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Salivary Gland Diseases

Margaret M. Grisius, DDS
Philip C. Fox, DDS

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Patients with salivary gland disease most frequently present with complaints of oral dryness, swelling, or a mass in a gland. This chapter first reviews briefly the anatomy and physiology of the salivary glands and then outlines a diagnostic approach to the patient who has signs and symptoms that are suggestive of salivary gland dysfunction. The examination of a patient with dry mouth is described, and the approach to the patient with a salivary mass is reviewed. Each of the major salivary gland disorders are described. At the end of the chapter, treatment options for the patient with salivary gland dysfunction are discussed.

▼ SALIVARY GLAND ANATOMY AND PHYSIOLOGY

There are three major salivary glands: parotid, submandibular, and sublingual. These are paired glands that secrete a highly modified saliva through a branching duct system. Parotid saliva is released through Stenson's duct, the orifice of which is visible on the buccal mucosa adjacent to the maxillary first molars. Sublingual saliva may enter the floor of the mouth via a series of short independent ducts, but will empty into the submandibular (Wharton's) duct about half of the time. The orifice of Wharton's duct is located sublingually on either side of the lingual frenum. There are also thousands of minor salivary glands throughout the mouth, most of which are named for their anatomic location (labial, palatal, buccal, etc). These minor glands are located just below the mucosal surface and communicate with the oral cavity with short ducts.

Saliva is the product of the major and minor salivary glands dispersed throughout the oral cavity. It is a highly complex mixture of water and organic and non-organic components. Most of the constituents are produced locally within the glands; others are transported from the circulation. The three major salivary glands share a basic anatomic structure. They

are composed of acinar and ductal cells arranged much like a cluster of grapes on stems. The acinar cells (the "grapes" in this analogy) make up the secretory endpiece and are the sole sites of fluid transport into the glands. The acinar cells of the parotid gland are serous, those of the sublingual gland are mucous, and those of the submandibular gland are of a mixed mucous and serous type. The duct cells (the "stems") form a branching system that carries the saliva from the acini into the oral cavity. The duct cell morphology changes as it progresses from the acinar junction toward the mouth, and different distinct regions can be identified.

While fluid secretion occurs only through the acini, proteins are produced and transported into the saliva through both acinar and ductal cells. The primary saliva within the acinar endpiece is isotonic with serum but undergoes extensive modification within the duct system, with resorption of sodium and chloride and secretion of potassium. The saliva, as it enters the oral cavity, is a protein-rich hypotonic fluid.

The secretion of saliva is controlled by sympathetic and parasympathetic neural input. The stimulus for fluid secretion is primarily via muscarinic cholinergic receptors, and the stimulus for protein release occurs through β-adrenergic receptors. Ligation of these receptors induces a complex signaling and signal transduction pathway within the cells, involving numerous transport systems.[1] An important point to consider is that loss of acini, as occurs in a number of clinical conditions, will limit the ability of the gland to transport fluid and to produce saliva. Also, muscarinic agonists will have the greatest effect in increasing saliva output as they are primarily responsible for the stimulus of fluid secretion. These points have implications for the treatment of salivary gland dysfunction.

▼ DIAGNOSTIC APPROACHES TO THE PATIENT WITH SALIVARY GLAND DISEASE

Evaluation of Dry Mouth

The subjective feeling of oral dryness is termed xerostomia. Xerostomia is a symptom, not a diagnosis or disease. The term is used to encompass the spectrum of oral complaints voiced by patients with dry mouth. It is important to recognize that a patient complaining of dry mouth cannot automatically be assumed to have a salivary dysfunction. While oral dryness is most commonly the result of salivary gland dysfunction, it may have other causes. Patients need careful objective examination to identify the basis of their problem. Since individuals with salivary gland dysfunction are at risk for a variety of oral and systemic complications due to alterations in normal salivary performance, they should be identified, and appropriate treatment should be implemented.

There are a number of nonsalivary causes of oral dryness complaints that should be considered, such as dehydration. Although dehydration may secondarily affect salivary gland output, changes in body water can affect mucosal hydration, which may lead to changes in the perception of wetness in the mouth. Central cognitive alterations and oral sensory disturbances can lead to a sense of mucosal dryness. There are also psychological conditions that can lead to the complaint of dry mouth.

Dysfunction of the salivary glands, however, is the most common cause of complaints of dry mouth. It is important to recognize that changes in salivary composition may be as important as a reduction in salivary output in some cases. Therefore, the demonstration of seemingly adequate salivary flow alone is not a guarantee of normal salivary gland function.

The differential diagnosis of xerostomia and salivary gland dysfunction is lengthy. The optimal approach to diagnosis is a sequential plan that first establishes the cause of the complaint, then determines the extent of salivary gland hypofunction that is present, and finally assesses the potential for treatment. An initial evaluation should include a past and present medical history, an oral examination, and an assessment of salivary function. Further techniques that may be indicated are salivary imaging, biopsy, and clinical laboratory assessment of hematologic variables. These are described below in more detail.

SYMPTOMS OF SALIVARY GLAND DYSFUNCTION

Symptoms in the patient with salivary gland hypofunction are related to decreased fluid in the oral cavity. Patients complain of dryness of all the oral mucosal surfaces, including the throat, and also of difficulty chewing, swallowing, and speaking. Many patients report a need to drink fluids while eating to help swallowing or report an inability to swallow dry foods. Most will carry fluids at all times for oral comfort and to aid speaking and swallowing. Pain is a common complaint. The mucosa may be sensitive to spicy or coarse foods, which limits the patient's enjoyment of meals.[2]

PAST AND PRESENT MEDICAL HISTORY

A critical first step is a thorough history. If the past and present medical history reveals medical conditions or medications that are known to be associated with salivary gland dysfunction, a diagnosis may be obvious. Examples would be a patient who has received radiