligaments or bone. Myofascial pain and dysfunction can also exist concurrently with ID. If these issues are not addressed both preoperatively and postoperatively, a patient will not attain the goals of the surgery.

Postoperative therapy involves a combination of physical therapy, pharmacologic management, and occasionally splint therapy, each playing an integral role in enabling the patient to achieve an acceptable postoperative pain level and condylar range of motion. Patients who have undergone discectomy are encouraged to begin conservative range of motion exercises shortly after surgery. Disc repositioning or repair patients are typically instructed to begin conservative stretching exercises within a week after surgery. Many who undergo an arthrotomy procedure regain a normal, or close to normal, range of motion in 2 to 3 months with a

regimented course of postoperative physical therapy. A Therabyte (ACTOS Medical) appliance is routinely prescribed as a part of the patient's physical therapy. Patients who do not exhibit a decreased range of motion preoperatively should regain a normal range of motion postoperatively without much difficulty. However, patients who had a poor range of motion preoperatively will have a more difficult time attaining a normal, or even near normal, range of motion postoperatively. Thus, strict adherence to a regimented physical therapy program becomes critical.

The role of physiotherapy on the recovery of patients [137]

ficial in maintaining a stable postoperative occlusion. More importantly, a splint is necessary if the patient resumes any documented preoperative parafunctional habits that may cause delayed pain reduction in the postoperative phase. The splint may require adjustment as postoperative changes in the soft and hard tissues of the joint occur. Postoperative joint noises that are asymptomatic should not create any concern for either the patient or surgeon.

Summary

The literature has clearly documented the benefits of surgery for ID.[6-14] Numerous studies have documented the nonsurgical treatment or other less invasive techniques may not always be indicated or even be considered better alternatives in some situations. Determining an accurate diagnosis is a critical first step, and obtaining the diagnosis is often marred by the challenge of the patient's lack of understanding of his/her own symptoms. Strict adherence to surgical treatment algorithms for ID is not always beneficial or possible because each patient's underlying disorder and symptoms are unique and must be treated as such. The surgeon must avoid overemphasizing radiographic findings when determining if arthrotomy will effectively treat the ID and not cause any unnecessary morbidity. Regardless, careful patient selection is a fundamental and essential factor prior to pursuing surgery, particularly arthrotomy.

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43

Temporomandibular Joint Replacement

LOUIS G. MERCURI

Introduction

Temporomandibular joint (TMJ) total joint replacement (TJR) presents unique problems because of the integral and complex role the TMJ plays in establishing and maintaining proper form and function within the stomatognathic system. The TMJ not only acts as a secondary growth center for the mandible in prepuberty, but its integrity is vital to the functions of mastication, speech, airway support, and deglutition in both children and adults.

Prior to the mid-1980s, the primary indications for TMJ TJR were the management of developmental maxillofacial deformities, ankylosis, severe inflammatory joint disease, or TMJ replacement after ablative tumor surgery or trauma.

procedures. Many of these patients' joints were anatomically distorted and functionless secondary to the failure of interpositional materials such as Proplast-Teflon (Vitek, Houston, TX) and/or Silastic (Dow-Corning-Wright, Arlington, TX) (Figure 43-1).

Considering not only function and form, but also a patient's neurologic and psychological issues, surgeons developed physiologically reasonable, biologically rational, technically achievable outcome objectives based on decades of orthopedic joint replacement experience.

The following TMJ replacement goals were developed:[1]

1. Improvement of mandibular function and form
2. Reduction of further suffering and disability
3. Containment of excessive treatment and cost
4. Prevention of further morbidity

End-stage disease and/or pathology with accompanying anatomic form and physiologic function distortions dictate the need for TMJ TJR. Due to the complex nature of its anatomic and masticatory muscle functional relationships, it is unreasonable to expect that a TMJ TJR will return a patient to their premorbid mandibular functional status. Therefore, as with orthopedic joint replacements, there will always be some functional disability after TMJ replacement.

Further, in multiply operated, anatomically distorted patients, chronic neuropathic and centrally mediated pain often play a major role in their disability. Therefore it is important that both the surgeon and the patient understand that the primary goal of TMJ replacement is the restoration of mandibular function and form, and that any subjective pain relief achieved must only be considered as a secondary benefit.[2]

Historic Perspective of TMJ Replacement

Autogenous TMJ Replacement

Bone—Vascularized and Non-vascularized

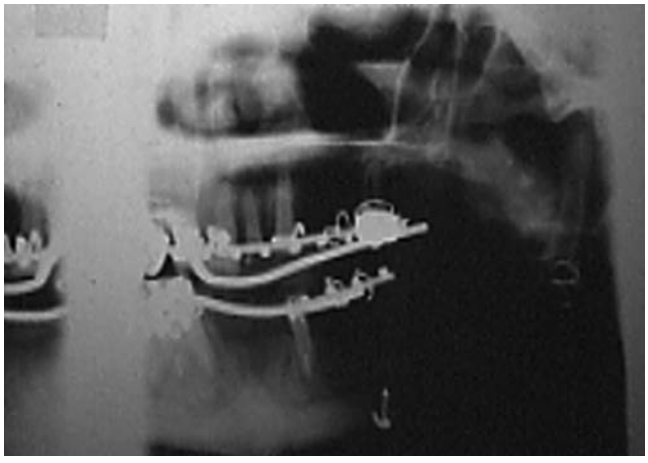
Earliest TMJ replacement involved the use of autogenous tissues. In 1909 Bardenheuer[3] performed a mandibular condyle replacement with the fourth metatarsal. This technique was also reported in 1920 by Gillies.[4] The use of an autogenous metatarsal head to reconstruct the mandibular condyle was also reported by Dingman[5] in 1964, Glahn[6] in 1967, and Spiessl[7] in 1972. Use of a non-vascularized metatarsophalangeal joint to correct a facial deformity was reported by Entin[8] in 1958 (Figure 43-2). Datillo[9] in 1986, and Dierks[10] in 2000 reported the use of a vascularized metatarsophalangeal joint to replace the TMJ.

TMJ replacement has also been performed using vascularized rib[11,12] and iliac crest.[13] Other autogenous tissues such as fibula[14,15] and iliac bone free grafts,[16-20] clavicle, and sternoclavicular joint have been used.[21-23] However, none of these reports provided long-term follow-up.

The non-vascularized costochondral free graft has been the most frequently recommended autogenous bone for TMJ replacement because of its conjectured ease of adaptation to the recipient site, its ostensibly gross anatomic similarity to the mandibular condyle, its low morbidity at the donor site, and its theoretic growth potential in juveniles[24-29] (Figure 43-3).



• **Figure 43-1** Anatomically distorted and functionless left TMJ attributable to Proplast-Teflon foreign body giant cell reaction. Note the osteolysis of the temporal zygomatic arch, articular eminence, glenoid fossa, and mandibular condyle.



• **Figure 43-2** Non-vascularized fifth metatarsal graft reconstruction of the left TMJ.

Tissue—Vascularized and Non-vascularized

A number of different autogenous tissues—temporalis fascia,[30-34] masseter, temporalis muscle flaps,[35-54] dermal grafts,[55-59] and fascia lata[60,61]—have been advocated as a replacement for the TMJ articular disc. However, the vascularized local temporalis muscle flap remains the most popular.

Vascularized Temporalis Muscle Flap

The advantages of the temporalis muscle flap are its proximity to the TMJ and its reliable blood supply.[51,52,54] Feinberg and Larsen[47] stated that one of the most important roles of the temporalis muscle flap is the maintenance of TMJ functional movements. These authors state that since the flap is attached to the coronoid process, when the mandible translates, the movement of the mandible pulls the muscle flap in an anterior direction, simulating the natural functional movements of the articular disc (Figure 43-4). Investigators reported that follow-up studies on patients with temporalis muscle replacement discovered the presence of viable muscle tissue within the joint.[51-53]

Tong and Tideman[62] reported the re-formation of a disc-like interpositional structure, after 18 months, with use of the pedicled temporalis muscle flap after TMJ discectomy in four Rhesus monkeys with osteoarthritis. They also reported a milder degree of osteoarthritis was observed histologically in three of the four monkey joints where the muscle flaps survived.

Henry and Wolford[63] offered the following contraindications for the use of the temporalis muscle/fascia graft: failed Proplast-Teflon (Vitek, Houston, TX) or Silastic (Dow-Corning-Wright, Arlington, TX) with continuing foreign body giant cell reaction;[64-66] rheumatoid arthritis or other high-inflammatory connective tissue diseases;[67] progressive osteoarthritis;[67] and two or more prior surgeries.[67,68]

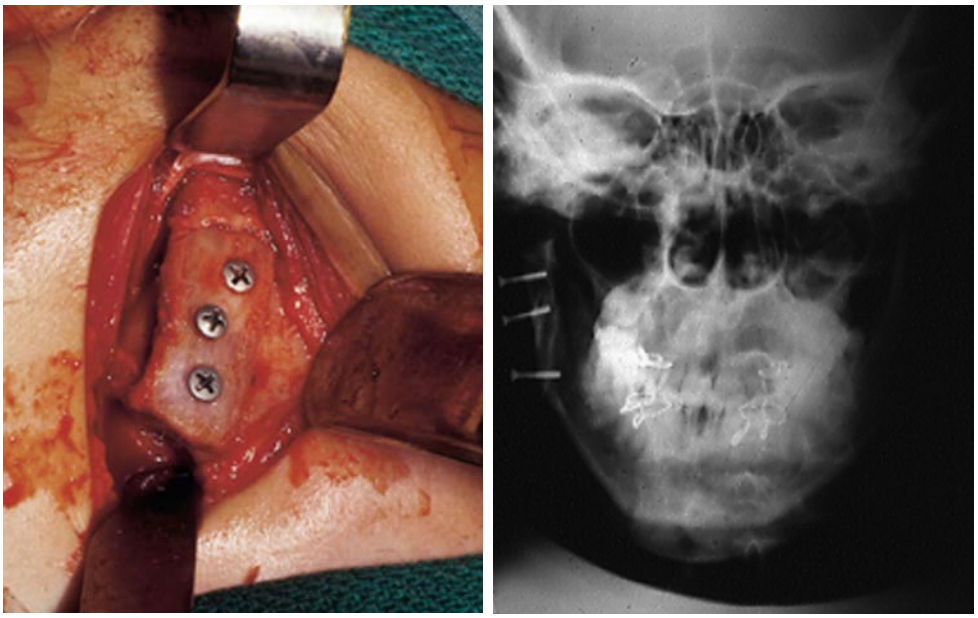
Auricular Cartilage

Ioannides and Maltha[69] reported use of autogenous auricular cartilage as a TMJ disc replacement in 1988. However, Takatsuka et al.[70] studied the use of auricular cartilage after discectomy in the rabbit TMJ. On histologic examination, these authors found fibrous adhesion of the grafted auricular cartilage to the condyle and the presence of a fibrous layer containing fragmented cartilage at the articular surface. They concluded that auricular cartilage did not appear to be an ideal material for disc replacement. Other investigators reported similar findings.[71,72]

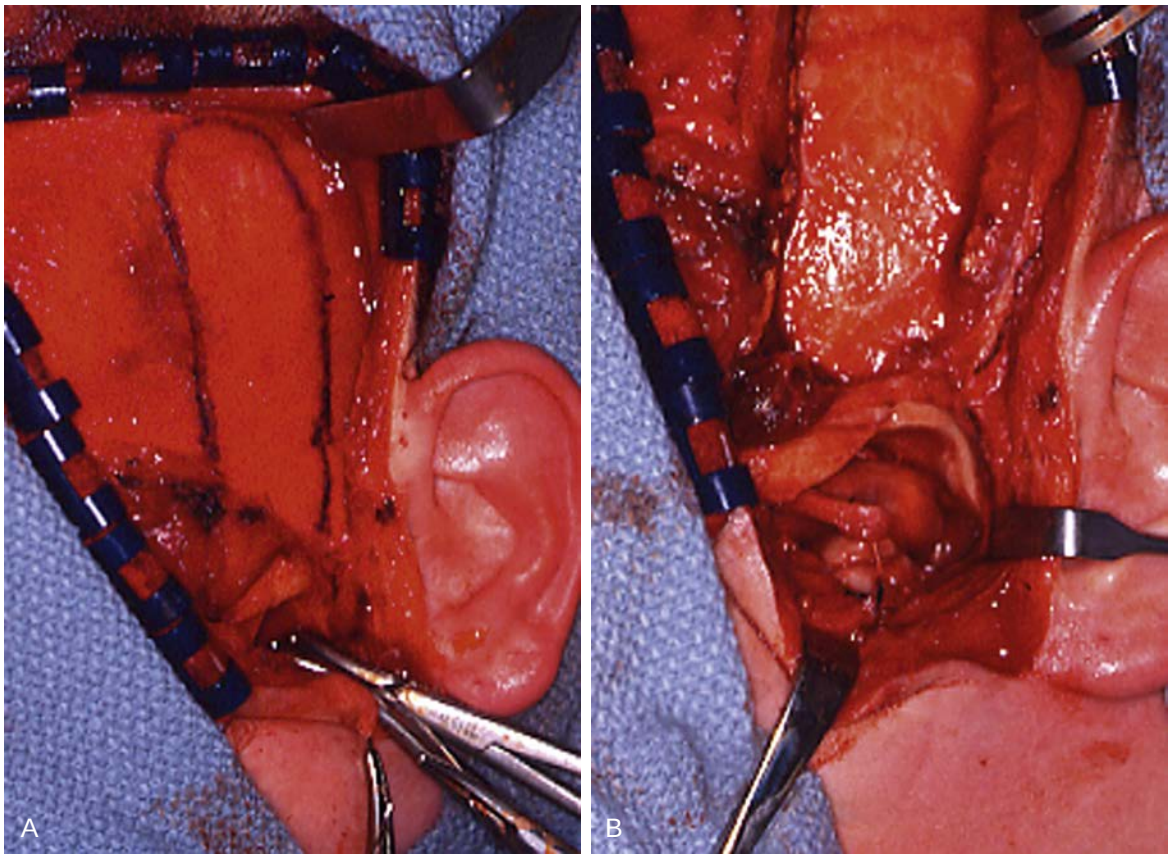
In the past, autogenous tissue has been called the "gold standard" for management of primary, uncompromised TMJ replacement. However, because of the potential morbidity associated with harvest of autogenous tissues, the inability of these tissues to survive either the transplantation process or the functional demands of the forces applied to them, and for the reasons discussed below, there arose the need for the development and use of alloplastic materials to replace the anatomically and functionally impaired TMJ. This is a similar course followed by orthopedic surgery in replacement of other end-stage diseased body joints.

Alloplastic TMJ Replacement

John Murray Carnochan,[73] a New York surgeon, was credited with the idea of interposing alloplastic material between the surfaces of diseased, excised joints in an attempt to prevent ankylosis and promote function. In 1840 he reported an attempt to mobilize a patient's ankylosed TMJ by placing a small block of wood between the raw bony surfaces of the residual mandible after gap arthroplasty.[73]



• **Figure 43-3** Non-vascularized costochondral graft reconstruction of the right TMJ.



• **Figure 43-4** Temporalis muscle flap. **A,** Outline of flap. **B,** Flap fed under temporal process of zygoma and into the glenoid fossa.

Tracing the use of alloplastic materials for the management of severe anatomic end-stage TMJ disease and associated mandibular dysfunction, ankylosis was the primary problem that led patients to surgery. Every new material developed was used in an attempt to manage any joint ankylosis, including the TMJ.[74-133]

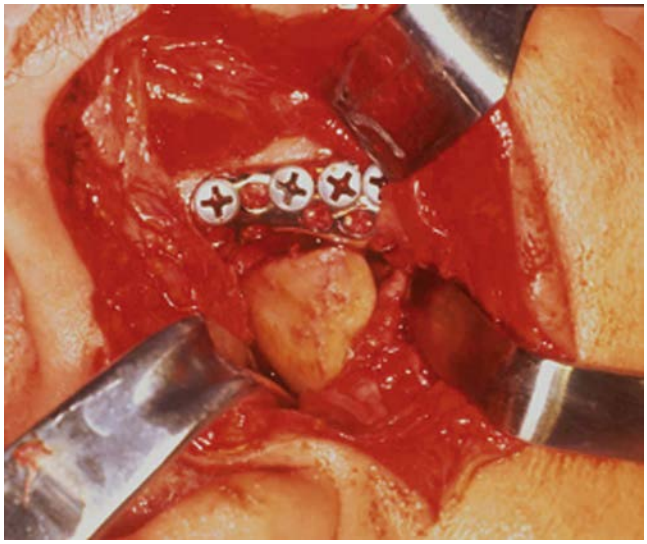
In 1960 Sir John Charnley reported the development of a total alloplastic prosthetic hip replacement system composed of a metal-backed polyethylene acetabular cup articulating with a metal femoral head, attached to a metal femoral shaft which was cemented into place with polymethylmethacrylate.[134] Modifications of Charnley's device have become

the "gold standard" for hip, knee, and shoulder total joint replacement devices in orthopedic surgery.[135]

In 1963, 1964, and 1970, Christensen[84-86] reported the use of a thin cast vitallium fossa-eminence prosthesis for management of TMJ ankylosis (Figure 43-5). He later added a cast vitallium ramus-condyle with a polymethylmethacrylate head to create a total joint device (Figure 43-6).

Between 1974 and 1985, a number of reports were published involving the use of partial and total alloplastic TMJ replacement devices. These were typically case reports with small numbers of patients for whom the diagnosis was ankylosis or reconstruction after ablative malignant neoplasia surgery.[95-99,106-123] Of these, the two most significant reports were those by Kiehn[111,112] and Kummoona.[117]

In 1985[119] and again in 1990[120] S. Sonnenburg and M. Sonnenburg reported the use of a TMJ TJR device consisting of a cast chromium-cobalt-molybdenum ramus-condyle component articulating against an ultra–high-molecular-weight polyethylene fossa, mimicking the materials and geometry used in the design of alloplastic joint devices by orthopedic surgeons.

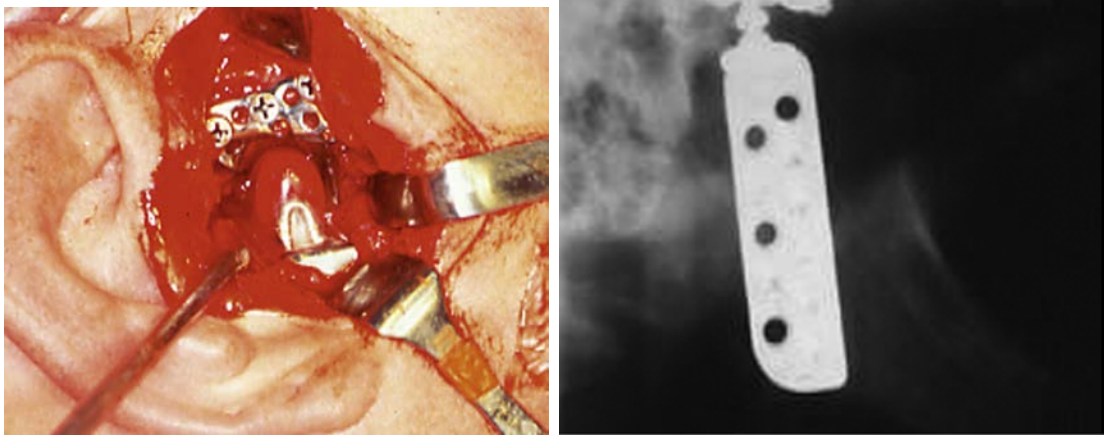


• **Figure 43-5** Alloplastic thin cast vitallium fossa-eminence device (TMJ Inc., Golden, CO), right TMJ.

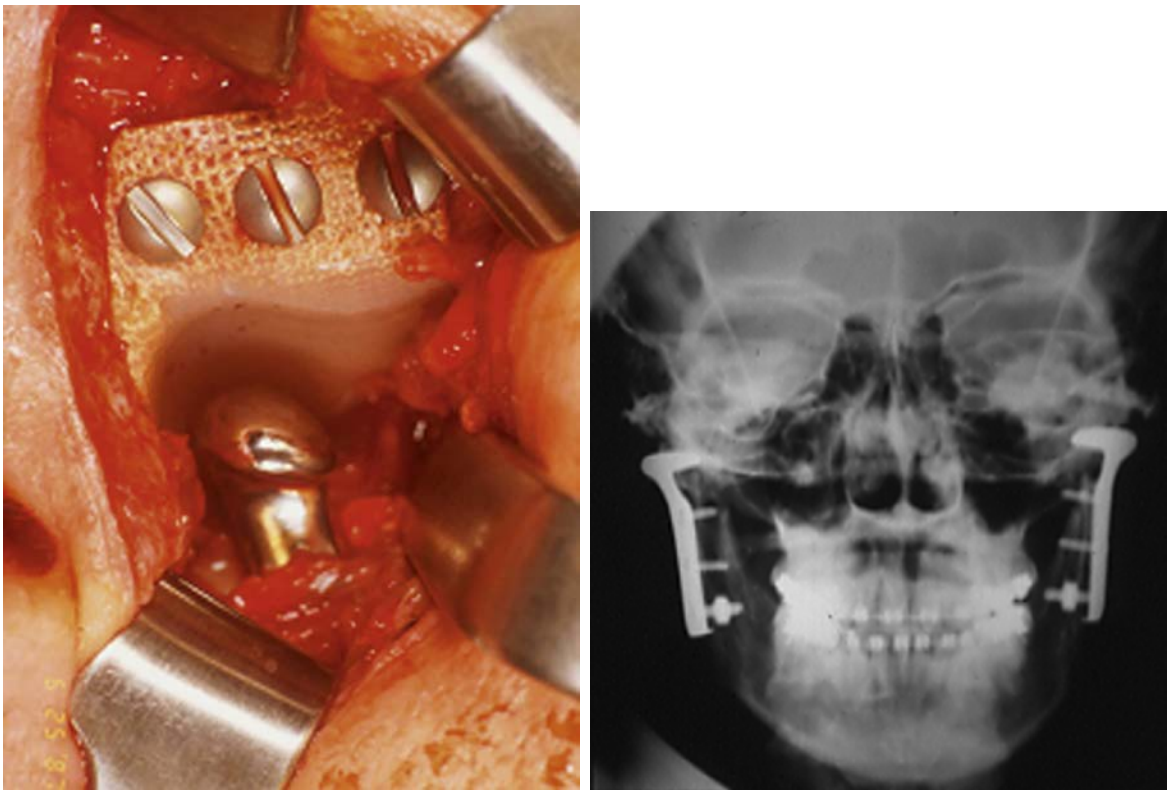
Hinds, Homsy, and Kent[107] in 1974 reported the use of a Proplast-Teflon-coated vitallium ramus-condyle component for hemi-articulation reconstruction of the TMJ. Kent, in 1983, reported the use of a Dacron/Proplast-Teflon (VK-I) and later a Dacron/Proplast-Teflon/ultra–high-molecular-weight polyethylene (VK-II) fossa.[108,109] The ramus-condyle and fossa components were then used as TMJ TJR devices (Vitek, Houston, TX). In 1993 Kent et al.[110] reported a long-term follow-up study using these devices (Figure 43-7).

From 1990 to 1995, reports surfaced regarding the development and use of alloplastic partial and total TMJ replacement devices. The indications for use ranged from ankylosis to reconstruction after ablative surgery and trauma to the unsuccessfully managed, multiply operated patient.[124-130]

In 1993 Henry and Wolford[66] reported prospective results with the use of the Techmedica (Camarillo, CA; now TMJ Concepts, Ventura, CA) computer assisted designed/computer aided manufactured (CAD/CAM) TMJ TJR device used to manage end-stage TMJ disease in 26 patients followed a mean of 46 months with anatomically divergent, functionless TMJs after Proplast-Teflon exposure and failure. Wolford, Cottrell, and Henry[23] then reported in 1994 the use of the same device in 56 multiply operated TMJ patients followed for a mean of 30 months. Mercuri et al.[130] in 1995 reported the preliminary results in a prospective multicenter clinical study with the Techmedica device in 215 patients followed for a mean of 4 years. In 2004 Mercuri et al.[131] published a 10-year follow-up study; and in 2006 Edibam et al.[132] reported a 14-year follow-up study of these



• **Figure 43-6** Cast vitallium ramus-condyle and fossa-eminence components of a total TMJ alloplastic device with polymethylmethacrylate condylar head (TMJ Inc., Golden, CO).

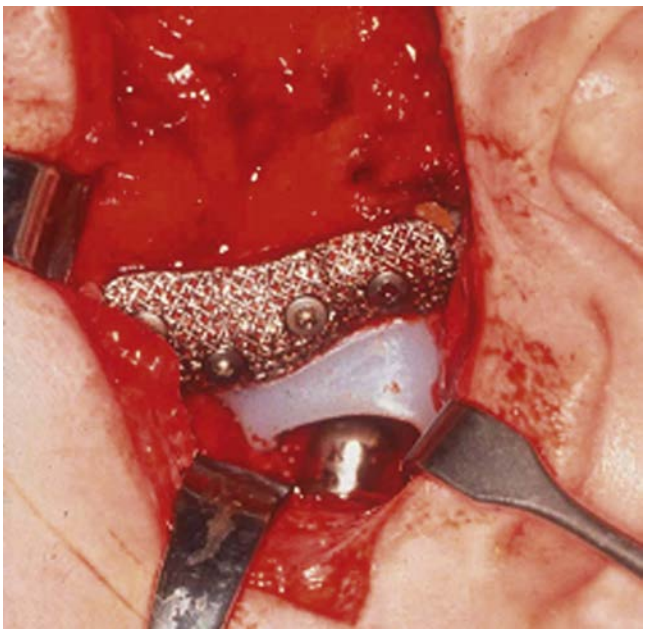


• **Figure 43-7** Cast vitallium Proplast-Teflon coated ramus-condyle and Dacron/Proplast-Teflon/ultra–high-molecular-weight polyethylene components of a total TMJ alloplastic device (Vitek, Houston, TX), right TMJ.

patients (Figure 43-8). In 2015, Wolford et al. reported a 20-year follow-up of 99 Techmedica/TMJ Concepts TMJ TJR devices. The results indicated that these devices continue to function well and patients showed sustained improvement in TMJ pain, jaw function, ability to eat solid food, and quality of life.[133,134]

In 1995 Chase et al.[87] reported retrospective results with the use of the Christensen (TMJ Inc., Golden, CO) TMJ TJR device in 21 patients followed for a mean of 2.4 years. Garrett et al.[88] reported the use of a custom modification of the standard Christensen total TMJ device employed in 20 multiply operated patients followed for a mean of 7.5 months. In 2000 Gerard and Hudson[135] reported on the use of the modified metal-on-metal Christensen TMJ device implanted in 23 patients followed for a mean of 26 months (Figure 43-9).

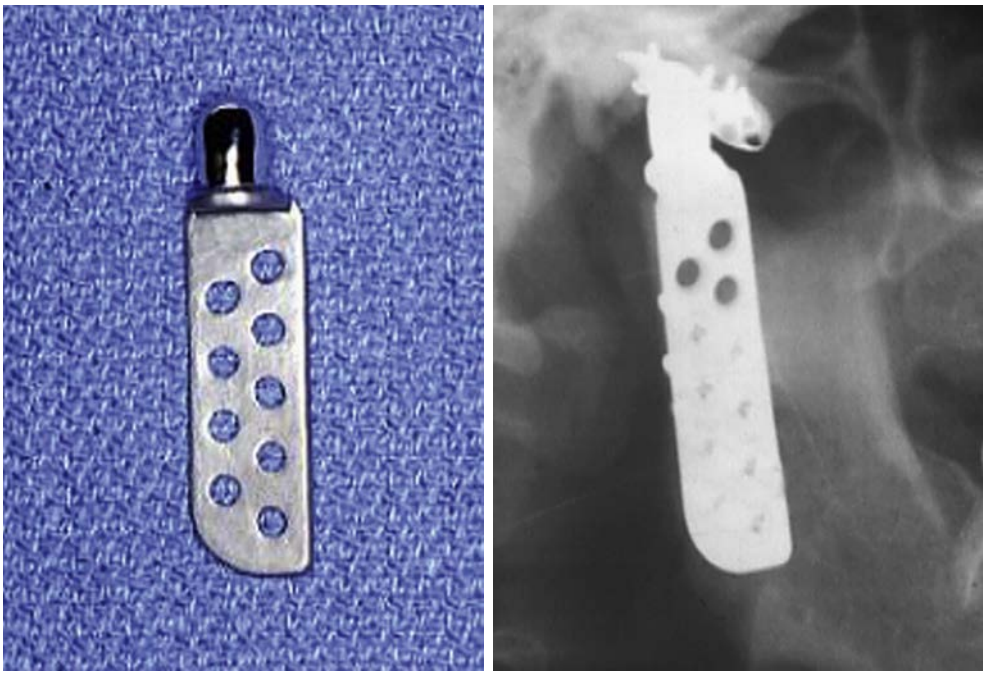
Wolford et al.[136] presented the first comparison of pre-



• **Figure 43-8** Wrought alloyed titanium ramus, cobalt-chrome-molybdenum condyle, and commercially pure titanium and ultra–high-molecular-weight polyethylene fossa components of a patient-fitted alloplastic total TMJ device (Techmedica, Camarillo, CA).

Concepts, Ventura, CA) and TMJ, Inc. TMJ TJR device (Golden, CO; now Nexus CMF, Salt Lake City, UT). These authors found statistically significant better outcomes in both domains in patients implanted with the Techmedica TMJ TJR device than the TMJ, Inc.

All implanted alloplastic devices (dental implants, orthopedic, and TMJ TJR) depend on the principle of osseointegration of their fixation components for their ultimate stability and longevity. Osseointegration implies the direct incorporation of the implant fixation into the bone without the preliminary phase of fibrous tissue in-growth. The requirements for osseointegration are



• **Figure 43-9** Cast vitallium ramus-condyle and fossa-eminence components of a total TMJ alloplastic device with vitallium condyle (TMJ Inc., Golden, CO).

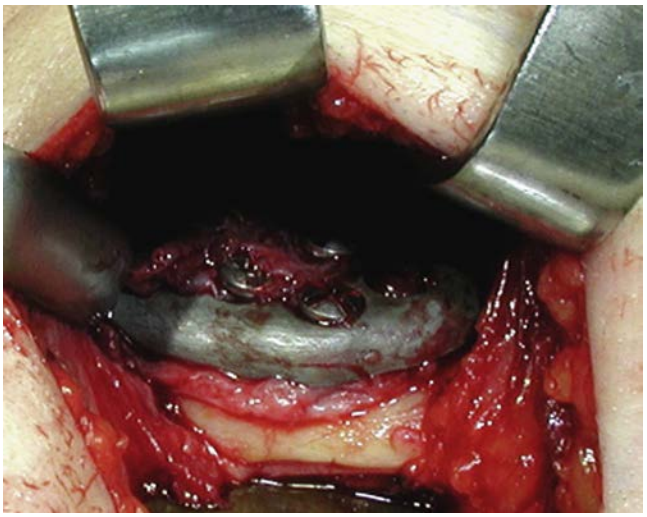
essentially the same as for primary fracture healing: the transmission of forces from the implant to the bone and vice versa must occur without relative motion or without intermittent loading.[137] Therefore, just as with a dental implant, the most important principle in TMJ TJR is primary stability of the device fixation and components from the moment they are implanted.

In orthopedic surgery, TJR devices can be initially stabilized by press-fitting or, now less frequently, cementation of the components into the host bone. In the case of the TMJ, the anatomy of both the mandible and the temporal glenoid fossa does not provide for such a fixation option. Therefore screw fixation of both TMJ TJR fossa and the ramus/condyle components must be utilized to provide initial fixation and stabilization.

Compounding the normal TMJ stability issues are patients who have distorted anatomy following prior surgical and/or material failures, or the result of local or systemic pathology. This makes it extremely difficult to replace the TMJ with an "off-the-shelf" or so-called "stock" device and obtain primary component stability.

Using TMJ TJR stock devices, the surgeon may be tempted to bend, shim with bone or alloplastic cement, or remove precious host bone to make them fit. Any of these maneuvers can lead to component material fatigue or overload, promoting micromotion or breakage.

Micromotion or movement under functional loading leads to the formation of a fibrous connective tissue interface between any mobile TMJ TJR component and the host bone. This can result in early loosening of that component and potential early catastrophic or later premature device failure (Figure 43-10).



• **Figure 43-10** Failed "stock" alloplastic total TMJ device. Note loose screws and fibrous connective tissue interface between the ramus component and the host mandibular bone caused by micromotion under function, right TMJ.

Therefore a patient-fitted or custom-made TMJ TJR device appears to be the most appropriate solution for such complex cases.[130-134] Patient-fitted or custom TMJ TJR devices, designed and manufactured for each specific anatomic situation, conform to any unique anatomic condition. They require no alteration or supplementation to achieve initial implantation stability. The screw fixation of TMJ TJR custom devices secures the components with accuracy to the host bone, mitigating any chance for micromotion while maximizing the opportunity for osseointegration of the fixation screws (Figure 43-11).



• **Figure 43-11** Wrought alloyed titanium ramus, cobalt-chrome-molybdenum condyle, and commercially pure titanium and ultra–high-molecular-weight polyethylene fossa components of a patient-fitted alloplastic total TMJ device (TMJ Concepts, Ventura, CA) on a CT-generated stereolithographic model.

When calculating procedural costs, it is important not only that the price of the TMJ TJR device is considered, but also that all factors associated with its implantation should be evaluated. The major advantage of alloplastic TMJ TJR over autogenous TMJ replacement is that alloplastic TMJ TJR does not require a second surgical site. Therefore, the potential morbidity of the second surgical donor site, associated intraoperative time, and postoperative hospital expenses are all greatly decreased. Despite the fact that TMJ TJR devices can be expensive, the relative costs involved with their use overall is either equal to or ultimately less than costs for autogenous TMJ replacement procedures.

Indications For TMJ Replacement

TMJ TJR is indicated to manage any of the following conditions,[1] each of which is described in detail in the following sections:

1. Inflammatory arthritis involving the TMJ not responsive to other modalities of treatment
2. Recurrent fibrosis and/or bony ankylosis not responsive to other modalities of treatment
3. Failed tissue grafts (bone and soft tissue)
4. Failed alloplastic joint reconstruction
5. Loss of vertical mandibular height and/or occlusal relationship attributable to bony resorption, trauma, developmental abnormalities, or pathologic lesions

Inflammatory Arthritis Involving the TMJ

In 1988 Lindqvist[138] presented a clinical 10-year mean follow-up study of 16 of the 60 patients he previously reported. Of the 16, all were unilateral and 4 had the preoperative diagnosis of "severe TMJ arthritis." There was no indication whether the 4 "severe TMJ arthritis" patients suffered from low-inflammatory or high-inflammatory arthritis. However, based on the symptoms described, one might surmise that these patients had low-inflammatory TMJ arthritic disease (osteoarthritis), which demographically is more common unilaterally than is high-inflammatory TMJ arthritis. The authors concluded that their long-term clinical results utilizing autogenous costochondral TMJ grafting in adult patients were "fairly good."

Obeid,[139] in a mean 5-year (range 2 to 11 years) retrospective follow-up study, reported results with autogenous costochondral TMJ grafting in 22 patients (14 unilateral). He concluded that autogenous costochondral grafting was a successful method for replacement of the TMJ, despite a 10% infection rate and an unpredictable growth rate in the younger patients, all of whom required later corrective osteotomies.

In 1994 Perrott[140] presented a retrospective study of TMJ autogenous costochondral grafting in 26 patients, 7 growing and 19 nongrowing, with a mean follow-up of approximately 4 years. One of the non-growing patients had a diagnosis of "autoimmune arthritis" (high-inflammatory arthritis) and two others "DJD" (degenerative joint disease, that is, osteoarthritis). When reviewing the follow-up data, the "autoimmune arthritis" patient demonstrated on radiographic measurement significant bilateral loss of posterior mandibular vertical dimension, and the only incidence of a decrease in maximum interincisal opening (MIO). However, follow-up data for the two "DJD" patients revealed that their radiographic measurements and MIO corresponded with the other nonarthritic pre-reconstruction diagnoses. These authors concluded that their results indicated that costochondral grafting may be used to successfully replace the TMJ.

MacIntosh[141-143] discussed a rationale and provided clinical examples for the use of autogenous costochondral grafting in the management of the functional and esthetic consequences of TMJ osteoarthritis, rheumatoid arthritis, and juvenile arthritis, but provided no clinical data upon which to evaluate his clinical results. He advocated disc preservation in early-stage high-inflammatory arthritic disease and two-stage autogenous temporalis flap and autogenous costochondral grafting in late-stage high-inflammatory TMJ arthritic disease.[142] MacIntosh[142] stated, "Absolute guidelines for determining the appropriate time to operate on the rheumatoid arthritis patient do not exist. The author has found a quiescent period of 2 years, during which the number of affected body articulations remain stable (although not normal), and imaging of the temporomandibular joint and status of jaw position-occlusion remain unchanged, to offer reasonable expectations for postsurgical stability." However, again, no data were provided to support this observation or his management recommendations.

Frietas et al.[144] reported 12 arthritic, adult patients (24 joints) requiring TMJ TJR. Six were managed utilizing

mean of 48.8 months and 58.5 months respectively. The authors reported that based on the study criteria, the TMJ TJR device patients demonstrated statistically significantly better subjective and objective domain outcomes than did those replaced with autogenous bone. In light of these results, the authors concluded that TMJ TJR devices were more appropriate for the management of patients with end-stage low- or high-inflammatory arthritic disease. TMJ TJR avoided the need for another operative site and its potential morbidity, decreased the operating room time, and allowed for simultaneous mandibular advancement, all with predictable long-term results and stability.[145]

Troulis et al.[146] studied 10 patients (17 joints) followed a mean of 17 months (range 8 to 38 months) who underwent endoscopic condylectomy and autogenous costochondral grafting. They reported satisfactory clinical results with low morbidity over the short period of this initial study and stated they would be pursuing long-term follow-up studies. To date neither longer follow-up nor any further studies have been reported.

Saeed and Kent[147] retrospectively reviewed 76 TMJ costochondral grafts (57 patients) with a mean follow-up of 53 months (range 24 to 161 months). Nine patients (three with ankylosis and six without ankylosis) had a preoperative diagnosis of arthritis. They never stated whether it was a low-inflammatory or a high-inflammatory arthritic condition. They concluded that in patients with no previous TMJ surgery, arthritic disease, or congenital deformity, the costochondral graft performed well. However, a preoperative diagnosis of ankylosis was associated with a high complication rate, suggesting caution when using the autogenous costochondral grafts in ankylosis patients.

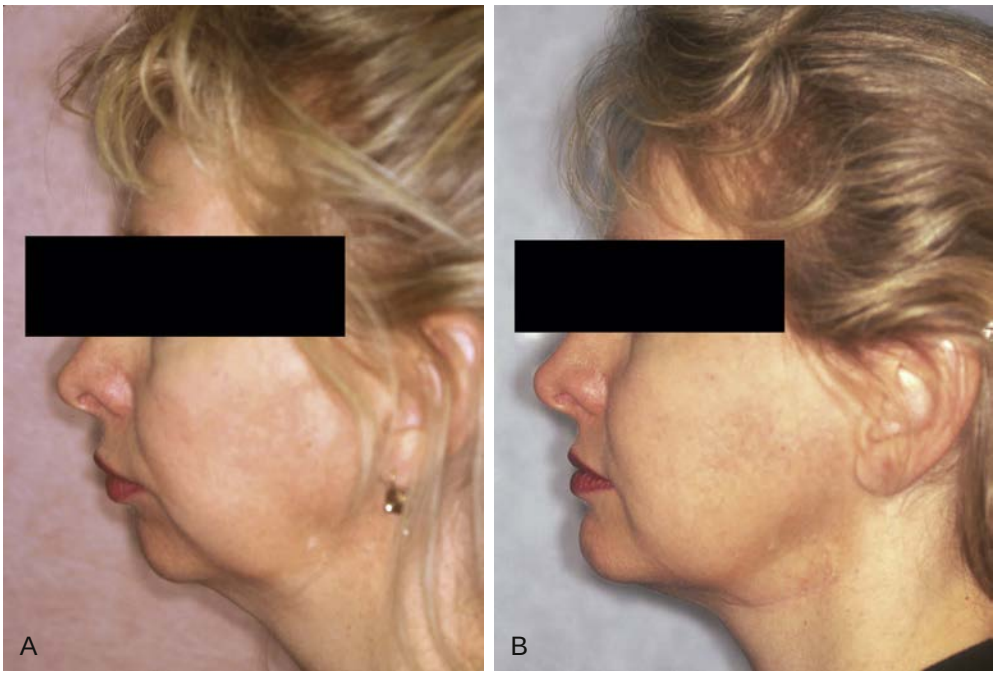
Neither orthopedic textbooks nor journal articles published recently discuss the use of autogenous bone in the replacement of any joint in the adult patient affected by either end-stage low- or high-inflammatory arthritic disease. Alloplastic total joint replacement is the recommended management modality when orthopedic joint replacement is required in such cases[148,149] (Figure 43-12).

Other high-inflammatory arthritic conditions affect both the upper and the lower compartment of the TMJ. This may account for the poor performance of costochondral grafting resulting in ankylosis often experienced in these cases.

The role of TMJ TJR in the management of juvenile idiopathic arthritis (JIA) has not been studied.[150] Despite the many clinically successful applications of the costochondral graft, its use in children has been associated with excessive cartilaginous growth, resulting in malocclusion and facial deformity.[155-158]

Peltomäki,[159] in the marmoset, and Ellis,[160] in the monkey, studied the growth of the mandible after costochondral grafting with emphasis on the amount of cartilage included in the graft. Peltomäki found that depending on the amount of cartilage in the unilateral costochondral graft, the mandible shifted toward the nonoperated side. This occurred during the entire period of growth, which the authors concluded indicated a strong hormonal influence.

Ellis compared the use of sternoclavicular grafts to costochondral grafts and concluded that both behaved similarly with regard to growth/over-growth in the monkey. Ellis suggested that in growing patients, maintenance of biomechanical architecture and reasonably normal function may be more important than the nature of the autogenous graft used for condylar replacement. Further, Ellis recommended



• **Figure 43-12** Rheumatoid arthritis. Bilateral patient-fitted alloplastic TMJ reconstruction. **A,** Preoperative. **B,** Postoperative.

retaining as little cartilage as possible to prevent over-growth when replacing the mandibular condyle with a costochondral graft in growing individuals.

In light of the data supporting the reports by Frietas,[144] Mehra,[145] Saeed et al.,[161,162] and the orthopedic experience in other synovial joints,[148,149] it appears that autogenous costochondral grafting should be re-evaluated for use in adult patients afflicted with low- and high-inflammatory TMJ arthritis requiring TMJ replacement.

Recurrent Fibrosis and/or Bony Ankylosis

The traditional management of complete bony TMJ ankylosis has been gap arthroplasty with autogenous tissue graft replacement or alloplastic hemiarthroplasty. While the autogenous grafting techniques can lead to improved mandibular function and form, function is delayed due to the healing process required. Since graft micromotion during healing will jeopardize its incorporation into the host environment by compromising neovascularization, early mandibular mobility often leads to graft/host interface failure. Matsuura[163] reported a high incidence of failure and ankylosis of autogenous TMJ costochondral grafts in sheep after condylectomy if the jaws were only partially immobilized.

Saeed and Kent[164] reported a high incidence of re-ankylosis in patients with ankylosis who underwent TMJ autogenous costochondral replacement. They advised caution when employing this technique for ankylosis cases. For the patient with re-ankylosis, placing autogenous bone into an area where reactive or heterotopic ossification has occurred intuitively makes no sense. In similar situations in other joints, orthopedic surgeons will opt for total alloplastic joint replacement.[148,149]

In light of the biologic facts and the orthopedic experience, TMJ TJR should be considered in the management of recurrent fibrosis and bony ankylosis of the TMJ (Figure 43-13, Table 43-1).

Failed Tissue Grafts

The success of any autogenous tissue graft requires a rich vascular bed at the recipient site. Scar tissue that inevitably develops around the TMJ in the multiply operated patient does not provide an environment conducive to the predictable success of an autogenous tissue graft. Marx reports that capillaries can penetrate a maximum thickness of 180 to 220 μm of tissue, whereas scar tissue surrounding previously operated bone averages 440 μm in thickness.[165] This fact may account for the clinical observation that free, non-vascularized autogenous tissue grafts, such as cartilage, costochondral, and sternoclavicular grafts, often fail in the case of the multiply operated patient or those patients with severe anatomic architectural discrepancies resulting from pathology (e.g., failed autogenous materials).

Reitzik[166] reported, in an analogous situation to autogenous costochondral grafting, cortex-to-cortex healing after vertical ramus osteotomy in monkeys required 20 weeks and probably 25 weeks in humans. Typically in patients reconstructed with costochondral grafts, maxillo-mandibular fixation is maintained for only 4 to 6 weeks to prevent ankylosis. Despite screw/plate fixation, micromotion of these non-vascularized free grafts will invariably occur after this short period of immobilization based on Reitzik's work. Early mandibular function results in shear movements of the graft that lead to poor neovascularization, nonunion, and/or failure.[167] This, along with the compromise in vascularity discussed previously undoubtedly accounts for autogenous costochondral graft failures. Therefore, in light of the fundamental biologic and mechanical issues discussed, TMJ cases involving multiply operated patients—especially those exposed to failed autogenous tissue grafts and/or those with anatomically distorted and severe intra-articular end-stage pathology—should be managed with TMJ TJR devices to achieve optimal functional and esthetic outcomes (Figure 43-14).

Failed Alloplastic Materials

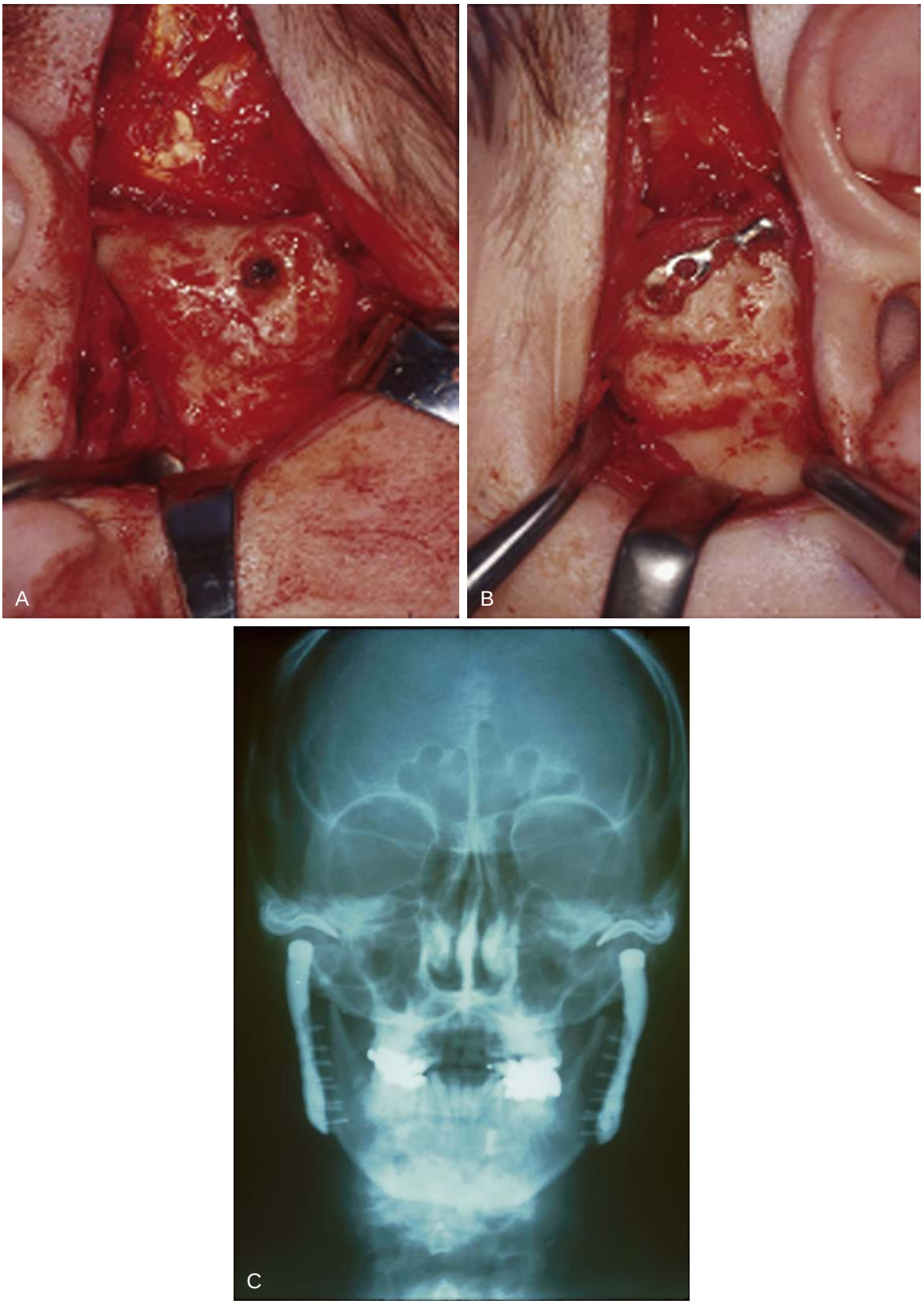
As a result of the osteolysis around failed TMJ replacement alloplasts and the resultant host bone architectural discrepancies, it is difficult to adapt and fixate replacement TMJ TJR devices stably to the bony remnants of either the fossa or the ramus. As discussed above, the foreign body giant cell reactions associated with failed or failing devices provide a poor vascular environment into which to introduce an autogenous graft.[66]

Mercuri and Giobbe-Hurder[131] discussed this issue at length in a report where they evaluated long-term outcomes with TMJ TJR in patients with prior exposure to failed Proplast-Teflon and/or silicone rubber. They found that the TMJ TJR devices remained functional long-term (60.2 months mean), but that patients exposed to failed materials had lower subjective domain improvement scores (pain, appropriate to replace TMJs affected by prior failed alloplasts with TMJ TJR devices rather than autogenous tissues (Figure 43-15).

Orthopedists and biomedical engineers have been studying the effect of failed and failing devices on the long-term outcomes of future implanted alloplastic devices. There is now evidence that failure of a prior implanted device in some patients results in a cell-mediated immune response that bodes poorly for the outcomes of any future implanted alloplast.[168-171]

Loss of Vertical Mandibular Height and/or Occlusal Relationship

Loss of TMJ bone stock leading to decreased posterior mandibular vertical dimension is caused by developmental abnormalities, pathology, or traumatic injury. This condition results in maxillomandibular form and function discrepancies. These situations should be managed

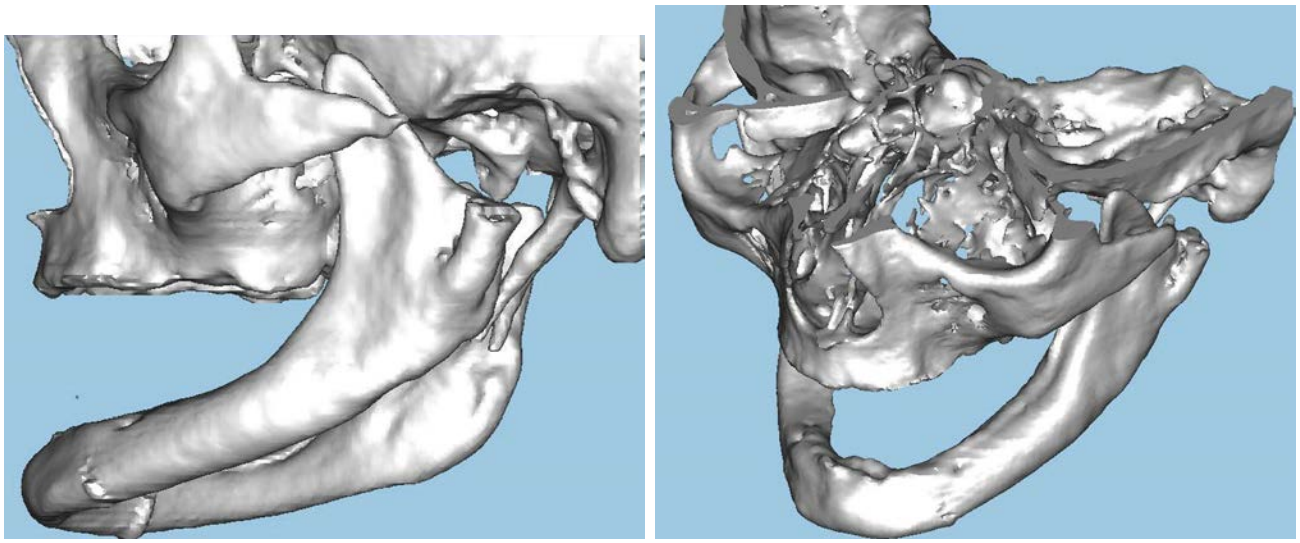


• **Figure 43-13** Bilateral TMJ ankylosis. **A,** Preoperative right TMJ. **B,** Preoperative left TMJ with embedded fossa-eminence device. **C,** Postoperative bilateral patient-fitted alloplastic TMJ reconstruction.

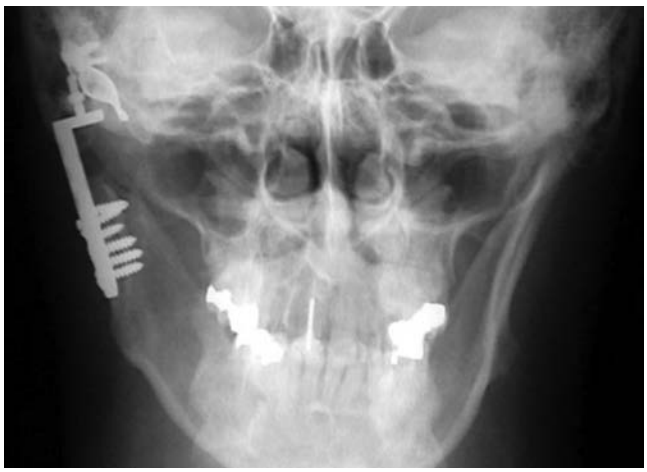
TABLE 43-1 Indications for the Use of Various Modalities for TMJ Replacement

	Autogenous	Alloplast	Distraction*	Bio-engineered*
Inflammatory arthritis		+++		
Ankylosis		+++	+	++
Failed autogenous graft		+++		++
Failed alloplast		+++		
Loss of vertical height	+†	+++	+†	++*

*Future potential after further in vitro and in vivo studies.
†Growing children.



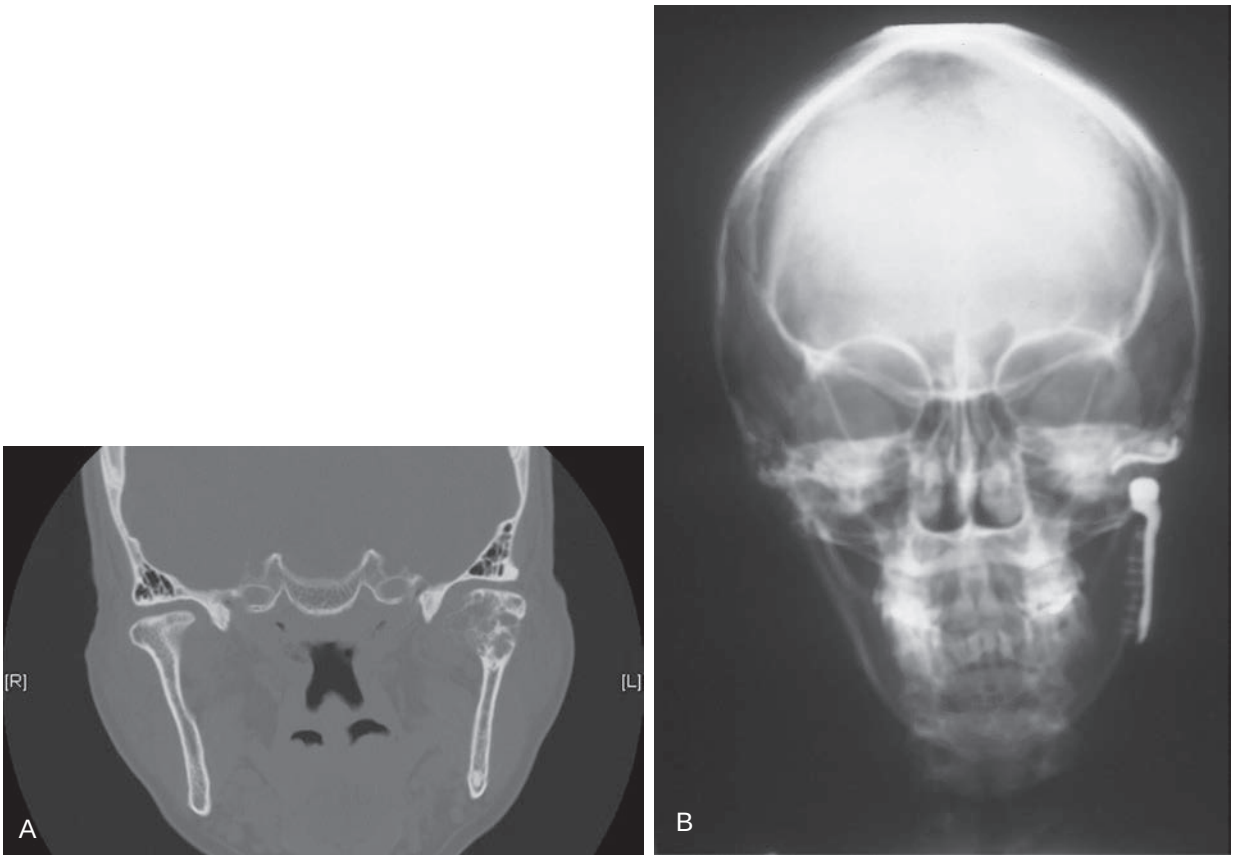
• **Figure 43-14** Preoperative CT images of a failed costochondral graft, left TMJ, in an edentulous patient who had been exposed to failed Proplast-Teflon. Note the destruction of the left temporal process of the zygoma and glenoid fossa.



• **Figure 43-15** Failed alloplastic TMJ reconstruction caused by the inability of a stock device to accommodate the lateral flare of the mandibular ramus. Note the resultant fracture/displacement of the vitallium fossa and lateral displacement of the polyethylene condylar component.

by identifying the etiology of the problem and correcting it at the site directly affected by the pathology. In the case of a primary TMJ etiology (i.e., high-inflammatory arthritis, benign neoplasia), TMJ TJR rather than osteotomy should be considered. The surgeon must understand the nature of the pathology leading to the loss of vertical mandibular height, the patient's prior local surgical history, and the state of the host bone architecture before deciding on the type of TMJ replacement best suited to the situation (Figure 43-16).

Further, there is always a component of counterclockwise mandibular rotation in the surgical management of loss or posterior mandibular vertical height. Expecting a free, non-vascularized autogenous costochondral graft, or end-stage disease affected compromised condyloid process remnant to withstand functional loading forces generated after orthognathic surgery or distraction is fraught with the relapse potential.[172] The long-term stability using patient-fitted TMJ TJR in such cases is well documented.[173-176]



• **Figure 43-16** **A,** Low-grade fibrosarcoma of the left TMJ, preoperative. **B,** Patient-fitted alloplastic reconstruction of the left TMJ, postoperative.

The Skeletally Immature Patient

Theoretically, in growing patients, autogenous costochondral grafts will "grow with the patient." However, the growth potential of costochondral grafts used to replace the TMJ in growing patients has been reported to be unpredictable or result in ankylosis. Either or both can occur as the consequence of graft and/or fixation failure or the uncooperative nature of the young patient with regard to the rigorous physical therapy required after surgery.[139,177-180] Some studies have even questioned the necessity for using a cartilaginous graft to restore and maintain mandibular growth.[15,160]

Long-term reports of mandibular growth in children who underwent autogenous costochondral TMJ TJR reveal that excessive growth on the treated side occurred in 54% of the 72 cases examined and growth equal to that on the opposite side occurred in only 38% of the cases.[140,181-185] Furthermore, Peltomäki et al., in an investigation of mandibular growth after CCG, supported previous experiments with regard to the inability of the graft to adapt to the growth velocity of the new environment.[159, 186-187]

Reported unreliability of autogenous costochondral TMJ TJR in children includes graft failure, unpredictable growth, ankylosis, and potential for donor-site morbidity. On the basis of the orthopedic experience and success reported with alloplastic TJR in improving the quality of life of growing patients with severe anatomic and functional joint disorders,[188] it seems reasonable to consider alloplastic TMJ TJR for the following conditions in children:

1. High-inflammatory TMJ arthritis unresponsive to other modalities of treatment
2. Recurrent fibrosis and/or bony ankylosis unresponsive to other modalities of treatment
3. Failed tissue grafts (bone and soft tissue)
4. Loss of vertical mandibular height and/or occlusal relationship because of bony resorption, trauma, developmental abnormalities, or pathologic lesions

To continue to re-operate children with failed, overgrown, or ankylosed costochondral grafts employing the same autogenous tissues that failed when there may be an appropriate solution available seems myopic. These patients would be better managed with TMJ TJR devices understanding that, depending on growth, revision and/or replacement surgery may be required in the future. This would appear to be a sounder option rather than incurring continued autogenous tissue failures that will also very likely require future surgical intervention.[188]

Future Considerations

Distraction Osteogenesis

Distraction osteogenesis, which induces new bone formation along the vector of pull without the use of a bone

graft, has been employed as a reconstruction method for mandibular defects.[189-191] Stucki-McCormick et al.[192,193] reported the application of transfer osteogenesis to reconstruct the mandibular condyle in two patients. Cavaliere et al.[194] reported using similar methods to manage hemifacial microsomia patients with 1- and 2-year follow-up. The long-term growth potential for the use of this modality in the reconstruction of prepubescent cases also has yet to be determined.

Despite the short-term promising clinical results, the histomorphologic changes in the associated joint structures (i.e., cartilage, disc, and masticatory musculature) have not been elucidated completely. Experimental studies with rabbits and monkeys addressing this issue are appearing in the literature.[195,196]

Based on their animal experiments, Hu et al.[196] list several potential advantages of mandibular condyle reconstruction using transport distraction over conventional autogenous bone grafting:

1. Donor site morbidity is avoided.
2. The rigid distraction device allows for immediate postoperative physical therapy, which allows for the formation of a pseudo-arthrosis and prevents ankylosis.
3. The risk of bone graft necrosis and resorption is greatly reduced compared to non-vascularized free bone grafts

However, these experimental studies were carried out in animals with normal temporomandibular joints, and extrapolation of these data to patients with compromised temporomandibular joint anatomy caused by prior surgery or pathology remains a question and concern when using this technique.

Tissue Engineering

Mandibular condyle tissue engineering has been proposed to address limitations of both autogenous and alloplastic reconstructions.[197] A tissue-engineering strategy would incorporate a biodegradable scaffold delivering biologics such as cells, genes, and/or proteins to regenerate the bone/cartilage tissues of the mandibular condyle. Tissue engineering could be applied to regenerate localized defects or, theoretically, the entire articulating condylar surface. Implementation could take one of three approaches: (1) ex vivo growth of tissue on the scaffold/biologic composite in a bioreactor before implantation on the mandible, (2) implantation of the scaffold/biologic composite at a secondary surgical site before implantation on the mandible, and (3) direct implantation at the mandible site.[198]

While this modality holds the potential to revolutionize TMJ reconstruction in the future, there are many biologic, physiologic, mechanical, regulatory, and ethical issues that must be tested and addressed before it becomes a reality.

Summary

At the present time, based on the available published clinical data, TMJ TJR appears to provide the most predictable functional and esthetic outcomes for patients with end-stage low- and high-inflammatory TMJ arthritis, re-ankylosis, failed alloplastic TMJ replacements, and loss of posterior mandibular vertical dimension.[199-200]

Soft tissue (temporalis muscle) appears to have limited use in TMJ replacement surgery as an interpositional material in the initial management of ankylosis.

Osteodistraction may supplant autogenous bone grafting in the future as more long-term studies are reported. Tissue-engineered TMJ replacement, while still in its infancy, may ultimately provide an answer for TMJ cases in the future. However, both osteodistraction and tissue engineered TMJ replacements suffer from the same local and systemic biologic and pathologic issues as autogenous tissue grafting discussed above.

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Chronic Facial Pain: Evaluation, Differential Diagnosis, and Management Strategies

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Introduction

According to the National Health Interview Survey (NHIS) conducted by the Centers for Disease Control and Prevention (CDC) in 2005, approximately 7% of Americans suffer from facial pain each year.[1] The term facial pain may be used to describe any unpleasant, annoying, or descriptive sensation in the facial region, including those emanating from the oral cavity, dentition, maxilla, mandible, sinus, orbital, cranial, and nasal regions of the head and neck. While it is clear that facial pain is mediated primarily by nerve fibers of trigeminal nerve origin, other sensory nerves and nerve fibers may also play a role in facial pain transmission. In order to understand facial pain, one must first understand the neurophysiology of pain: from the release of pain-producing neurotransmitters and the interaction with receptors on peripheral nerve fibers innervating head and neck structures to the complex cortical reorganization and processing that occurs in chronic pain. This chapter will highlight the key neurophysiologic mechanisms that underlie both acute and chronic facial pain entities.

Chronic facial pain is one of the most challenging entities for a clinician to diagnose and treat. It is usually of greater than 6 months' duration, unrelenting, and recalcitrant to conventional modes of pharmacotherapy and/or surgical intervention.[2] The chronic pain patient who relies on chronic opioid therapy poses a particular challenge to the oral and maxillofacial surgeon from an intraoperative and postoperative pain management standpoint. This chapter will discuss differential diagnoses of chronic facial pain, treatment recommendations, and barriers that currently exist for the management of the chronic facial pain patient. Identifying the barriers and eliminating them through discussions with the patient and health care providers will allow for effective pain management and abolition of biases that currently affect many chronic pain sufferers.

Facial pain, like other types of pain, can be complex and multidimensional and therefore clinical evaluation becomes an important aspect in the diagnosis of the facial pain patient. Many clinical specialties play a role in the diagnosis and management of facial pain. These include anesthesiologists, dentists, endodontists, oral and maxillofacial surgeons, facial pain experts, otolaryngologists, neurologists, neurosurgeons, physical therapists, psychiatrists, psychologists, and chemical dependency physicians. In complex cases of facial pain, a team approach is usually taken, resulting in improved therapeutic outcomes.[3] With an understanding of the complex neurophysiology that exists in the facial pain patient, an idea of how to delineate the correct facial pain diagnosis, and an understanding of the alternative treatment modalities that currently exist, the clinician will be enabled to manage one of the most complex and challenging pathologic entities—a patient with chronic facial pain.

Neurophysiology of Pain

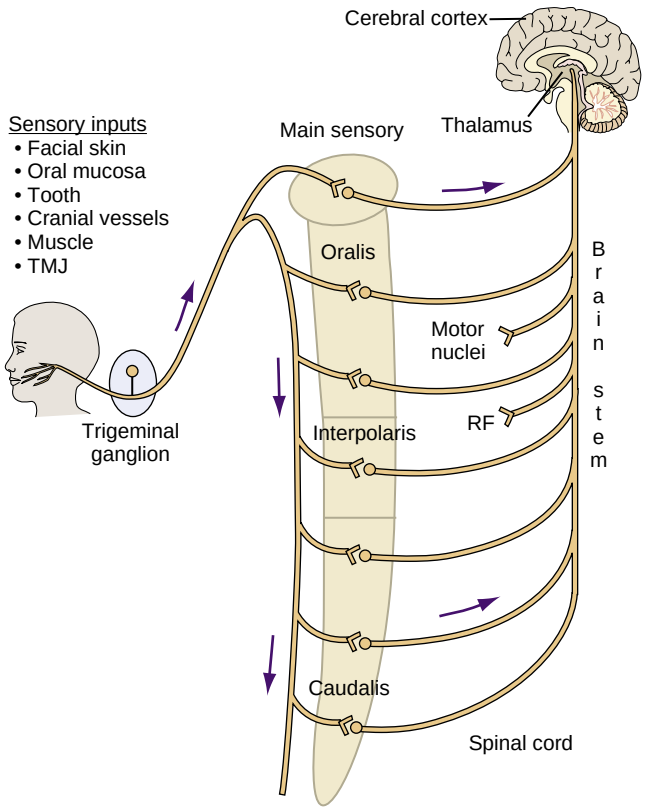
Trigeminal Anatomy

A thorough understanding of neuroanatomy and neurophysiology is imperative to fully appreciate the complex nature of facial pain. While it is clear that other sensory fibers are important in the transmission of painful information from the head and neck (e.g., cervical spinal nerves, sympathetic fibers), the majority of pain in the head and neck is transmitted via branches of the fifth cranial nerve—the trigeminal nerve. The trigeminal nerve is considered the largest of the cranial nerves. The primary sensory neurons (also known as first-order neurons) of the trigeminal nerve are located within the largest ganglia in the human body—the trigeminal ganglia. The trigeminal ganglia are

carotid artery and cavernous sinus. It is considered a bipolar neuron in that its primary afferent (peripheral nerve) fibers terminate within the head and neck while its central fibers terminate within the medullary dorsal horn and cervical spinal cord. Its extensive distribution highlights the amount of sensory input the head and neck receives.

The trigeminal sensory fibers synapse with second-order neurons located within the spinal trigeminal nuclear complex. The trigeminal brainstem nuclear complex is subdivided into the (1) chief main sensory nucleus, (2) spinal trigeminal nucleus oralis, (3) spinal trigeminal nucleus interpolaris, and (4) spinal trigeminal nucleus caudalis. The spinal trigeminal nucleus caudalis has been implicated as the main nucleus that receives painful or nociceptive input from peripheral targets. There is a significant convergence of non–trigeminal nerve fibers arising from the cervical spine and vagus and glossopharyngeal nerve terminals onto trigeminal nuclei. The large convergence of cranial and spinal nerves explains the presence of referred pain to non–head and neck structures in the facial pain patient.

Neurons within the spinal trigeminal sensory nuclear complex project to higher brain centers such as the *thalamus* and *reticular formation.* The pathways are known as the trigeminothalamic and trigeminoreticular tracts, respectively, and they project to higher-order neurons located within the somatosensory cortex and anterior cingulated cortex. The processing of both discriminative (quality, severity, and location) and affective (emotional) components of pain occurs at these cortical levels[4] (Figure 44-1).



• **Figure 44-1** Trigeminal nerve pain pathway. Pain information within the head and neck is transmitted via the branches of the trigeminal nerve (cranial nerve V), whose sensory neurons are located in the trigeminal ganglion. Information is further processed as it courses through second-order neurons in the spinal trigeminal nuclear complex within the brainstem, thalamus, and cerebral cortex. (From Sessle BJ: Acute and chronic craniofacial pain: brainstem mechanisms of nociceptive transmission and neuroplasticity, and their clinical correlates, *Crit Rev Oral Biol Med* 11(1):57-92, 2000.)

Peripheral Mechanisms of Pain

Considerable advances have been made in the past 2 decades in identifying cellular and molecular mechanisms involved in facial pain transmission. Injury to peripheral tissues certainly occurs during oral and maxillofacial surgical procedures. Pain generally occurs during tissue damage and is a result of release of neurotransmitters, cytokines, and factors from damaged cells, adjacent blood vessels, and nerve terminals. Prostaglandins, substance P, calcitonin gene–related peptide (CGRP), bradykinins, histamine, interleukin-1 and interleukin-6, and serotonin are examples of proinflammatory mediators that are involved in the generation of the inflammatory state that accompanies tissue destruction.[5-7]

tures that detect a diversity of chemical and thermal stimuli (Figure 44-2). During minor tissue damage, proinflamma-

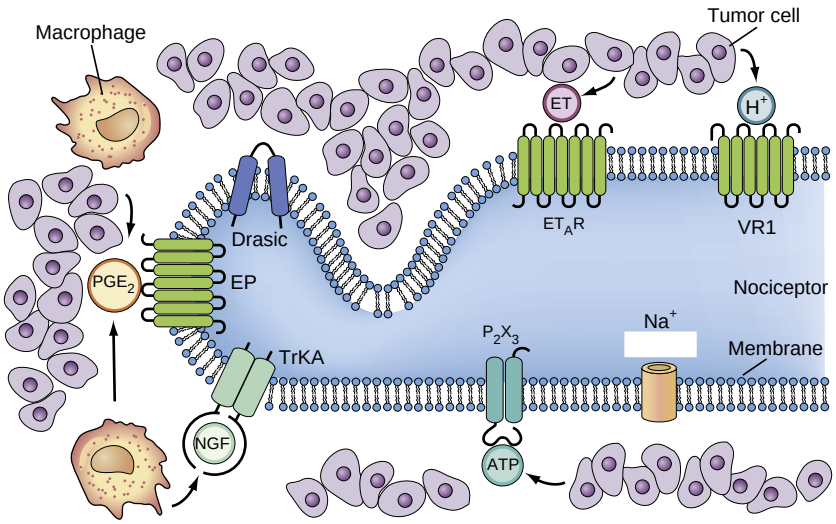
nerve becomes sensitized because of constant stimulation and

ously silent pain receptors or nociceptors.[8-9]

Neurophysiology of Peripheral Nerve Fibers

myelinated and have fast conduction velocities (35-120 m/sec). These fibers transmit mechanosensory information and have specialized terminals called Meissner's, Pacinian, Merkel's, and Ruffini's corpuscles located within skin.[10] Although this fiber type does not transmit painful information, current studies have now demonstrated their role in chronic pain states. Nerve fibers that transmit pain and thermal information are known as A delta and C fibers and are lightly myelinated and unmyelinated, respectively. The A delta (Aδ) fibers have relatively fast conduction velocities (5-30 m/sec) when compared to C fibers (0.5-2 m/sec). Both Aδ and C fibers terminate in skin, bone, muscle, and joints as free nerve endings.

Peripheral nerve fibers that innervate the head and neck arise from the ophthalmic (V1), maxillary (V2), and mandibular (V3) divisions of the trigeminal nerve (cranial nerve V [CN V]) as well as cutaneous inputs from cervical spinal nerves as far caudal as spinal C7.[4,11] The extensive rostrocaudal input of painful information from the head



• **Figure 44-2** Interaction between inflammatory mediators and receptors. Schematic diagram of a inflammatory mediators and their cognate receptor results in pain transduction and signaling. (From Mantyh PW, Clohisy DR, Koltzenburg M, et al: Molecular mechanisms of cancer pain, *Nature Rev Cancer* 2(3):201-209, 2002.)

and neck as well as significant convergence of input from other cranial and spinal nerves (e.g., CN X, CN XII, cervical spinal nerves) may in part explain the referral patterns in the chronic pain patient.[12]

Central Mechanisms of Pain

Centrally mediated pain is defined as pain initiated or caused by a primary lesion or dysfunction in the central nervous system. While it is rare in practice to see patients with primary CNS lesions, it is not uncommon for chronic facial pain patients to be first evaluated by an oral and maxillofacial surgeon. The primary mechanism for chronic pain lies in neuroplastic changes that occur within the central nervous system in response to chronic painful stimuli.[13] Much of the research in central pain mechanisms is related to other chronic pain conditions such as traumatic neuropathy and diabetic neuropathy in both animal and human models.[14] Certainly animal models of chronic facial pain exist that have increased our understanding of the pathophysiology of centrally mediated chronic facial pain.[4]

Central Sensitization

Central sensitization refers to the heightened reactivity of central nervous system neurons in the face of sustained peripheral neural input. While this may occur within the thalamus and cortex, research has been primarily focused on the dorsal horn of the spinal cord. Electrophysiologic and anatomic studies have demonstrated a change in the activity and responsiveness of dorsal horn neurons in response to persistent painful stimulation.

Persistent stimulation of unmyelinated C fibers results in the increased activity and responsiveness of spinal neurons that receive input from the stimulated unmyelinated C fiber. This increased responsiveness is of short (10 sec) duration and is known as *wind up*. Sensitization can also occur when persistent stimulation results in phenotypic changes in neurons that do not receive persistent painful stimulation, but are adjacent to neurons that do receive painful input. Typically these neurons receive input from Aβ fibers that normally do not transmit painful stimuli. However, once sensitized, these neurons are capable of transmitting both nonpainful and painful information. Central sensitization is

EP, and tyrosine kinase B (trkB), respectively. Upregula-

(allodynia) may result from central sensitization.[4,13]

Descending Inhibitory Control

A protective mechanism exists in which adrenergic and serotoninergic fibers arising from the hypothalamus and periaqueductal gray matter descend and terminate in the medulla and superficial dorsal horn. This descending pathway controls or dampens painful sensory input from primary afferent fibers arising from the periphery. Chemical denervation of the inhibitory pathway results in an increased response to a stimulus that is normally painful (hyperalgesia). Inhibitory receptors have also been shown to be reduced in animal models of chronic pain. Thus disruption of inhibitory pathways that are normally tonically active may also result in chronic pain.[15]

The constant barrage of neurochemicals that are implicated in pain transmission results in changes in the activity and phenotype of nerve fibers and neurons within the

peripheral and central nervous system. These changes result in a chronic and debilitating condition that is recalcitrant to many conventional modes of acute pain therapy. The chronic pain patient has a "pain portrait" that is distinct from the acute pain patient and its management reflects this difference. However, not all chronic facial pain entities are alike. Diagnosis of the facial pain patient requires meticulous investigation and educated elimination of other pain entities.

Evaluation of the Facial Pain Patient

The chronic facial pain patient poses one of the most challenging cases to the oral and maxillofacial surgeon. One major reason is because pain is primarily subjective in nature. It is difficult to measure pain objectively because it cannot be seen nor is it palpable on clinical exam. The clinician is required to gather clinical and historical information, formulate a list of differential diagnoses, and systematically eliminate least likely entities until a final diagnosis is achieved. To formulate a list of differential diagnoses assumes that the most common and simplest forms of pain have been eliminated. A thorough assessment of the patient's history of present illness can be obtained by asking pointed questions that may identify the etiology or etiologies of the patient's facial pain. Questions regarding incidence, character, and duration as well as treatment modalities—particularly those that have already been employed to treat the pain—may also assist in the diagnosis of facial pain. The key to successful diagnosis of the chronic facial pain patient lies in comprehensive and accurate inquiry aimed to identify and answer key questions to develop a list of differential diagnoses.

Chief Complaint

The patient's chief complaint should always be documented in his/her own words with the use of parentheses. The severity of the patient's pain at time of examination must be documented. The two most frequently used methods to assess pain intensity are the visual analogue scale (VAS) and the numeric pain rating scale (NPRS). In the VAS the patient marks a line to indicate pain severity which will be measured in centimeters from 0 (no pain) to the patient marked rating on a horizontal or vertical 10-cm line.[16] The NPRS is different in that the patient verbalizes a number corresponding to the extent of his/her pain: 0 is no pain and 10 is the worst pain imaginable.

History of Present Illness

Pain onset and duration are important to determine whether the onset was acute in nature or developed gradually over time. This is a particularly challenging task with most facial pain patients. In general, there is an association made with an event, procedure, or circumstance that may not have a role in the generation of the symptoms. If the facial pain is acute, one must further question the events surrounding its onset. If the facial pain is chronic, one must further question acceleration and remission periods. A history of previous surgical and nonsurgical therapies to treat facial pain must also be elucidated to establish a diagnosis, assess prognosis, and define a surgical plan if indicated.

The location, quality, character, and radiation of pain should be assessed in the facial pain patient. Diffuse or localized pain will identify whether the pain is isolated to a single anatomic entity or whether multiple structures are involved. The patient must be asked to indicate, by one finger pointing to the area, where the pain is most severe. Descriptions of pain character such as "dull and throbbing" or "sharp and stabbing" will help to identify what dominant peripheral nerve fiber type is involved, which will assist in determining type of facial pain entity. Facial pain may radiate or be referred to adjacent muscular structures and the forehead, sometimes suggesting generalized myofascial pain disorder.

The pain impact on the patient's sleeping, function, and quality of life is very significant for numerous reasons. Sleep disturbance may imply an acute dental condition such as irreversible pulpitis or acute dentoalveolar abscess.[17] Sleep disturbance may result in generalized muscle pain, reduced pain thresholds, and reduced coping ability. Sleeping and daily function can influence treatment protocols and prognosis.[17]

The patient should be asked about analgesics used in attempts to alleviate facial pain and whether these analgesics are efficacious. The chronic use of opioids, spasmolytics, and antidepressants to manage facial pain is typically seen in patients with a preexisting diagnosis of chronic facial pain. Questions should be directed towards identifying therapies or medications that relieve pain. For example, if nonsteroidal anti-inflammatory drugs and heat packs relieve pain, the patient likely suffers from mild inflammation of the muscle and/or joint. Habits should also be assessed to determine if the etiology of facial pain arises from parafunctional habits such as repetitive jaw motion or extreme jaw forces from gum chewing or clenching, respectively.

Past Medical History Related to the Facial Pain Patient

The review of a patient's medical history is always important; however, it is clear that certain systemic conditions are commonly observed in the chronic facial pain patient. It is important to determine whether anxiety, depression, and/or other psychogenic disorders are present and appropriately managed. Clearly, facial pain patients with concomitant depression derive benefit from antidepressant medication. Fibromyalgia is another chronic pain entity that affects 4% of Americans. It is generally associated with diffuse generalized pain and fatigue and occurs in approximately 15% to 20% of facial pain patients.[12] Other systemic disorders that are commonly observed in the chronic facial pain patient include autoimmune diseases such as osteoarthritis, rheumatoid arthritis, and

migraine symptoms and headaches.[18] The concomitant comorbidities of systemic disease and chronic facial pain add to the complexity of the diagnosis and management of this challenging condition.

Clinical Examination

A thorough dental examination must be performed to rule out odontogenic sources of pain and avoid unnecessary dental treatments (Figure 44-3). In most clinical practice, the referring general dentist or clinician will have diagnosed the most common entities that cause pain: dental caries and infection. Facial pain may be referred from teeth and/or supportive structures and therefore pathology associated with such structures must be ruled out.

The most common and frequently seen pathology that results in facial pain includes the following:

- Tooth fractures
- Caries
- Temporomandibular disorders (TMDs)
- Salivary gland disease
- Ulcers
- Infection
- Neoplasms

Although the clinical examination and radiologic findings associated with these pathologies are beyond the scope of this chapter, it is important to exclude these entities to obtain the diagnosis of chronic facial pain. In addition, patients with no observable etiology of facial pain cannot be dismissed as hypochondriacs. Some insidious neoplasms, both benign and malignant, develop slowly. Pain may be the first sign that a neoplasm is present before progressing to a size that is detectable by either clinical evaluation or imaging.

The clinical examination of the chronic facial pain patient is very challenging because there is no visible entity that can easily be seen or felt. Instead, the clinical examination should focus on the following aspects to derive a list of differential diagnoses:

- Location
  - Identify etiology of pain by location (sensory nerve innervation).
  - Does the pain arise from dental, gingival, dentoalveolar or other structures?
  - Does the pain arise from stimulation of a specific sensory nerve distribution?
  - Is the pain limited to a specific sensory distribution?
  - Does the pain radiate to other structures within or beyond the head and neck?
  - Do the involved structures demonstrate abnormalities in color, temperature, turgor, or sensation?
- Duration
  - Identify whether the pain is intermittent or constant.
  - If evoked, identify the type of stimuli that causes the pain.
  - Is the pain sharp and stabbing when stimulated?
  - Is the pain reproducible and consistent?
  - Does the pain spontaneously resolve?
- Character
  - Identify the general pain sensation.
  - Is the pain sharp, dull, or lancinating?
  - Is the pain a burning sensation?
  - Are there any sensations other than pain that coexist (for example, tingling, numbness, formication)?
- Presence of sensory or motor deficits
  - Quantitative clinical neurosensory testing must be performed for all patients with documented sensory deficits.[19]



• **Figure 44-3** Panoramic radiograph of a facial pain patient who underwent multiple root canal therapies to treat her facial pain. Following referral to an appropriate facial pain specialist, the patient was properly diagnosed and medically managed. (Courtesy Donald Nixdorf, University of Minnesota.)

- Level A testing assesses spatiotemporal sensory discrimination using two methods: brush stroke directional testing and two-point discrimination. Both methods assess the discriminatory competency of myelinated Aβ fibers.
- Level B testing assesses static sensory discrimination using Semmes-Weinstein nylon monofilaments of graded thicknesses. Electronic versions are available.
- Level C testing assesses sharp-dull discrimination and pain thresholds. Specialized equipment such as calibrated thermodes or pain algometers is available although a sharp instrument (e.g., needle) may be used. This level of testing assesses the competency of unmyelinated C fibers and lightly myelinated Aδ fibers.
- Responses to interventions
- Are there any modalities, activities or action that reduces or eliminates the pain?
- Is the pain diminished, changed or resolved by pharmacologic agents, including over the counter interventions, opioids, or other analgesics?

Pain Descriptors

A sensory map should be developed based on the clinical neurosensory examination. In unilateral cases, both sides

now be described using conventional pain terminology (Table 44-1). Following the patient interview and clinical examination, the clinician is now able to describe the facial pain entity. Utilization of appropriate terminology will improve communication between health care professionals, assist in formulating a list of differential diagnoses, and assess the progress of both the pain condition and the treatment rendered.

Imaging Modalities

Appropriate imaging studies may be necessary to allow the clinician to derive a list of differential diagnoses and exclude certain conditions. Depending on the source, character, and complexity of pain, multiple imaging modalities may be considered. While it is appropriate to consider imaging studies, chronic facial pain is difficult to diagnose with imaging studies as there is a lack of definitive abnormalities that are characteristic or pathognomonic for facial pain.[20]

- Orthopantomogram: The orthopantomogram is the most common screening film used in the oral and maxillofacial surgery practice. It is both economical and practical in its use and provides minimum radiation exposure to the patient. Additionally, patients often have panoramic radiographs that predate the consultation visit or date of onset of pain that can be used as a reference or baseline image. While panoramic imaging may not establish the clinical diagnosis, it has its utility as a screening tool before requesting more advanced imaging.[21]

TABLE 44-1 Pain Definitions

Type of Pain	Definition
Allodynia	Pain evoked with stimulus that normally does not provoke pain
Analgesia	Absence of pain in response to stimulation that would normally be painful
Causalgia	A syndrome of sustained burning pain, allodynia, and hyperpathia after a traumatic nerve lesion, often combined with vasomotor and sudomotor dysfunction and later trophic changes
Dysesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked
Hyperesthesia	Increased sensitivity to stimulation
Hypoesthesia	Diminished sensitivity to stimulation
Hyperalgesia	Increased pain from a stimulus that normally provokes pain
Hypoalgesia	Diminished pain in response to a normally painful stimulus
Hyperpathia	A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold
Neuralgia	Pain in distribution of nerve or nerves
Neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system
Neuropathy	A disturbance of function or pathologic change in a nerve: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, polyneuropathy
Paresthesia	An abnormal sensation, whether spontaneous or evoked

From Merskey H, Bogduk N, editors: IASP Task Force on Taxonomy. In *Classification of chronic pain,* ed 2, Seattle, 1994, IASP Press, pp 209-214.

- Computed tomographic (CT) imaging including cone beam CT scans (CBCT): Although CT imaging is not a standard modality for chronic pain, newer techniques that use CT technology are being used for facial pain patients. CT imaging is useful mostly to evaluate the bony elements of the TMJ. 3D CT and a stereolithography model fabrication are crucial in the processing of planning complex reconstructive surgeries.
- The role of single photon emission computed tomography with technetium 99m methylene diphosphonate (SPECT with 99mTc-MDP) and computed tomography (CT) to diagnose facial pain has been reported.[22] This technology uses radiolabeled technetium to identify areas of increased bone metabolism and uses diphosphonates, which display strong affinity to hydroxylapatite crystals within bone. Using SPECT technology, data are acquired in all three planes (axial, coronal, and sagittal planes) to allow for three-dimensional mapping. When used in conjunction with conventional CT data, functional anatomic mapping is obtained, which allows for 3D rendering. Advantages include (1) low radiation requirements (0.00675 Gy per 70-kg adult) and (2) high sensitivity. Disadvantages include (1) the need for specialized equipment and staff, (2) cost, and (3) poor specificity. SPECT in conjunction with CT is currently being used in oncology as a surveillance tool.
- Magnetic resonance imaging (MRI): Clinical evaluation of the TMJ is a detailed evaluation of the anatomy as well as biomechanics of the joint through open and closed mouth imaging.[23] It is also used as a tool to eliminate any intracranial lesion that can mimic craniofacial pain symptoms.
- Functional magnetic resonance imaging (fMRI) is an indirect method used to assess neural activity within the central nervous system. It utilizes the BOLD effect, or changes in blood oxygenation, by quantifying the relative concentrations of oxyhemoglobin and deoxyhemoglobin. An increase in blood flow and, hence, neural activity results in a decrease in deoxyhemoglobin level. These changes are then mapped onto previously obtained anatomic maps of the patient's brain. Functional MRI has been used in studies of headache, acute dental pain, trigeminal neuropathy, and atypical facial pain to examine areas within the cortex that are involved in pain processing.[20,24] Both discriminative and affective components of pain have been mapped to the somatosensory cortex and anterior cingulate cortex, respectively, based on fMRI studies. While its utility in examining treatment success has been reported, its diagnostic capabilities remain limited because of a relative paucity of neuroimaging studies on trigeminal pain pathways.[24]

Differential Diagnosis

After establishing the character, duration, quantity, and quality of the facial pain entity, the clinician must eliminate more common facial pain causation or etiology. Then, augmenting information gleaned from the patient interview and exam with appropriate imaging modalities, the clinician is able to derive a list of differential diagnoses of chronic facial pain entities. While the differential diagnoses are only a partial listing of all chronic facial pain states, these are the most commonly encountered and the most challenging to diagnose.

Complex Regional Pain Syndrome (CRPS)

Complex regional pain syndrome (CRPS) is a pathology that has been described as occurring almost always in an appendage. However, there are patients in whom the face, head, and neck are affected. Very few patients were found to meet the International Association for the Study of Pain criteria for this disease. The clinical characteristics were similar to those of CRPS elsewhere in the body, with the main features being burning pain, hyperalgesia, and hyperesthesia starting after a trauma to the craniofacial region.[25] The diagnosis of CRPS is based almost exclusively on clinical examination. Two types of CRPS exist: type I or reflex sympathetic dystrophy (RSD) and type II or causalgia. Based on the 2005 consensus meeting of the International Association for the Study of Pain (IASP), the diagnosis of CRPS can be made if the following criteria are fulfilled:

- The presence of a noxious initiating event without nerve damage (type I: reflex sympathetic dystrophy) or with nerve damage (type II: causalgia)
- Spontaneous pain or hyperalgesia that is disproportionate to the inciting event and that extends beyond a single nerve territory
- Autonomic dysfunction: edema, cutaneous blood flow changes (increased or decreased), motor changes, and/or trophic changes
- All other diagnoses are excluded.

Nearly 75% of patients with CRPS type I or RSD will demonstrate pain that is described as aching, burning, or pricking in nature. Sometimes the pain can be "shooting" in character. All will describe some type of hyperalgesia to innocuous mechanical stimuli that may extend beyond the site of injury. This finding highlights the central sensitization that occurs in RSD. Muscle weakness or tremors may be observed in as high as 75% of RSD patients. Autonomic disturbances, such as edema and thermal cutaneous dysregulation, and trophic changes, such as disruptions in hair growth and skin atrophy, are seen in more severe cases of RSD.[14]

CRPS II or causalgia is distinguished from RSD if nerve damage is present. Similar to other neuropathic pain conditions, pain resulting from causalgia is described as electrical or shooting pain. Some patients may also exhibit areas of simultaneous hypoesthesia and extreme allodynia. Autonomic and motor disturbances similar to those seen in RSD are present.[26]

Management of CRPS should be aimed at reducing pain and enabling function. Pharmacologic treatment with tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), anticonvulsants, gabapentin, steroids, and opioids has been described.[27] In the head and neck region a treatment including a series of stellate ganglion anesthetic blocks was reported to have a good outcome.[25]

Neuralgia-Inducing Cavitational Osteonecrosis (NICO)

Since first described, the concept of NICO has been questioned by some clinicians.[28-30] NICO has been defined as a syndrome of chronic neuralgia-like facial pain associated with intraosseous cavity formation and long-standing cancellous bone necrosis of the jaws with minimal regenerative capabilities.[31] The pathophysiology of NICO is not clear. Multiple etiologies have been suggested including infection, bone marrow ischemia, coagulation related factors, and autoimmune concept based on antibodies to peripheral nerve myelin.[30,31] From an epidemiologic standpoint the prevalence of this condition is unknown. Patients with NICO complain of continuous or paroxysmal pain that is sharp, stabbing, burning, and lancinating in character. The location of pain is primarily at the site over the alveolar bone of a previously extracted tooth site. Symptoms have been reported to be unilateral or bilateral and involve both the maxillary and mandibular tooth-bearing areas. The symptoms may be referred to a larger area, often crossing midline structures.

Diagnosis requires a multifaceted approach that includes palpation, diagnostic anesthesia testing, radiographs, computed tomography scan, MRI (looking for chronic bone marrow ischemia), and Tc-99 scan. According to Bouquot, between 75% and 79% of patients with atypical facial neuralgia pain will demonstrated hot spots with technetium-99 scan.[28,30]

A definitive diagnosis of NICO is clinically difficult to establish and recommended treatment is moderately invasive. Treatment of NICO lesions has been primarily debridement of cavitary lesions with removal of cortical bone and exploration of medullary bone until "bone cavities" are identified. Long-term management includes either gauze-impregnated packing or injectable antibiotics for up to 9 weeks' duration. Approximately 70% of patients report decreases in pain after surgery; however, recurrence in pain symptoms is often seen. Management of NICO with warfarin and stanozolol has been reported; however, pain relief and side effect profiles limit their utility.

Persistent Idiopathic Facial Pain (Atypical Facial Pain)

Atypical facial pain (AFP) or persistent idiopathic facial pain (PIFP) is primarily a diagnosis of exclusion that is based primarily on history and clinical examination. Like many chronic facial pain entities, atypical facial pain cannot be diagnosed based on laboratory and/or radiologic findings as these are typically normal. AFP has an incidence of 1 in 100,000, affects mainly adults, and is equally distributed between men and women. The etiology of PIFP remains unknown. This syndrome consists of mostly unilateral long-lasting facial pain that lasts most of the day, and is described as a severe ache, burning, or crushing sensation. The level of the pain is mild to severe, and no autonomic abnormalities are noted.[32] According to the International Headache Society's 2004 classification, PIFP is "Persistent facial pain that does not have the characteristics of the cranial neuralgias and is not attributed to another disorder."[33]

There are four criteria to be met for the diagnosis:

1. There is pain in the face present for most of the day or all day and occurring daily.
2. Initially, the pain may be confined to a portion of the face, but is poorly localized and deep.
3. It is not associated with other physical signs or loss of sensation.
4. Workup in terms of imaging is unrevealing of an obvious anatomic or structural cause.

It may follow an operation or trauma to the face, teeth, or gums, but persists without a known local factor.

The treatment modalities can include pharmacologic treatment such as tricyclic antidepressants or anticonvulsant drugs. Topical anesthetic agents, Botulinum toxin A, and cannabis have been suggested as a treatment as well.

Atypical Odontalgia

Atypical odontalgia (AO) is one of the most challenging conditions an oral and maxillofacial surgeon will face. To fulfill the diagnostic criteria for atypical odontalgia, the following conditions must be met:

- Pain is located in the mouth or face.
- Pain is described as a constant, deep, and dull ache.
- Onset of pain is associated with a dental procedure (e.g., extraction, endodontic therapy) and develops within 1 month of the procedure and persists for more than 4 months.
- Sleep is undisturbed.
- The area of hyperalgesia associated with trauma is surrounded by an area of less hyperalgesia.
- Local anesthetic injections are equivocal.
- Radiographic and laboratory tests are negative.

Atypical odontalgia can occur in as many as 6% of patients who have undergone endodontic therapy and has a reported incidence rate of 25% within the chronic facial pain community.[34] It has a female predilection and occurs in the fourth decade of life. Psychogenic, neurovascular, and

neuropathic etiologies have been hypothesized. An association between atypical odontalgia and concomitant depression and/or personality disorder was shown in as many as 66% of sufferers. However, a deafferentation injury to trigeminal nerves appears to be the most accredited theory. Trauma to dentoalveolar structures has been hypothesized to result in both peripheral and central sensitization, resulting in allodynia and hyperalgesia commonly found in AO. Management of AO is primarily pharmacologic as dental intervention only worsens the condition.[35] The patient's psychogenic background should always be considered in the treatment and/or management of AO.[9]

Stomatodynia (Burning Mouth Syndrome)

Stomatodynia or burning mouth syndrome (BMS) is characterized by a burning mucosal pain with no evidence of mucosal pathology, often accompanied by dysgeusia and xerostomia. It commonly affects women more than men (7:1) in the age range of 38 to 78 years. The incidence of BMS worldwide ranges from 0.7% to 14.8% depending on diagnostic criteria used.

Inclusion criteria include the following:[16]

- Oral pain or dysesthesia of a burning quality
- Present daily and persisting most of the day
- Oral mucosa is of normal appearance
- Unremitting pain for at least 3 months
- Pain does not interfere with sleep

The pain associated with stomatodynia is described as a prolonged burning, tingling, and numbing pain, onset of which does not generally coincide with an inciting event. However, previous dental procedures have been implicated in some cases of stomatodynia. The pain never worsens from, but may be relieved by, eating or drinking. The duration of pain is typically greater than 3 months and may persist beyond 12 years. Spontaneous pain remission is rare. The pain is often accompanied by dysgeusia and/or xerostomia; more than half of stomatodynia patients complain of persistent taste alterations that are characterized as bitter and/or metallic. Xerostomia and salivary dysfunction are also a common finding in the stomatodynia patient.[13] BMS can be associated with mood changes or disruptions in personality traits.

The etiology of stomatodynia is poorly understood and remains elusive to many facial pain experts. It may be due to psychogenic, nutritional, and neuronal disturbances. The current neuronal disturbance etiology supports two main theories: a sensory neuropathy either peripheral and/or central or disturbance in the balance between the gustatory and sensory system. Systemic nutritional factors should be identified and corrected. Patients with stomatodynia and concomitant psychologic disturbances should be referred for appropriate management. Medical management of stomatodynia with systemic[36] and topical[11] capsaicin are described. Systemic and topical benzodiazepines (most frequently Clonazepam) were used with variable success.[37-41]

Medical management of stomatodynia with topical capsaicin, anticonvulsants, and tricyclic antidepressants has been proposed; however, these treatment options remain unsatisfactory. No definitive cure exists.

Nerve Injury From Dental Procedures

Chemical or traumatic nerve injury may occur following endodontic therapy, placement of endosseous implants, mandibular third molar extractions, and administration of local anesthetics. These types of nerve injuries may also occur in association with facial trauma and their subsequent treatment as well as during orthognathic surgery, particularly sagittal split ramus osteotomy. Nerve injury associated with trauma and orthognathic surgery is less likely to result in complaints of chronic facial pain compared to dentoalveolar procedures. Sensory disturbances may vary from partial anesthesia or paresthesia, to complete anesthesia, to dysesthesia with or without anesthesia. Multiple hypotheses regarding the pathophysiology of nerve injury exist and are dependent on the mode of injury.

- Direct surgical trauma/nerve manipulation (induced nerve injury): It is clear from review of the literature that the most likely common surgical procedure that results in temporary or permanent nerve injury is surgical removal of mandibular third molars. The incidence rates are as follows although some have opined that these rates of injury are a likely underestimation of true incidence: [42]
  - Inferior alveolar nerve (IAN) permanent injury: 4 per 1000 cases
  - Lingual nerve permanent injury: 1:1000 cases
  - 80% of IAN injuries have a known cause.
  - 57% of lingual nerve injuries have an unknown etiology.

Endosseous implant placement is a potential source of surgically induced nerve injury. Similar to third molar extraction, the inferior alveolar nerve canal and lingual nerve are adjacent to the surgical sites during mandibular implant osteotomy and placement. This proximity increases the likelihood of damaging the adjacent peripheral nerves. The prevalence of temporary sensory disturbances ranges from no damage to 43% while permanent damage may be as high as 13% of patients undergoing implant placement.[43,44] Prompt management is recommended if nerve damage is directly visualized.

When known, the likely etiology for both extraction-induced and implant placement–induced nerve injury is direct trauma to the neurovascular bundle (IAN) or nerve (lingual). The reader is directed to the dentoalveolar chapter for further information regarding surgical management of nerve injury.

- Endodontic therapy–induced nerve injury: The inferior alveolar nerve is more commonly damaged during endodontic therapy than the lingual nerve. Nerve injury is likely due to chemical injury from extrusion of root canal–filling materials beyond the apex of the root.[45,46] Materials such as paraformaldehyde-containing Sargenti

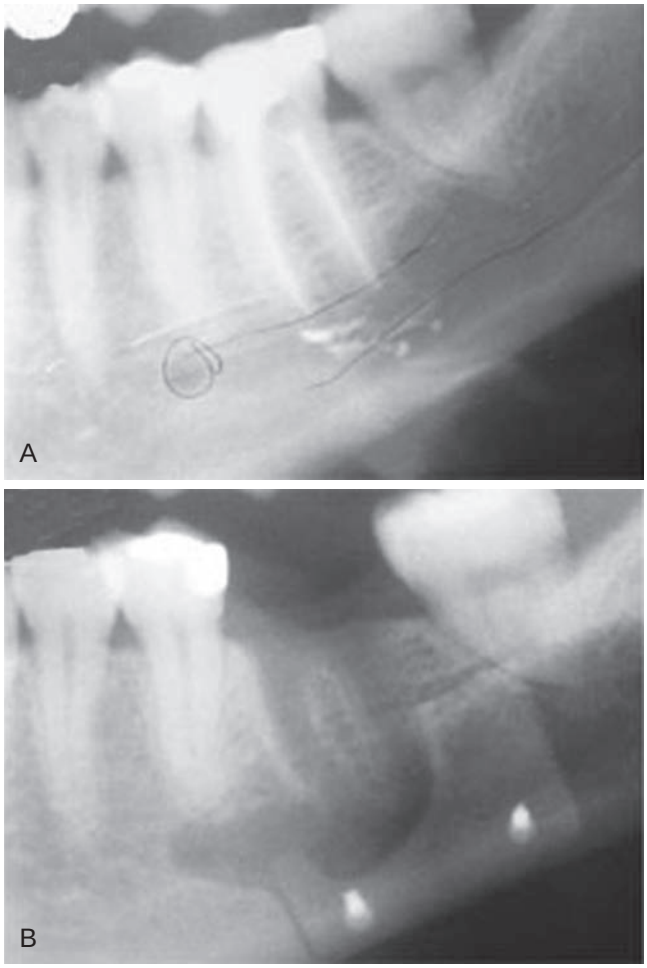
paste[47] (Figure 44-4) and inert gutta-percha[45] have been reported to cause painful dysesthesias following root canal treatment. Neurologic disturbances such as hyperesthesia and dysesthesias in the distribution of the IAN are commonly observed. Hyperesthesia is rarely seen. Surgical management in the form of careful debridement and decompression of the nerve with conservation of teeth has been reported.[46]

- Mandibular nerve block–induced nerve injury: Recent attention has focused on nerve injuries following administration of local anesthetics via the mandibular nerve block. The prevalence of temporary sensory deficits following block anesthesia ranges from 0.15% to 0.54% whereas permanent damage occurs with a much larger range: from as low as <0.01%[48] to as high as 3%.[49]

Many hypotheses exist regarding the etiology of nerve injury from mandibular block anesthesia. Direct fascicular damage to the nerve sheath has been proposed. This may be due to either direct needle penetration within the nerve or tearing of the epineurial sheath with a barbed needle. It has been well documented that the lingual nerve is more commonly injured during mandibular blocks. This may be due to the lingual nerve being ensheathed within the interpterygoid fascia, therefore being unable to deflect during needle contact. An electrical shock during initial needle placement has been reported in over 50% of patients with nerve injury[49] and further supports the direct injury theory.

Alternatively, the type and concentration of local anesthetic delivered have been examined.[5,48,50] In these studies, the most common local anesthetics associated with permanent sensory deficits were 4% articaine and 3% prilocaine with vasoconstrictors. Such high concentrations have been shown to cause microstructural damage to neural architecture in an experimental model; however, no gross structural abnormalities were observed clinically.[49] The volume of local anesthetic did not appear to influence onset or severity of nerve injury. Of the patients with sensory nerve deficits from mandibular block anesthesia, 85% to 94% will have symptoms that resolve spontaneously, and this occurs over an 8-week period. Of those who do not spontaneously resolve, more than two thirds will have permanent sensory impairment. Surgical intervention does not appear to resolve symptoms and may in fact worsen the clinical course.

It is difficult to determine or predict which patients with direct nerve injury will suffer from chronic pain. The patient who exhibits symptoms of paresthesia or anesthesia in conjunction with chronic facial pain symptoms may be a daunting diagnostic and treatment challenge. Treatment must be focused on goals of restoring sensation while at the same time controlling or eliminating pain. Many patients with facial pain will choose sensory deficit over facial pain if given a choice or ultimatum.



• **Figure 44-4** **A,** Panoramic radiographs of a patient who underwent endodontic therapy with Sargenti paste to tooth #19. Note the opaque material within the area of the inferior alveolar nerve canal. The patient complained of significant burning and shooting pain. She subsequently underwent multiple surgical procedures including lateral corticotomy, debridement, nerve decompression, and translocation, **B,** without resolution of her symptoms.

Facial Pain of Cardiac Origin

Case reports describing facial pain of cardiac origin have been documented[51-53] and may occur in as many as 18% of cardiac patients who complain of jaw and tooth pain.[53] This pain is primarily due to pain as a result of cardiac ischemia. The neurophysiologic basis for this occurrence is due to significant convergence of vagal nerve fibers arising from cardiac smooth muscle within the same spinal segments (medullary dorsal horn and cervical spinal cord) as trigeminal sensory neurons. Orofacial pain of cardiac origin most often will be described as burning and oppressive toothache that occurs spontaneously, usually in relation to exercise, and can be bilateral; the pain decreases with nitroglycerin tablets and is usually associated with chest pain, anterior neck pain, and/or shoulder pain, although it can also manifest as an isolated case. Toothache of cardiac origin may occur as a single clinical manifestation in the oral cavity, affecting adults as well as the elderly and children. There are also other craniofacial regions where this "heterotopic pain" (a pain in this region even though the source may be located elsewhere in the body) of cardiac origin can manifest in isolation as the paranasal sinuses, head, mandibular area, and

the temporomandibular joint region, though mainly it will be located in the mandible and throat. It can radiate to other craniofacial structures.[54] Clinicians should consider cardiac ischemia as a potential etiology of chronic constant or recurring facial pain without obvious dental or orofacial etiology. Prompt referral for cardiac evaluation is recommended.

Eagle's Syndrome

Eagle's syndrome is characterized by an elongated styloid process or calcified stylohyoid ligament and facial pain; this syndrome affects women more than men. The pain is variable and can be complex. Pain can be constant within the throat, ear, or temporal region or it can be elicited with

type are as follows: [55]
- Vague pain in neck
- Foreign body sensation
- Throat pain
- Pain on swallowing
-

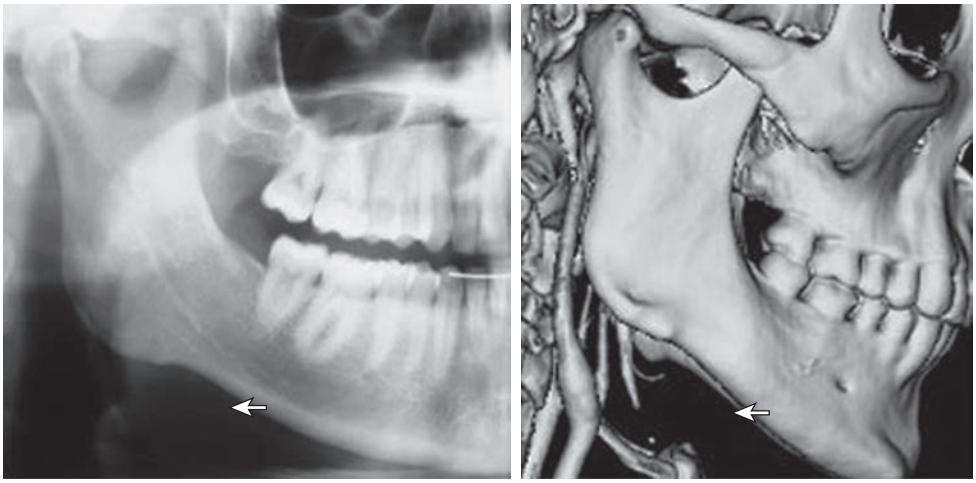
art
in the superior periorbital region. Dizziness, transient visual loss, syncope, stroke, Horner's syndrome, headache during

Eagle's syndrome is diagnosed based on the following criteria:
- Patient symptoms
- Palpation of the elongated styloid process overlying the tonsillar pillar
- Temporary relief of symptoms following administration of local anesthetic
- Radiographic evidence of an elongated styloid process or calcified stylohyoid ligament

The syndrome was seen most frequently in women in their fourth and fifth decades. Occasionally, Eagle's patients described prior styloid chain trauma (including tonsillectomy).[56]

The average length of the styloid process is approximately 20 to 30 mm and approximately 4% to 20% of the general population will demonstrate radiologic evidence of an elongated styloid process or mineralized stylohyoid ligament. Of those who present with an enlarged styloid process, less than 0.5% will report painful symptoms, suggesting a poor correlation between patient symptoms and radiologic findings.[57] Panoramic radiographs remain the most common radiologic modality to identify an elongated styloid process. However, lateral skull films, Towne's view radiographs, lateral oblique mandibular radiographs, and CT have all been utilized[58] (Figure 44-5). Because of the character of pain, it is important that the oral and maxillofacial surgeon rule out temporomandibular disorders because TMDs have been found in patients with Eagle's syndrome.[57]

The pathophysiology of Eagle's syndrome is likely caused by (1) impingement of the glossopharyngeal nerve, vagus nerve, or branches of the trigeminal nerve, (2) impingement of the carotid vessels, or (3) inflammation of the tendinous portion of the stylohyoid ligament. Management is by surgical excision of the elongated styloid process via a transoral or transcutaneous approach. Advantages of a transoral approach include that this approach has minimal scar formation, is safe, and is less time-consuming; also, a cutaneous scar is avoided. Disadvantages include poor visibility, risk for possible deep neck infection, and proximity to major vessels. The advantages of a transcutaneous approach include excellent visibility; however, risk for facial nerve injury and a neck scar are possible. While surgical excision remains the standard for managing patients with Eagle's syndrome, facial pain recurs in as many as 20% of



• **Figure 44-5** Reformatted 3D CT and panoramic radiograph of patient with Eagle's syndrome. Note the calcified stylohyoid ligament *(arrow).* Patient complained of vague neck and shoulder pain and dizziness with rotation of his head.

patients who have undergone surgery. Noninvasive management has been described to result in temporary relief of symptoms.

Facial Pain From Osteonecrosis

Radiation exceeding 6000 cGy and chronic intravenous antiresorptive therapy including bisphosphonates have been associated with the development of osteonecrosis of the maxilla and mandible. While the pathophysiology and surgical management of these entities can be found in other chapters within this text, it is important to understand the management of the chronic pain associated with these conditions. Radiation therapy and surgery is the most common treatment regimen used to treat oral cancers. However, it has a clear impact on the cancer survivor's quality of life from a functional, esthetic, and pain perspective. Patients may undergo dental and surgical reconstruction to reestablish masticatory, speech, and facial harmony; however, chronic pain may remain poorly treated.[59] Current pharmacologic strategies using nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics have only little to moderate benefit. Physical therapy is suggested to be a useful adjunct to manage chronic pain as some patients have shown modest improvement.[59]

Medication-Related Osteonecrosis of the Jaw

Medication-related osteonecrosis of the jaw (MRONJ) is a relatively newly diagnosed clinical entity that has had the medical and dental community concerned.[60,61] MRONJ refers to osteonecrosis cases associated with either bisphosphonates or other antiresorptive and antiangiogenic therapies. It is clear that these therapies improve survival and quality of life in this patient population. However, because of the prolonged life span and, subsequently, prolonged duration of treatment, clinicians must also consider how to manage the sequelae of the chemotherapeutic agent. Diagnostic criteria were established for MRONJ, and patients are considered to have MRONJ if all of the following characteristics are present:[62]

- Current or previous treatment with antiresorptive or antiangiogenic agents
- Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks
- No history of radiation therapy to the jaws or obvious metastatic disease to the jaws

Similar to other chronic pain conditions, the management of pain associated with MRONJ revolves around the use of NSAIDs and opioid analgesics. Depending on the presence of peripheral neuropathy, adjuvant medication can be considered. While the use of hyperbaric treatment to manage MRONJ remains under scrutiny, several reports have demonstrated its analgesic efficacy and it should be considered.[63-66]

Barriers to the Management of the Chronic Facial Pain Patient

The management of the chronic pain patient has been under scrutiny in recent years resulting in the development of chronic opioid therapy guidelines by the Centers for Disease Control in 2016. The guideline is intended to ensure that clinicians consider the safest and most effective drug therapies, while minimizing the development of adverse effects and/or side effects related to chronic opioid therapy.[67]

Multiple barriers exist between oral and maxillofacial surgeons and the adequate management of the chronic pain patient. Certainly concerns over addiction, tolerance, and side effect profiles of medication all play an important role in pain management strategies. Addiction is defined as a primary chronic disease with psychosocial and environmental factors that influence its development. Addictive behaviors include inability to control drug use, inability to discontinue use despite harmful sequelae, compulsive use of the drug, and craving of the drug. This is not to be mistaken for dependence, an adaptive state whereby discontinuation of drug results in specific withdrawal symptoms related to specific drug cessation or disruption. Finally, tolerance is an expected outcome during chronic drug therapy whereby chronic exposure to drug results in diminished drug effects, potentially necessitating increasing dosages for adequate pain relief. This may also relate to the side effect profile.[68]

In the management of the chronic pain patient, one must expect that dependence and tolerance will occur because of the chronicity of the pain disorder. It should be noted that in most cases, increasing analgesic requirements reflect more about the progression of disease rather than development of tolerance. Tolerance to the respiratory and CNS depressant effects and nausea from chronic opioid use has been observed. However, tolerance to other side effects such as constipation does not occur. Certainly, side effect profiles should not prevent surgeons from adequately treating pain. Such side effects should and can be managed with appropriate pharmacotherapy including antiemetics, promotility agents, and stool softeners.

It is critically important that surgeons discuss the postoperative pain management strategy with the chronic pain patient before surgery. This not only provides the patient with some satisfaction that his/her pain needs have been thoroughly considered, but also provides the platform for establishing an opioid contract.[69] For chronic pain patients who are managed by their primary care physician (PCP), a trilateral opioid contract may be made involving the patient, surgeon, and PCP.[70] The opioid contract should include the following:

- Address issues related to improper use of opioid (including overdosing, seeking medicines elsewhere, selling medicine, or abruptly stopping medicine)
- Terms for disciplinary action (including abuse, missing appointments, violating contract, inappropriate behavior)
- Establish limitations for replacing medications or changing prescriptions

- Inform surgeon of relevant information (e.g., side effects, changes in medical history)

Pain Management Considerations in the Substance Abuser

The substance abuser requires special consideration from a controlled substance pain management standpoint. Opioid and illicit drug abuse is seen in as high as one third of chronic pain patients receiving treatment for chronic pain.[68] The most common illicit drugs abused are marijuana, cocaine, and methamphetamines, occurring in 11%, 5%, and 2% of chronic pain patients, respectively. Approximately 50% of patients who are current illicit drug abusers have had a history of illicit drug abuse and 16% of them also abuse opioids. A history of illicit drug abuse, however, is not correlated with opioid abuse. The concern for substance abuse is a major barrier in the management of the chronic pain patient; however, it should not deter the surgeon from appropriately managing the pain.

Diversion of controlled substances can occur through illegal Internet pharmacies, drug theft, prescription medication forgeries, or through doctor shopping. Doctor shopping remains the most common way physicians believe their patients obtain controlled substances. The following key measures can be taken to help prevent diversion and abuse of controlled substances:

- Ensure that a single physician/surgeon/pain specialist manages all controlled substances.
- Establish an opioid contract.
- Obtain a thorough history including medication use and illicit drug use. Include type, duration, and chronicity of use.
- Obtain medication prescription history before long-term pain management. Discussions with previous physicians and pharmacists should be considered.

Treatment Modalities for Chronic Facial Pain

Currently 70 million Americans suffer from chronic pain and chronic pain results in $100 billion in lost productivity annually. The importance of pain assessment and management is highlighted in The Joint Commission's (TJC) statement mandating that pain be the "fifth" vital sign. Many states now require health care providers to provide appropriate pain management and have even reprimanded health care providers who fail to treat pain.[71] In the new era of chronic pain management, emphasis is placed on graded polypharmacy and utilization of nonpharmaceuticals to augment treatment strategies.

Physical Therapy

The benefits of physical therapy as an integral part of the multidisciplinary management of the facial pain patient are clear. Physical therapy modalities include cautious isometric and cold therapy including vapocoolant spray to release taut bands, and transcutaneous electrical neural stimulation (TENS). The main goals for physical therapy include decreasing or eliminating pain, increasing range of motion in patients whose myofascial pain limits mandibular opening, and returning masticatory function. Benefits include cost-effectiveness, reversibility, and noninvasiveness. Indeed, the success of physical therapy relies on the compliance of the patient. Thus patient education becomes critically important. Patients must understand that physical therapy is reversible and therefore they will require both short-term professional therapy and long-term home therapy.[72,73]

Opioid Therapy

For acute breakthrough pain, opioid analgesics may be used. Opioids remain the gold standard drug for the management of moderate to severe pain. They exert their analgesic effects by interacting primarily with mu (μ) receptors, but there are also kappa (κ) opioid receptors located in spinal sites. Expression of μ receptors in peripheral nerve fibers suggests peripheral actions of opioids as well.[74] Side effects of opioid analgesics are related to dosing and patient sensitivity and include nausea and vomiting, sedation, respiratory depression, constipation, and physical dependence. Unfortunately, the concern for abuse and physical dependence has unnecessarily limited clinicians in their willingness to prescribe opioids. Opioids commonly used for acute pain management include codeine, hydrocodone, and oxycodone.

For the chronic pain patient, it is clear that management strategies must be altered compared to managing acute pain. First, a stepwise approach must be initiated where scheduled (or "round the clock") medications are given for the constant pain while rescue medications are given for breakthrough pain. Dose escalation can then be performed by the practitioner until pain is appropriately controlled (Table 44-2). Long-acting opioids should always be used instead of short-acting opioids for round the clock dosing. Morphine sulfate is the most common orally available opioid used for the management of chronic pain.

Fentanyl is an opioid derivative that is 80 times more potent than morphine. It is available in injectable, transdermal, and transmucosal forms, the latter two being more commonly used for chronic pain management.[75] Fentanyl should NOT be used in opioid-naïve patients. Opioid-tolerant individuals are defined as those who require at least (1) 60 mg of oral morphine daily, (2) 30 mg of oral oxycodone daily, or (3) 8 mg of oral hydromorphone daily (Duragesic prescribing information pack, Janssen Pharmaceutica Products, Titusville, NJ). Calculations for transdermal fentanyl (Duragesic) dose conversion are based on the following:

1. Calculate the previous 24-hour analgesic requirements (mg/day).

TABLE 44-2 Management of Chronic Pain With Orally Available Morphine Sulfate

Steps	Morphine Sulfate Immediate Release: Scheduled	Morphine Sulfate Immediate Release: Rescue	Morphine Sulfate Controlled Release: Scheduled	Morphine Sulfate Controlled Release: Rescue
I	10 mg q4h	5 mg q1h	30 mg q4h	7.5 mg q1h
II	15 mg q4h	7.5 mg q1h	60 mg q4h	15 mg q1h
III	30 mg q4h	15 mg q1h	90 mg q4h	15 mg q1h
IV	45 mg q4h	22.5 mg q1h	100 mg q4h	30 mg q1h

Adapted from Lee KF, Ray JB, Dunn GP: Chronic pain management and the surgeon: barriers and opportunities, *J Am Coll Surg* 193(6):689-701, 2001.

TABLE 44-3 Conversion Table for Common Oral Opioids to Transdermal Fentanyl Patch

Current Analgesic	Daily Dosage (mg/d)			
Oral morphine	60-134	135-224	225-314	315-404
IM/IV morphine	10-22	23-37	38-52	53-67
Oral oxycodone	30-67	67.5-112	112.5-157	157.5-202
Oral codeine	150-447	448-747	748-1047	1048-1347
Oral hydromorphone	8-17	17.1-28	28.1-39	39.1-51
IV hydromorphone	1.5-3.4	3.5-5.6	5.7-7.9	8-10
IM meperidine	75-165	166-278	279-390	391-503
Oral methadone	20-44	45-74	75-104	105-134
	⇓	⇓	⇓	⇓
Recommend DURAGESIC dose	25 mcg/h	50 mcg/h	75 mcg/h	100 mcg/h

Table 44-3 should not be used to convert from DURAGESIC to other therapies because this conversion to DURAGESIC is conservative. Use of Table 44-3 for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible. DURAGESIC (fentanyl transdermal system), CII Prescribing Information. Janssen Pharmaceuticals, Inc. April, 2014.

2. Convert amount to equianalgesic oral morphine dose (mg/day).
3. Use manufacturer-recommended conversion table (Table 44-3).

The transdermal fentanyl patch has an elimination half-life of 20 to 27 hours and therefore may take as many as 6 days to achieve steady-state concentrations. During the first 16 hours of transdermal therapy, analgesics must be prescribed for chronic breakthrough pain and to prevent withdrawals. The transdermal patch is replaced every 72 hours and should never be cut as this will result in a rapid release and absorption of a potentially fatal dose of fentanyl. Fentanyl patches are commercially available in 12, 25, 50, 75, and 100 mcg/hr systems. These patches are not indicated for the management of acute pain associated with surgical procedures.

Gaining a clear appreciation of the extent of the patient's pain and an understanding of pain management including "round the clock" and "breakthrough" rescue dosing with opioids, using adjunctive pharmacologic and behavioral therapies, and, most importantly, ensuring management of all medications by a single clinician will ensure the most appropriate treatment for the chronic pain patient.[68-70]

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally used to treat the inflammatory component of facial pain. NSAIDs exert their actions by inhibiting prostaglandin biosynthesis in the arachidonic acid cascade. There are two main types of NSAIDs, nonselective and selective. The terms nonselective and selective refer to different NSAIDs' ability to inhibit specific types of cyclooxygenase (COX) enzymes. Nonselective NSAIDs inhibit both COX-1 and COX-2 enzymes. Examples of nonselective NSAIDs commonly used are ibuprofen (Advil, Motrin, Nuprin), and naproxen (Aleve). Selective NSAIDs inhibit COX-2. The

TABLE 44-4 Pharmacotherapy for the Management of Acute and Chronic Facial Pain

	Initial Dose (Maximum Daily Dose)	Maintenance Dose Range (Maximum Daily Dose)
NSAID and Opioid Analgesics for Acute Pain		
Ibuprofen (Advil, Motrin)	200-400 mg q6-8h	400-800 mg q6-8h (2400 mg)
Naproxen (Naprosyn, Aleve)	250-375 mg bid	500 mg bid
Celecoxib (Celebrex)	100 mg bid or 200 mg once a day	up to 400 mg daily
Hydrocodone/acetaminophen 5/500 mg (Vicodin)	1-2 tablets q4-6h prn breakthrough pain (4 g acetaminophen)	Not to be used as maintenance drug
Oxycodone/acetaminophen 5/325 mg (Percocet)	1-2 tablets q4-6h prn breakthrough pain	Not to be used as maintenance drug
Antidepressants		
Amitriptyline (Elavil)	10-25 mg nightly	75-100 mg nightly
Venlafaxine (Effexor XR)	37.5 mg /day	75-225 mg/day
Duloxetine	20-40 mg/day	60-120 mg/day
Anticonvulsants		
Gabapentin (Neurontin)	100-300 mg nightly or tid	1200-2400 mg per day
Pregabalin (Lyrica)	50 mg tid or 75 mg bid	50-100 mg tid or 75-150 mg bid up to 300mg/day
Muscle Relaxants		
Clonazepam (Klonopin)	0.25 mg nightly or bid	0.5-1.0 mg qid max
Cyclobenzaprine (Flexeril)	10 mg nightly or tid	10-20 mg nightly or tid max
Diazepam (Valium)	5 mg nightly	5 mg tid max
Tizanidine (Zanaflex)	2-4 mg nightly to qid	36 mg/day max
Corticosteroids		
Betamethasone (Celestone)	6 mg IM	9 mg/day max
Methylprednisolone (Depo-Medrol)	10-80 mg IM	Dose interval 1-5 weeks
Dexamethasone (Decadron)	4-16 mg IM	Dose interval 1-3 weeks
Topical Medication		
Capsaicin cream (Zostrix)	0.075% qid topical	Dose interval up to 8 weeks

role of COX-2 in peripheral inflammation and in development of central hyperalgesia had been demonstrated,[76] and these NSAIDs are less likely to cause gastrointestinal injury. Celecoxib (Celebrex) is a selective NSAID that is available in the United States. Other selective NSAIDs that can be found elsewhere in the world include etoricoxib (Arcoxia) and lumiracoxib (Prexige). Selective COX-2 inhibitors were initially promoted for chronic use in patients with osteoarthritis, rheumatoid arthritis, dysmenorrhea, and dental pain. However, an increased risk for significant adverse effects on cardiovascular and renal systems was noted when compared to NSAIDs and controls.[77] Because of these recent findings, Merck withdrew rofecoxib (Vioxx) from the market in September 2004 and Pfizer has placed a "black box warning" on celecoxib (Celebrex) and suspended sales of valdecoxib (Bextra) in both the United States and European Union as of April 2006.

Chronic use of NSAIDs is discouraged because of the risk for developing upper gastrointestinal complications, major vascular events, renal toxicity and/or failure, and abdominal pain and cramping. Therefore, for chronic use, if necessary, close monitoring is recommended. Suggested dosing regimens are listed in Table 44-4.

Antidepressants

Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been shown to be useful in many chronic pain states including fibromyalgia and those related to clinical depression. It is particularly useful in myofascial pain patients with sleep disturbances and in those with a neuropathic pain component. Although the mechanism of action of TCAs is poorly understood, it is believed to be the inhibition of reuptake of norepinephrine,

dopamine, and serotonin. In contrast, the SSRIs selectively block the reuptake of serotonin only. The analgesic efficacy of TCAs and SSRIs in facial pain appears to be independent of its antidepressant properties and is supported by reduced dose requirements to alleviate facial pain.[78] TCAs provide effective pain relief for a period of 2 to 8 weeks whereas SSRIs provide effective pain relief for a period of 3 to 6 months.[79] If used clinically as an antidepressant, clinicians trained in the diagnosis and treatment of depression should be responsible for its prescription. Adverse effects include sedation, xerostomia, constipation, dizziness, and confusion.

Venlafaxine was initially developed as an antidepressant, although it is now used as a neuropathic agent. It is considered a bicyclic antidepressant as it prevents the reuptake of serotonin, dopamine, and norepinephrine. Although used primarily to treat anxiety and depression, it has been used off-label to treat migraines and diabetic neuropathy. It is only modestly efficacious in the treatment of facial pain.[80] Side effects include headache, nausea, sedation, xerostomia, dizziness, insomnia, and sexual dysfunction.

Anticonvulsant drugs, including gabapentin (Neurontin), pregabalin (Lyrica), topiramax (Topamax), and carbamazepine (Tegretol), are often tried in chronic neuropathic pain and are thought to be indicated especially when the pain is lancinating or burning. Their molecular mechanisms

practitioners.[32]

Anticonvulsant Agents

Gabapentin (Neurontin) and pregabalin (Lyrica) have been used as adjuvants to manage both neuropathic and myofascial pain disorders. The exact mechanism of action of gabapentin is unknown. The molecular structure of gabapentin resembles the inhibitory neurotransmitter gamma-aminobutyric acid (gaba), although it does not bind to the gaba receptor; rather, it is believed that gabapentin interacts with the $\alpha_2\delta$ subunit of the voltage-gated calcium channel[81] within the central nervous system to disrupt calcium ion conduction, resulting in inhibition. Gabapentin is not

ing from 5 to 12 weeks and are recommended for patients with neuropathic pain. Common side effects include dizziness, sedation, ataxia, and peripheral edema.[79]

Muscle Relaxants

Muscle relaxants are used to reduce muscle hyperactivity and tone and are commonly prescribed to manage TMDs. Their mode of action is primarily disruption of spinal reflexes within the brainstem and spinal cord to inhibit firing of motor neurons. Some relaxants such as cyclobenzaprine have been found to be particularly efficacious when prescribed with an NSAID and physical therapy.[82] In contrast, diazepam is efficacious when used alone.[83] Although no randomized controlled studies have been performed, tizanidine (Zanaflex), an α_2-adrenergic agonist, appears to be effective in treating muscle spasms. Because of their activity within the central nervous system, muscle relaxants have CNS side effects including sedation, somnolence, and cognitive dysfunction. Chronic use should be avoided.

Therapeutic Injections

Injections of aqueous solutions of local anesthetics, corti-

ent neural pathways within the contracted muscles to allow for muscle elongation. Combination local anesthetic with corticosteroid injections can be used; however, combination injection is not clinically superior to local anesthetic or steroid injection alone.[84] Injection of normal saline (0.9%) appears to be as efficacious as local anesthetics in reducing myofascial pain.[85]

Local anesthetics commonly used are 0.5% to 2% lidocaine without vasoconstrictor or 0.25% to 0.5% bupivacaine without vasoconstrictor. Local anesthetics exert

potentials and thus sensory and motor activity. Side effects include CNS depression, seizures, tinnitus, and dysrhythmias and are related to exceeding maximum single daily dose. In addition, risks associated with injection technique have been discussed, including soft tissue infection, necrosis, and, less commonly, accidental intrathecal injection resulting in respiratory depression and hemiplegia requiring endotracheal intubation.[86] Careful aspiration before injection is recommended. Local anesthetic injections may also be used as a diagnostic tool to rule out neuropathic central pain syndromes including trigeminal and glossopharyngeal neuralgias.

Implantable pump systems such as the On-Q Pain Management System, the Pain Buster Pain Management System, the Don Joy Pain Pump, and the Stryker Pain Pumps are commercially available that allow for controlled amounts of local anesthetics to be administered in a specific anatomic area for postoperative pain management. Medication is delivered directly to the surgical wound site or in close proximity to the nerves associated with the surgical area. These systems are used for the management of acute postoperative pain and remain implanted for 3 to 7 days depending on the system used. Although a paucity of data exist in the oral and maxillofacial surgery literature, such systems have been found to be efficacious in the plastic and reconstructive, gastrointestinal, and orthopedic literature. Common side effects include wound infection, toxicity of drug, and accidental premature removal.

Corticosteroid injections either alone or in combination with local anesthetics have been advocated. Steroids exert their analgesic effect by inhibition of phospholipase A_2 production within the arachidonic acid cascade. This blocks the formation of the proinflammatory mediators prostaglandin and leukotriene within damaged or traumatized tissues. Commonly used corticosteroids include methylprednisolone (Depo-Medrol), dexamethasone (Decadron), and betamethasone (Celestone), and each differs based on solubility. Betamethasone is the most soluble injectable corticosteroid and therefore has the least risk for development of muscle wasting, fat atrophy, hypopigmentation, and tendon rupture. The more insoluble methylprednisolone has greater duration of action than either dexamethasone or betamethasone. Adverse reactions include facial flushing, insomnia, dizziness, and nervousness. Use steroids with caution in patients with poorly controlled diabetes, active infections, ulcerative colitis, severe gastroesophageal reflux disease, renal disease, and congestive heart failure. Chronic steroid injections are not recommended because of related systemic side effects. Repeat dosing intervals of 1 to 5 weeks are generally recommended to decrease risk of side effects.

Botulinum Toxin Injections

Botulinum toxin is produced by the bacterium *Clostridium botulinum,* and eight distinct types exist (types A, B, C1, C2, D, E, F, and G). Two types—botulinum toxin A (BTA, Botox, and Botox Cosmetic, Allergan Inc., Irvine, CA) and botulinum toxin B (BTB, Myobloc, Elan Pharmaceuticals Inc., New York, NY)—are commercially available in the United States. Primary indications for BTA are treatment of blepharospasms, strabismus, tension headaches, hyperhidrosis, spasmodic dysphonia, oromandibular dystonia, torticollis, cosmetic treatment of facial rhytides, myofascial pain that is resistant to physical therapy and oral pharmacotherapy, and muscle spasticity related to cerebral palsy, cerebrovascular accidents, and multiple sclerosis.[87] The mechanism of action is disruption of acetylcholine release from the neuromuscular junction. This prevents the repetitive and consecutive muscular contraction and development of local tissue ischemia.

Botox is supplied in 100 mouse unit vials and must be reconstituted with unpreserved saline before use. One unit is equal to the amount that would be lethal in 50% of mice. The human lethal dose for Botox is 3,000 units or 40 to 50 units/kg. Flaccid paralysis occurs after 3 days and lasts for 3 to 5 months. Typically, 1 mL of unpreserved saline is carefully injected into the vial and gently mixed so as not to incorporate bubbles. A 1-mL tuberculin syringe with a 30-gauge 1-inch needle is then used to draw up the solution with a final concentration of 10 units per 0.1 mL. Other authors have advocated using 6 mL of unpreserved saline and placing the solution into six 1-mL tuberculin syringes with a final concentration of 1.7 units/0.1 mL.[88] The manufacturer recommends using Botox within 4 hours of reconstitution although it may be stored refrigerated for ments.[89] The maximum dose in a single muscle is 25 units with a maximum 30-day cumulative dose of 200 units.

The most common side effects associated with Botox injection are postinjection ecchymosis, bruising, and unwanted temporary paralysis of the facial muscles of expression. If possible, patients should refrain from platelet inhibitors such as aspirin and NSAIDs 7 to 14 days before injections. Contraindications for Botox injections include pregnancy (category C) and breastfeeding, prior allergic reaction, and injections into sites of infection or inflammation. Use with caution in patients with neuromuscular diseases such as myasthenia gravis, amyotrophic lateral sclerosis, and Lambert-Eaton syndrome. Approximately 6% of patients will develop neutralizing antibodies against botox A and become nonresponsive to treatment. In this population, botox B (Myobloc) may be used.[90] Myobloc is supplied in 2500-unit to 10,000-unit vials and is not equivalent to Botox. One unit of Botox is equivalent to 50 units of Myobloc. Injection doses exceeding 4500 units of Myobloc have been associated with an increased incidence of side effects including ptosis, burning on injection, visual disturbances, xerostomia, xerophthalmia, headache, and facial muscle weakness. Paralysis lasts for 7 weeks and increases to 8 weeks with higher doses.

Botulinum toxin may be used to treat myofascial pain and for neuropathic pain with presumed local pain generation as third-line therapy mainly because of insufficient evidence of therapeutic benefit.[79]

Topical Capsaicin

Topical capsaicin is used for a variety of chronic pain conditions including causalgia, herpetic neuralgia, diabetic neuropathy, osteoarthritis, and rheumatoid arthritis.[91] The compound capsaicin, alkylamine with the chemical formula C18H27NO3 found in various chili peppers, has long been known to produce a hot, burning, stinging sensation, whether on ingestion of spicy food or when applied to the skin. As somewhat of a paradox, capsaicin has also been known to provide superficial pain relief despite, again, an initial unpleasant sensation. Although this has been known for a century, the molecular target and mechanism for capsaicin's effects have only relatively recently been investigated and brought to light. Modern scientific technique has allowed for a more complete characterization of not only capsaicin and its action but also of its target—the TRPV1 receptor—itself and the class of receptors to which it belongs.[92]

High-concentration topical capsaicin (8%) can be used to treat postherpetic neuralgia and HIV neuropathy.[93] Topical capsaicin has been available for some time in a low dose (i.e., less than 1%). Many studies have been published in an attempt to evaluate its efficacy and safety. Again, it is important to note that "low-dose capsaicin" here actually refers to two different concentrations: 0.025% and 0.075%.

According to meta-analysis of randomized controlled trials to determine the efficacy of topical (0.075%) capsaicin in the treatment of chronic pain from neuropathic and musculoskeletal disorders, it is efficacious in at least 50% pain reduction in 60% of patients with painful neuropathies when used for an 8-week period and in 57% of patients concentration was lower as well. With manipulation of those data for neuropathic conditions, in patients using topical capsaicin 0.075%, for approximately every six patients, one would achieve at least a 50% reduction in pain in patients who would not have experienced pain reduction if given placebo.[94]

Winocur et al. in a double-blind 4-week study on 30 TMD patients found that capsaicin cream (0.025%) produced no statistically significant influence on measured variables when compared to placebo.[95]

The Cochrane review by Derry et al.[93] based on the existing data available, concluded that there are insufficient data to draw any conclusions about the efficacy of low-concentration capsaicin cream in the treatment of neuropathic pain. The data do suggest that low-concentration topical capsaicin is without meaningful effect beyond that found in placebo creams. Local skin irritation, which was often mild and transient but may lead to withdrawal, was common. Systemic adverse effects were rare.

Thus, although the majority of available data do seem to suggest that low-dose capsaicin for neuropathic or musculoskeletal pain is not an effective treatment option, there are some data to suggest that in some patients low-dose capsaicin may be a reasonable therapeutic option when others have failed to provide sufficiently complete pain relief and quality of life improvement.

Surgical Intervention

Chemical denervation with potent preservatives such as alcohol or glycerol has been reported as a treatment regimen for chronic facial pain, especially trigeminal neuralgia. Performed as a transcutaneous gasserian block, each compound is delivered via a spinal needle at a volume of 0.2 to 0.5 mL. Although many patients report symptomatic relief hours after injection, recurrence may occur within 1 year following injection. Injections are performed in an temporary cutaneous hyperesthesia, dysesthesia or anesthesia, anesthesia dolorosa, cutaneous necrosis, risk for corneal abrasion (for permanent V1 anesthesia), pain recurrence, and failure to achieve relief.[7,96]

Surgery may be considered in the facial pain patient who remains refractory to conventional nonsurgical modalities and is often viewed as the "last resort." Surgical techniques such as nerve transection, microvascular decompression, thermorhizotomy, and stereotactic gamma knife radiosurgery have all been described in the literature for treating chronic facial pain.[97] The latter three surgical techniques are commonly used for managing trigeminal neuralgia and are beyond the scope of this chapter. However, nerve transection may be performed for intractable pain developing from branches arising from the trigeminal nerve. While success rates are minimal, many chronic facial pain patients are willing to give up somatic sensation if pain is even slightly diminished. As to be expected, complete anesthesia in the distribution of the transected nerve is expected with no recovery of sensation. Diagnostic tests in the form of local anesthetic blockade are necessary before proceeding with surgical denervation to ensure that central sensitization has not occurred. Surgical or chemical denervation will not successfully resolve chronic pain disorders that have a central pain component.

Clinically Based Comprehensive Pain Management Programs

Many clinical specialties play a role in the diagnosis and management of facial pain. For more complex cases, a team approach is usually considered.[3] In all chronic pain conditions, the more severe cases involve some degree of psychologic disturbance.[98] It is unclear whether, for example, the depression that accompanies many chronic pain states is a result of or contributes to the underlying disease process. Because it is clear that pain has both a discriminatory and an affective component, focusing treatment on one aspect will have less successful results. The multidisciplinary approach to chronic pain management ensures all aspects of the pain disorder are treated. The pain clinic team may be comprised of psychologists, psychiatrists, physical therapists, anesthesiologists, TMD specialists, oral and maxillofacial surgeons, neurologists, neurosurgeons, and integrative medicine specialists. There is evidence demonstrating the psychologic ramifications that chronic facial pain has on diagnosis and treatment outcomes[99,100] and the need for the multidisciplinary approach.

Future Directions in Pain Management

Pain research has significantly improved our understanding of acute and chronic pain mechanisms. By highlighting key molecular mechanisms involved in pain transmission, new drugs are currently being investigated as potential novel and selective therapies. Currently available medications such as opioids are certainly fraught with side effect profiles that the available data that while low-dose capsaicin is generally ineffective as an analgesic in either musculoskeletal or multiple forms of chronic neuropathic pain in adults, high-dose capsaicin has shown efficacy in certain forms of chronic neuropathic pain. A logical evolution in research into investigation of TRPV1 agonism, then, most likely ought to

focus on either 8% topical capsaicin in musculoskeletal pain or forms of chronic neuropathic pain not yet investigated, be it diabetic peripheral neuropathy, or distal painful polyneuropathy. Further investigation into TRPV1 antagonists may continue to yield fruitful results

Growth factors are important in the differentiation, maturation, and plasticity of cells within the nervous system. Key growth factors that have been implicated in pain include nerve growth factor (NGF), glial-derived growth factor (GDNF), and brain-derived growth factor (BDNF).[101] Receptors for such growth factors are expressed on C fibers and Aδ fibers that terminate within the spinal cord. In animal models of chronic pain, NGF levels are elevated in damaged peripheral tissues. Neutralizing antibodies against NGF are effective, at least in animal models, in reducing and, in some cases, preventing chronic pain. Interestingly, administration of NGF has also been shown to reduce neuropathic pain. Phase III clinical trials are currently underway assessing the efficacy of recombinant NGF to treat diabetic neuropathy. BDNF has been implicated in the modulation of central sensitization as its expression is increased in nociceptive neurons in models of peripheral neuropathy. BDNF sensitizes C fiber activity, resulting in hyperalgesia and allodynia. Inhibition of BDNF and its cognate receptor trkB results in decreased C fiber firing and a reduction in pain behaviors. Finally, GDNF is important in the survival of sensory neurons and supporting cells. Neuropathic pain behaviors commonly observed in animal models of chronic pain are prevented or reversed following GDNF administration. The timing of administration determined whether treatment was protective or therapeutic in nature.

Other directions for further investigation could include randomized controlled trials of the effectiveness of botulinum toxin injections. Further trials measuring the safety and the efficacy of autologous administration of stem cells for neuropathic trigeminal pain reduction may offer a viable treatment option.[102] Evaluation of neuromodulation with electrical stimulus to treat atypical neuropathic pain refractory to other treatments also may prove to be of value. Development of novel compounds to improve safety and tolerability of NSAIDs may also be beneficial in the treatment of chronic facial pain.

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45

Temporomandibular Muscle Disorders: Diagnostic and Management Considerations

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Intrinsic pain of the masticatory muscles is sometimes perceived by oral and maxillofacial surgeons as a vaguely defined syndrome managed by somewhat mysterious—but definitely nonsurgical—treatment. In fact, myogenous temporomandibular disorders (TMDs), or masticatory myalgias, are characterized by pain and dysfunction arising from a number of well-defined, distinct pathologic and functional processes in the masticatory muscles. These include myofascial pain (MFP), myositis, muscle spasm, and muscle contracture.[1] The surgeon who would operate on the temporomandibular joint (TMJ) must also be familiar with the diagnosis and nonsurgical management of these muscular problems. This chapter defines these disorders and suggests effective and evidence-based therapies for each.

MFP is the most common muscle pain disorder.[2] It is an acute to chronic condition that includes the presence of regional pain associated with tender areas called *trigger points* (TrPs), which are expressed in taut bands of skeletal muscles, tendons, or ligaments. Although the pain most often occurs in the region over the TrP, pain can be referred to areas distant from the TrP (e.g., the temporalis referring to the frontal area and the masseter referring into the ear and/or the posterior teeth). Reproducible duplication of pain complaints with specific palpation of the tender area is often diagnostic.

Myositis is an acute condition with localized or generalized inflammation of the muscle and connective tissue and is associated with pain and swelling overlying the muscle. Most areas in the muscle are tender, with pain in active range of motion. The inflammation is usually due to local causes such as overuse, excessive stretch, drugs (e.g., ecstasy), local infection from pericoronitis, trauma, or cellulitis. Myositis is also termed *delayed onset muscle soreness* in cases of acute overuse.

Muscle spasm is also an acute disorder characterized by a brief involuntary tonic contraction of a muscle. It can occur as a result of overstretching of a previously weakened muscle, from protective splinting of an injury, as a centrally mediated phenomenon such as prochlorperazine (Compazine)-induced spasm of the lateral pterygoid muscle, or through overuse of the muscle. A muscle in spasm is acutely shortened and painful, causing limited range of motion in the affected joint. Lateral pterygoid spasm on one side can also cause a shift of the occlusion to the contralateral side.

Muscle contracture is a chronic condition characterized by continuous gross shortening of the muscle with significant limited range of motion. It can begin as a result of factors such as trauma, infection, or prolonged hypomobility. If the muscle is maintained in a shortened state, muscular fibrosis and contracture may develop over several months. Pain is often minimal in the process from protection of the muscle.

Etiology and Epidemiology

Prevalence

Muscle pain disorders are the most common cause of persistent pain in the head and neck, affecting about 50% of a chronic head and neck pain population.[3] They are also a common cause of pain in the general population, with 20% to 50% of people having muscle pain disorders and about 6% having symptoms severe enough to warrant treatment.[4,5]

Etiologic Factors

Onset factors for myogenous TMDs include both direct or indirect macrotrauma to the muscle and repetitive strain activities.[6] Macrotrauma includes a direct blow to the jaw and opening the mouth too wide or for too long a period during activities such as undergoing dental work, eating, yawning, or engaging in sexual activity. Indirect trauma due to a whiplash-type injury may initiate muscle pain in some cases. Local infection and trauma may cause myositis and lead to muscle contracture if not resolved. Occupational and repetitive strain injury may result in MFP and, if acute, muscle spasm. Sleep disturbance and nocturnal habits can contribute to MFP. Psychosocial stressors such as relationship conflicts, monetary problems, feelings of hurriedness, overscheduling, and poor pacing skills can also play an indirect role.

Postural strain caused by a forward head posture, increased cervical or lumbar lordosis, some occlusal abnormalities, and poor positioning of the head or tongue have also been implicated in MFP; so have static postural problems such as unilateral short leg, small hemipelvis, occlusal discrepancies, and scoliosis or functional postural habits such as forward head, jaw thrust, shoulder phone bracing, and lumbar lifting. In a study of postural problems in 164 head and neck muscle pain patients, poor sitting and standing posture in 96%, forward head in 84.7%, rounded shoulders in 82.3%, lower tongue position in 67.7%, abnormal lordosis in 46.3%, scoliosis in 15.9%, and leg length discrepancy in 14.0% were found to contribute to muscle pain.[2]

Oral parafunctional muscle tension produces habits such as teeth clenching, jaw thrust, gum chewing, and jaw tensing. Nocturnal bruxism is often cited as a common cause of MFP but probably is better thought of as a perpetuating cofactor.

Pathophysiology and Mechanisms

Because there are no specific anatomic changes in the myogenous pain, there are no conclusive mechanisms identified in nontrauma cases. Therefore there are several processes that may explain the development and persistence of masticatory myogenous pain.[6]

Repetitive Strain Hypothesis

Repetitive strain from oral parafunctional habits contributes to localized progressive increases in oxidative metabolism and depleted energy supply (decrease in the levels of adenosine triphosphate [ATP], adenosine diphosphate [ADP], and phosphoryl creatine and abnormal tissue oxygenation). The result is changes in the muscle nociception, particularly with type I muscle fiber types associated with static muscle tone and posture. Tenderness and pain in the muscle are mediated by type III and IV muscle nociceptors, which may be activated by locally released noxious substances such as potassium, histamine, kinins, or prostaglandins, causing tenderness.

Neurophysiologic Hypothesis

Tonic muscular hyperactivity may be a normal protective adaptation to pain instead of its cause. Phasic modulation of excitatory and inhibitory interneurons supplied by high-threshold sensory afferents may be involved.

Central Hypothesis

Convergence of multiple afferent inputs from the muscle and other visceral and somatic structures in the lamina I or V of the dorsal horn on the way to the cortex can result in perception of local and referred pain.[7]

Central Biasing Mechanism

Multiple peripheral and central factors may inhibit or facilitate central input through modulatory influence of the brainstem. This may explain the diverse factors that can either exacerbate or alleviate the pain, such as stress, repetitive strain, poor posture, relaxation, medications, temperature change, massage, local anesthetic injections, and electrical stimulation.

Clinical Presentation

The major characteristics of masticatory myalgia include pain, muscle tenderness, limited range of motion, and other symptoms such as fatigability, stiffness, and subjective weakness. Comorbid conditions and complicating factors are also common and discussed. Each will be discussed for the different subtypes.

Pain

The common sites of pain in the masticatory system include jaw pain; facial pain; temporal, frontal, or occipital headaches; preauricular pain; earache; and neck pain. The pain is often a constant steady dull ache that fluctuates in intensity and can be acute to chronic. The duration may vary from hours to days.

Muscle Tenderness

In MFP the tenderness is in a deep, localized (2 to 5 mm), taut band of skeletal muscle, a TrP, which is associated with consistent patterns of pain referral. In contrast, muscle tenderness in myositis and muscle spasm can be generalized over the whole muscle. Myofascial TrPs are very common and may be active or latent. Active TrPs are hypersensitive and display continuous pain in the zone of reference that can be altered with specific palpation. Latent TrPs display only hypersensitivity with no continuous pain. This localized tenderness has been found to be a reliable indicator of the presence and severity of MFP with both manual palpation and pressure algometers.[8-10] However, the presence of taut bands appears to be a characteristic of skeletal muscles

in all subjects regardless of the presence of MFP. Palpating the active TrP with sustained deep single finger pressure on the taut band will elicit an alteration of the pain (intensification or reduction) in the zone of reference (area of pain complaint) or cause radiation of the pain toward the zone of reference. This can occur immediately or be delayed a few seconds. The pattern of referral is both reproducible and consistent with patterns of other patients with similar TrPs (Figure 45-1). This enables a clinician to use the zone of reference as a guide to locate the TrP for purposes of treatment.

Limited Range of Motion

tis, all of which must be ruled out by clinical examination and joint imaging. In MFP, limitation in range of motion may be slight (10% to 20%) and unrelated to joint restriction, whereas in muscle spasm, myositis, and contracture it may be gross (50% or more). A study of jaw range of motion in patients with MFP and no joint abnormalities demonstrated a slightly diminished range of motion of 35 to 45 mm (approximately 10% compared with unaffected individuals) and pain in the full range of motion. This is

TrPs in the same muscle and in other agonist muscles. This can cause multiple TrPs with overlapping areas of pain referral, with subsequent changes in pain patterns over time as TrPs are inactivated.

Other Symptoms

Other associated signs and symptoms that may occur include increased fatigability, stiffness, subjective weakness, pain in movement, otologic symptoms including dizziness, tinnitus, and plugged ears, paresthesias including numb feelings, decreased sensation and tingling, and dermatographia including increased redness of the skin on palpation or rolling. The affected muscles may also display an increased fatigability, stiffness, subjective weakness, pain in movement, and slight restricted range of motion that is unrelated to joint restriction.[1,4-7] The muscles are painful when stretched, causing the patient to protect the muscle through poor posture and sustained contraction.[12] There are no neurologic deficits associated with muscle pain disorders unless a nerve entrapment syndrome with weakness and diminished sensation coincides with the muscle tightness. Although routine clinical electromyography (EMG) shows no significant abnormalities associated with TrPs, some specialized EMG studies reveal differences.[13-16] The consistency of soft tissues over the TrPs has been found to be denser than over adjacent muscle.[17,18] Skin overlying the TrPs in the masseter muscle appears to be warmer as measured by infrared emission.[19,20] Routine clinical utility of these measurements remains controversial, however.

Comorbid Conditions and Complicating Factors

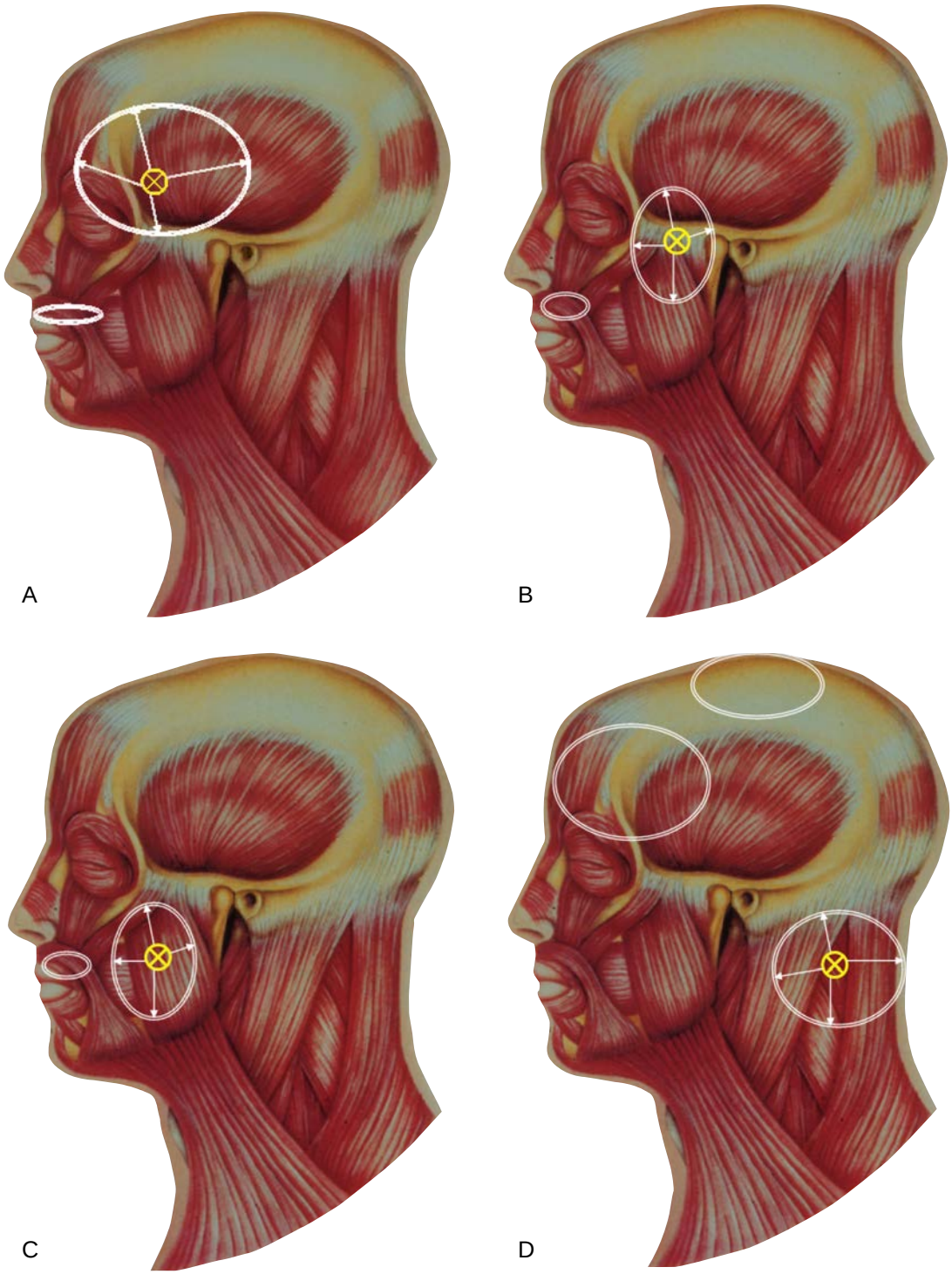
There are many comorbid conditions with myogenous TMD pain that reflect both common causative factors and mechanisms of pain. In most recent classifications, the regional pain found with MFP is distinguished from the widespread muscular pain associated with fibromyalgia (FM). These two disorders have many similar characteristics and may represent two ends of a continuous spectrum. For example, as Simons[21] points out, 16 of the 18 tender point sites in FM lie at well-known TrP sites. Many of the clinical characteristics of FM such as fatigue, morning stiffness, and sleep disorders can also accompany MFP. Bennett[22] compares these two disorders and concludes that they are two distinct disorders but may have similar underlying pathophysiology. The clinical significance of distinguishing between them lies in the more common centrally generated contributing factors in FM (sleep disorders, depression, and stress) versus the more common regional contributing factors in MFP (trauma, posture, and muscle tension habits) as well as the better prognosis in treatment of MFP as compared with FM.

Other comorbid conditions that have often been cited to accompany myogenous disorders include joint disc displacement and osteoarthritis, malocclusion and functional occlusal dysfunction, connective tissue diseases, neuropathic pain disorders, migraine and tension type headaches, gastrointestinal disorders, and hypothyroidism. It is not clear what mechanism underlies the coexistence of these conditions. Common central and peripheral pain mechanisms and causes may play a role.

Furthermore, many associated behavioral and psychosocial factors can accompany the chronic pain associated with myogenous disorders, including behavioral factors such as muscle tension, oral parafunctional, and maladaptive postural habits; psychologic factors such as frustration, anxiety, and depression; secondary gain from pain behaviors such as pain verbalization and avoidance of activities; medication dependencies; and sleep disturbance.

Diagnostic Tests

Diagnoses of masticatory myalgia are typically determined through the clinical diagnostic criteria that are listed in Box 45-1. However, some diagnostic strategies can be helpful. In MFP, injections of local anesthetic into the active TrP will reduce or eliminate the referred pain and the tenderness. Imaging studies often used to evaluate for dental or TMJ disease, including radiographs and magnetic resonance imaging, are generally normal. Routine clinical EMG studies are abnormal in muscle spasm only. Some specialized EMG studies (twitch response) reveal differences in cases of MFP but have limited applicability in routine clinical



• **Figure 45-1** Trigger points in myofascial pain with associated patterns of referral in the jaw, head, and neck. **A,** The pain source is the anterior temporalis trigger point. Pain occurs as temple, frontal, and retro-orbital headaches and pain in the maxillary anterior teeth. These muscles are activated by clenching, bruxism, and other oral parafunctional habits. **B,** The pain source is the deep masseter trigger point. Pain occurs as preauricular pain, earaches, and pain in the maxillary posterior teeth. These muscles are also activated by clenching, bruxism, and other oral parafunctional habits. **C,** The pain source is the middle masseter trigger point. Pain occurs as temple, frontal, and retro-orbital headaches and as pain in the maxillary anterior teeth. These muscles are also activated by clenching, bruxism, and other oral parafunctional habits. **D,** The pain source is the splenius capitus trigger point in the posterior cervical area. Pain occurs as posterior cervical pain, vertex headache, and frontal headache. These muscles are also activated by clenching and forward head pressure.

• BOX 45-1 Diagnostic Criteria for Masticatory Myalgia Disorders

Myofascial Pain—Repetitive Strain

- Dull aching pain in the jaw, face, ear, temples, or forehead
- Localized tenderness (trigger points) in specific taut muscle bands with tenderness on the same side as the pain; see Figure 45-1 for sites and referral patterns
- Duplication of the pain with palpation of the tender trigger points

Muscle Spasm—Acute Overuse

- Acute onset of pain in the jaw, face, ear, or temples at rest and in function
- Moderate to severe acute limited range of motion due to continuous muscle contraction; in lateral pterygoid spasm, the jaw has a shift to one side with subsequent acute malocclusion that is reversible
- Generalized tenderness of the muscle

Myositis—Injury or Infection

- Pain, usually continuous, in a localized muscle area after injury or infection; pain is increased with mandibular movement
- Diffuse tenderness over the entire muscle area involved
- Moderate to severe limited range of motion
- Swelling over muscle area involved

Muscle Contracture—Muscle Fibrosis

- Gross limited range of mandibular motion
- Unyielding firmness on passive stretch (hard end feel)
- Little or no pain unless the involved muscle is forced to lengthen
- Remote history of trauma, infection, or long period of disuse and limited range of motion

practice. Blood and urine studies are generally normal unless caused by a concomitant disorder. Pain questionnaires such as the Chronic Pain Battery and TMJ Scale may identify contributing factors including emotional issues, somatization, secondary gain, and disability.

Treatment

Simple to Complex

Treatment of myogenous pain can range from simple cases with transient single muscle syndromes to complex cases involving multiple muscles and many interrelating contributing factors. Many authors have found success in treatment of myogenous pain using a wide variety of techniques such as exercise, TrP injections, vapocoolant spray and stretch, transcutaneous electrical nerve stimulation (TENS), biofeedback, posture correction, tricyclic antidepressants, muscle relaxants and other medications, and addressing of perpetuating factors.[13,23-25] However, the management challenge lies in the critical need to match the level of complexity of the management program with the complexity of the patient. Failure to address the entire problem, including all involved muscles, concomitant diagnoses, and contributing factors, may lead to failure to resolve the pain or, worse, perpetuation of the pain.

• BOX 45-2 Criteria for Complex Cases

Fulfilling any one of these criteria suggests that this patient's case is complex and may require the use of team treatment to address the contributing factors and improve the prognosis.

- Persistent pain (daily or regular) longer than 6 months in duration
- Significant lifestyle disturbances such as loss of work, social activities, or home activities
- High use of past health care including medications for problem or related problems
- Emotional difficulties related to problem including depression, anxiety, or anger
- Daily oral habits such as clenching or grinding of the teeth
- Significant stressful life events such as pacing problems, divorce, or recent death in family

Although there are no prospective studies examining progression of chronic pain syndromes, results from clinical studies reveal that many patients with muscle pain have seen many clinicians and received numerous medications and multiple other singular treatments for years without receiving more than temporary improvement. In one study of 164 muscle pain patients, the mean duration of pain was 5.8 years for males and 6.9 years for females, with a mean of 4.5 past clinicians seen for the study.[2] In another study of 102 consecutive TMJ and craniofacial pain patients including 59.8% muscle pain patients, the mean duration of pain was 6.0 years, with 28.8 previous treatment sessions, 5.1 previous doctors, and 6.4 previous medications.[26] These and other studies of chronic pain suggest that regardless of the pathogenesis of muscular pain, a major characteristic of many of these cases is the failure of traditional approaches to resolve the problem. Therefore each clinician confronted with a patient with muscle pain needs to recognize and address the whole problem to maximize the potential for a successful outcome.

Treating only those patients whose complexity matches the treatment strategy available to the clinician can improve success. Simple cases with minimal behavioral and psychosocial involvement can typically be managed by a single clinician. Complex cases (Box 45-2) should be managed within an interdisciplinary pain clinic setting that uses a team of clinicians to address different aspects of the problem in a concerted fashion. Box 45-3 presents a hierarchy of treatment strategies depending on whether the condition is acute, simple, or complex.

Treatment Goals

The short-term goal is to restore the muscle to normal length and posture and allow full joint range of motion through exercises and TrP therapy. This is followed long term with a regular muscle stretching, postural, and strengthening exercise program, as well as control of contributing factors.

• BOX 45-3 Protocol Checklist for Managing Masticatory and Cervical Myalgia Pain

I. Evaluation
  A. Identify masticatory and cervical muscles involved
  B. Identify each area of pain
    - Frequency
    - Duration
    - Intensity
  C. Identify contributing factors
    - Direct macrotrauma (e.g., blow to jaw)
    - Indirect macrotrauma (e.g., whiplash injuries)
    - Repetitive postural strain (e.g., phone bracing)
    - Oral parafunctional habits (e.g., clenching and grinding of teeth)
    - Dietary factors (e.g., caffeine)
    - Sleep disturbance
    - Psychosocial stressors
    - Anxiety and depression
  D. Determine simple versus complex
    - Simple: single clinician evaluation and treatment
    - Complex: team evaluation including dentist, physical therapist or chiropractor, psychologist

II. Management
  A. Acute
    - Palliative self-care
  B. Simple case management with single clinician
    - Self-care
    - Splint
    - Jaw exercises
    - Vapocoolant spray or other modality with stretching
    - Oral habit instruction
  C. Complex case management
    - Self-care
    - Splint
    - Trigger point or muscle injections
    - Medications (muscle relaxants and anti-inflammatories as needed)
    - Exercises with physical therapist
    - Cognitive-behavioral therapy
    - Counseling as needed

Long-term control of pain depends on patient education, self-responsibility, and development of long-term doctor-patient relationships. This often requires shifting the paradigms implicit in patient care as listed in Table 45-1. The difficulty in long-term management often lies not in treating the TrPs, but rather in the complex task of changing the identified contributing factors because they can be integrally related to the patient's attitudes, lifestyles, and social and physical environment. Interdisciplinary teams integrate various health professionals in a supportive environment to accomplish both long-term treatment of illness and modification of these contributing factors. Many approaches, such as habit reversal techniques, biofeedback, and stress management, have been used to achieve this result within a team approach.

Management follows goals including self-care, muscle exercises, muscle therapy, and reducing all contributing factors and is directed at rehabilitating the muscle to improving tenderness and range of motion, reducing tenderness, and reducing or eliminating contributing factors. Muscle rehabilitation is focused on exercise to improve range of motion, relaxation, and strength of the muscle. Reduction of contributing factors includes reducing biomechanical strain to the muscles from oral parafunctional habits such as clenching, gum chewing, and other repetitive strain activities. In addition, improved posture of the head, neck, and tongue will reduce sustained muscle activity and encourages healing. Reducing tenderness can be accomplished by inhibiting peripheral neural input through various treatment modalities such as cold, heat, analgesic medications, massage, muscle injections, and TENS. Reducing central modulating factors requires the patient to manage contributing factors such as improving stress, sleep, anxiety, and depression.

TABLE 45-1 Shifting Paradigms in Patient Care

Shifting the doctor-patient paradigms involves each member of the team following the same concepts by conveying the same messages implicit in the dialogue with the patient.

Concept	Statement
Self-responsibility	You have more influence on your problem than we do.
Self-care	You will need to make daily changes in order to improve your condition.
Education	We can teach you how to make the changes.
Long-term change	It will take at least 6 months for the changes to have an effect.
Doctor-patient relationship	We will support you as you make the changes.
Patient motivation	Do you want to make the changes?

Control of Contributing Factors

One of the common causes of failure in managing masticatory myalgia is failure to recognize and subsequently control contributing factors that may perpetuate muscle restriction and tension. As noted earlier, postural contributing factors, whether behavioral or biologic, perpetuate muscle pain if not corrected. In general, a muscle is more predisposed to developing problems if it is held in sustained contraction in the normal position and especially if it is in an abnormally shortened position. Such a situation exists with structural problems such as loss of posterior teeth, an excessive lordosis of the cervical spine, a unilateral short leg, or a small hemipelvis.[11] An occlusal imbalance can be corrected with an occlusal stabilization splint, also termed a *flat plane* or *full-coverage splint*. Other postural factors that can be corrected include a foot lift for a unilateral leg length discrepancy, a pelvic lift for a small hemipelvis, and proper height of arm rests in chairs for short upper arms.

• BOX 45-4 Palliative Self-Care Program for Acute Episodes of Masticatory Myalgia

- Eat a soft diet and avoid caffeine.
- Keep your tongue up and gently resting on the palate. Keep teeth apart as the rest position of the jaw.
- Chew on both sides at the same time or alternate sides to minimize strain to muscles.
- Avoid oral parafunctional habits such as clenching and grinding the teeth, jaw tensing, or gum chewing.
- Avoid excessive or prolonged opening of mouth.
- Avoid sleeping on your stomach to minimize strain to the jaw during sleep.
- Use over-the-counter analgesics or nonsteroidal anti-inflammatories as directed for pain.
- Use heat or ice over the tender muscles.

Behavioral factors causing sustained muscle tension can also occur with habits such as a receptionist cradling a phone between the head and shoulder for hours each day, a laborer lifting with lumbar strain, a student studying with the head forward for hours at a time, or bruxism, clenching, gum chewing, or other oral parafunctional habits. Correcting poor habits through education and long-term reinforcement is essential to preventing a reduced TrP from returning. Biofeedback, meditation, hypnosis, stress-management counseling, psychotherapy, antianxiety medications, antidepressants, and even placebos have been reported to be effective in treating masticatory myalgia.[26-30] Many of these treatments are directed toward reducing muscle tension that produces habits such as bruxism or bracing of muscles. Teaching control of habits is a difficult process because of the relationship that muscle tension may have to psychosocial factors. Simply telling a patient to stop the habits may be helpful with some, but with others it may result in noncompliance, failure, and frustration. An integrated approach involving education, increased awareness, and other treatments, such as behavior modification, biofeedback, hypnosis, or drug therapy, may prove to be more successful.

Simple Management

Self-Care

Most acute recent symptoms are self-limited and resolve with minimal intervention. Initial treatment should be a self-care program (Box 45-4) to reduce repetitive strain of the masticatory system and encourage relaxation and healing of the muscles.

This strategy includes jaw range of motion exercises, oral habit change, and protective gentle use of the jaw. Most patients respond well to self-care in 4 to 6 weeks; if not, further assessment and treatment are indicated.

Orthopedic Intraoral Splints

Orthopedic intraoral splints can encourage relaxation of the muscles, alter muscular recruitment patterns, and reduce oral habits. Stabilization splints allow passive protection of the jaw and reduction of oral habits owing to the flat passive occlusal surface on mandibular or maxillary teeth. Mandibular splints can be smaller and result in higher patient satisfaction in some cases. Splints should be adjusted to achieve mutually protected occlusion with bilateral balanced contact on all posterior teeth with the condyles in their most seated positions, with anterior guidance (lateral and protrusive) provided by the canines and/or incisors.

Anterior repositioning splints can be efficacious for concomitant joint problems with intermittent jaw locking with limited range of motion, especially on awakening, and are recommended for short-term, part-time use, primarily during sleep. Long-term or continuous use must be avoided because they can cause occlusal changes.

Partial coverage splints may cause occlusal changes in some patients. Splints should cover all of the mandibular or maxillary teeth to prevent movement of uncovered teeth resulting in iatrogenic malocclusion.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) approaches can help change maladaptive habits and behaviors that contribute to myalgia such as jaw tensing, teeth clenching, and teeth grinding. Although many simple habits are easily abandoned when the patient becomes aware of them, changing persistent habits requires a structured program that is facilitated by a clinician trained in behavioral strategies. Habits do not change themselves, and patients are responsible for initiating and maintaining behavior changes.

Habit reversal can be accomplished by becoming more aware of the habit, knowing how to correct it (e.g., what to do with the teeth and tongue), and knowing why to correct it. Correcting a habit during the day will also help reduce it at night. These educational points from the clinician must be combined with the patient's commitment to conscientious self-monitoring and focus on the goal.

Muscle Exercises

The most useful exercise techniques for muscle rehabilitation include muscle stretching, posture, and strengthening exercises.[13,24,25,31] In patients with muscle pain, a home program of active and passive muscle stretching exercises will reduce the activity of muscle pain, and postural exercises will reduce susceptibility to reactivation of pain by physical strain (Figure 45-2). Strengthening and cardiovascular fitness exercises will improve circulation, strength, and durability of the muscles.

Pharmacotherapy

Pharmacotherapy is a useful adjunct to initial treatment muscle relaxants, tranquilizers (ataractics), sedatives, and antidepressants. Analgesics are used to allay pain; muscle



• **Figure 45-2** Jaw exercises. These jaw stretching exercises can be used for initial postural correction and range of motion restoration for masticatory myofascial pain. They can restore normal joint function and mobility and result in a more comfortable and normal jaw position. They are performed gradually and gently six times daily for about 1 minute each. The jaw should be progressively stretched slightly beyond the point of tightness and pain. Caution should be taken to avoid overstretching with acutely strained jaws or capsulitis of the temporomandibular joint. Place one finger between the teeth for 1 minute. Rest and repeat. Then place two fingers between the teeth for 1 minute. Rest and repeat. In some cases without significant joint restriction, using three fingers to stretch may be needed.

relaxants and tranquilizers for anxiety, fear, and muscle tension; sedatives for enhancing sleep; and antidepressants for pain, depression, and enhancing sleep.[23]

Randomized clinical trials on NSAIDs such as ibuprofen and piroxicam suggest that for myalgia, short-term use of these medications for analgesic and/or anti-inflammatory effects certainly can be considered as a supplement to overall management. Chronic, long-term use is undertaken with caution owing to the long-term systemic and gastrointestinal effects. If some therapeutic result is not apparent after 7 to 10 days or if the patient develops any side effects, especially gastrointestinal symptoms, the medication should be discontinued.

For muscle pain, especially with stress and sleep disturbance, benzodiazepines, including diazepam and clonazepam, have been shown to be effective. Experience suggests that these are best used before bedtime to minimize sedation while awake. Cyclobenzaprine (Flexeril) has also been shown in clinical trials of myalgia to be efficacious in reducing pain and improving sleep[32,33] and can be considered when a benzodiazepine is too sedating. These medications, with or without NSAIDs, can also be considered for a 2- to 4-week trial with minimal habituation potential. However, long-term use has not been adequately tested.

Advanced Management

Cognitive-Behavioral Therapy

When necessary, basic habit reversal may be supplemented with additional behavioral strategies such as biofeedback, meditation, stress management, or relaxation techniques. It may also be important to address poor pacing or hurrying related to a day overloaded with commitments, depression, anxiety, sleep disorders, or emotional problems. This may require behavioral and psychologic therapy and/or medications and is best managed by a competent psychologist or psychiatrist.

Muscle Exercises

Passive and active stretching of the muscles will increase the opening to the normal range as well as decrease the pain. Passive stretching of the masticatory muscles during counter stimulation of the tender muscle can be accomplished through placing a properly trimmed and sterile cork, tongue blades, or other object between the incisors while the spray and stretch technique is accomplished. It must be emphasized to avoid rapid, jerky stretching or overstretching of the muscle to reduce potential injury to the muscle.

Postural exercises are designed to teach the patient mental reminders to hold the body in a balanced relax position and use the body with positions that afford the best mechanical advantage. In improving posture, specific skeletal conditions such as structural asymmetry or weakness of certain muscles need to be considered. For the masticatory system the patient should be instructed to place the tongue gently on the roof of the mouth and keep the teeth slightly apart. For the cervical spine, a forward or lateral head posture must be corrected by guiding the chin in and the head vertex up. The shoulders will naturally fall back if the thorax is positioned up and back with proper lumbar support. Patients need to be instructed in proper posture for each position—sitting, standing, and lying down—as well as in movements that are done repetitively throughout the day such as lifting or turning the head to the side. Sleeping posture on the side or back is particularly important for patients who wake up with soreness.

Improved posture is also facilitated by regular physical conditioning. Patients need to be placed on a conditioning program to facilitate increased aerobic capacity and strength. Aerobic programs, such as becoming involved in an exercise class, regular running, walking, biking, or swimming, will improve comfort, endurance, and functional status of patients with muscle pain.[11]

Muscle Therapy

There are many methods suggested for providing repetitive stimulation to tender muscles. Massage, acupressure, and ultrasound provide noninvasive mechanical disruption to

reduce tenderness. Moist heat applications, ice packs, fluoromethane, and diathermy provide skin and muscle temperature change as a form of counter stimulation. TENS, electroacupuncture, and direct current stimulation provide electric currents to stimulate the muscles and TrPs. Acupuncture and TrP injections of local anesthetic, corticosteroids, or saline cause direct mechanical or chemical alteration of TrPs. However, the two most common techniques for treating muscle pain include spray and stretch technique and TrP injections.

With the spray and stretch technique, an application of a vapocoolant spray such as fluoromethane over the muscle with simultaneous passive stretching can provide immediate reduction of pain, although lasting relief requires a full management program.[8] The technique involves directing a fine stream of fluoromethane spray from the finely calibrated nozzle toward the skin directly overlying the muscle with the TrP. A few sweeps of the spray are first passed over the TrP and zone of reference before the addition of sufficient manual stretch to the muscle to elicit pain and discomfort. The muscle is put on a progressively increasing passive stretch while the jet stream of spray is directed at an acute angle from 30 to 50 cm (1 to 1½ feet) away. It is applied in one direction from the TrP toward its reference zone in slow even sweeps over adjacent parallel areas at a rate of about 10 cm/sec. This sequence can be repeated up to four times if the clinician warms the muscle with his or her hand or uses warm moist packs to prevent overcooling after each sequence. Frosting the skin and excessive sweeps should be avoided because they may lower the underlying skeletal muscle temperature, which tends to aggravate TrPs. The range of passive and active motion can be tested before and after spraying as an indication of responsiveness to therapy. Failure to reduce TrPs with spray and stretch may be due to inability to secure full muscle length because of bone or joint abnormalities, muscle contracture, or the patient avoiding voluntary relaxation; incorrect spray technique; or failure to reduce perpetuating factors. If spray and stretch fails with repeated trials, direct needling with TrP injections may be effective.

TrP muscle injections have also been shown to reduce pain, increase range of motion, increase exercise tolerance, and increase circulation of muscles.[9,10,14] The pain relief may last from the duration of the anesthetic to many months, depending on the chronicity and severity of TrPs and the degree of reduction in perpetuating factors. Because the critical factor in relief appears to be the mechanical disruption of the TrP by the needle, precision in needling of the exact TrP and the intensity of pain during needling appear to be the major factors in TrP inactivation.[15] TrP injections with local anesthetic are generally more effective and comfortable than dry needling or injecting other substances, such as saline, although acupuncture may be helpful for patients with chronic TrPs in multiple muscles. The effect of needling can be complemented with the use of local anesthetics in concentrations less than those required for a nerve conduction block. This can markedly lengthen the relative refractory period of peripheral nerves and limit the maximum frequency of impulse conduction. Local anesthetics can be chosen for their duration, safety, and versatility. Three percent chloroprocaine (short acting) and 5% procaine (medium acting) without vasoconstrictors are suggested.

Pharmacotherapy

Research on medications for FM, especially with sleep disturbances, indicates that tricyclic antidepressants such as amitriptyline (Elavil) have a significant impact on sleep disturbances, anxiety, and pain in FM patients. Therefore these medications can be used in appropriate cases long term.[34] However, the side effects with amitriptyline can be significant, and nortriptyline (Pamelor) can be considered an analogous medication with fewer side effects. Typically the dose for either of these medications in patients without depression is in the 25- to 75-mg range, taken at bedtime. The use of selective serotonin reuptake inhibitors (SSRIs) has been suggested for depression and pain but may also have the common side effect of increasing muscle tension and aggravating the pain.

For chronic pain conditions that are resistant to interventions, use of opioids can be considered. Tramadol has been shown to be effective in FM. However, there are no randomized clinical trials evaluating the appropriateness of opioids in the long-term treatment of chronic pain. At this time, chronic opioid use is mainly indicated for patients with chronic intractable severe pain conditions that are refractory to all other reasonable treatments because of their side effects, including constipation, sedation, potential for dose escalation, and unknown effects with long-term use.

Despite the advantages of medications for pain disorders, there exists an opportunity for problems to occur owing to their misuse. The problems that can occur from use of medications include chemical dependency, behavioral reinforcement of continuing pain, inhibition of endogenous pain relief mechanisms, side effects, and adverse effects from the use of polypharmaceuticals. For this reason the use of medication should proceed with caution.

Pain Clinic Team Management

Although each clinician may have limited success in managing the "whole" patient alone, the assumption behind a team approach is that it is vital to address different aspects of the problem with different specialists in order to enhance the overall potential for success.[17-19] Although these programs provide a broader framework for treating the complex patient, they have added another dimension to the skills needed by the clinician: working as part of a coordinated team. Failure to adequately integrate care may result in poor communication, fragmented care, distrustful relationships, and eventually confusion and failure in management.

However, team coordination can be facilitated by a well-defined evaluation and management system that clearly integrates team members.

A prerequisite to a team approach is an inclusive medical model and conceptual framework that places the physical, behavioral, and psychosocial aspects of illness on an equal and integrated basis.[20,35] With an inclusive theory of human systems and their relationship to illness, a patient can be assessed as a whole person by different clinicians from diverse backgrounds. Although each clinician understands a different part of the patient's problem, she or he can integrate understanding with other clinicians' perspectives and see how each part is interrelated in the whole patient. For example, a physician or dentist will evaluate the physical diagnosis, a physical therapist will evaluate poor postural habits, and a psychologist will evaluate behavioral problems or social stressors. Each factor will become part of the problem list to be addressed in the treatment plan. In the process, the synergism of each factor in the cause of the disorder can become apparent to clinicians. For example, social stressors can lead to anxiety, anxiety can lead to poor posture and muscle tension, the poor posture and muscle tension can lead to MFP syndrome, the pain contributes to more anxiety, and a cycle continues. Likewise, a reduction of each factor will work synergistically to improve the whole problem. Treatment of only one factor may improve the problem, but relief may be partial or temporary. Treatment of all factors simultaneously can have a cumulative effect that is greater than the effects of treating each factor individually.

The problem list for a patient with a specific chronic illness includes both a physical diagnosis and a list of contributing factors. In establishing the problem list the clinician needs to determine if the patient's case is complex and requires a team approach. Recommended criteria for determining complexity include any one of the following: multiple diagnoses, persistent pain longer than 6 months in duration, significant emotional problems (depression, anxiety), frequent use of health care services or medication, daily oral parafunctional habits, and significant lifestyle disturbances. The use of a screening instrument such as IMPATH, the McGill Pain Questionnaire, or the Multidimensional Inventory can readily elicit the degree of complexity of a case at initial evaluation.[1,36-38] The more complex the case is, the greater the need for a team approach. The decision to use a team must be made at the time of evaluation and not partway through a failing singular treatment plan. If a team is needed, the broad understanding of the patient is then used to design a long-term management program that both treats the physical diagnosis and helps reduce these contributing factors.

The primary goals of the program include reducing the symptoms and their negative effects and helping the patient return to normal function without need for future health care. The patient first participates in an educational session with each clinician to learn about the diagnoses and contributing factors, why it is necessary to change these factors, and how to do it. The dentist or physician is responsible for establishing the physical diagnosis, providing short-term medical or dental care, and monitoring medication and patient progress. The health psychologist is responsible for providing instruction about contributing factors; diagnosing, managing, or referring for primary psychologic disturbances; and establishing a program to support the patient and family in making changes. The physical therapist is responsible for providing support, instruction, and a management program for specifically assigned and common contributing factors, such as an exercise and posture program. Depending on the therapist's background and the patient's needs, this person may also provide special care such as physical therapy modalities or occupational therapy. Each clinician is also responsible for establishing a trusting, supportive relationship with the patient while reaffirming the self-care philosophy of the program, reinforcing change, and ensuring compliance. The patient is viewed as responsible for making the changes. The team meets weekly to review current patient progress and discuss new patients.

Summary

Goals of treatment of masticatory myalgia include reducing or eliminating pain, restoring normal jaw function, reducing the need for future health care, and restoring normal lifestyle functioning. The short-term strategy is to restore the muscle to normal length, posture, and full joint range of motion with exercises. The long-term strategy includes reducing the symptoms through muscle rehabilitation while helping the patient reduce contributing factors and return to normal function without the need for future health care.

Recent onset cases can often be managed with palliative self-care strategies designed to protect the muscles and encourage healing. Simple cases with minimal behavioral and psychosocial involvement can be managed by a single clinician (monodisciplinary fashion) with self-care, exercises, and a stabilization splint. Complex cases can be most effectively managed within an interdisciplinary pain clinic setting that uses a team of clinicians to address different aspects of the problem in a concerted fashion. Behavioral and psychosocial evaluation should be conducted on all patients with persistent pain to determine complexity and contributing factors. To improve outcomes, it is important to match the level of complexity of the management program with the complexity of the cases and use a pain clinic team approach to facilitate success in complex cases. Employing clinical paradigms of self-care, education, and self-responsibility in care will enhance long-term outcomes and maintain positive relationships between the patient and clinician.

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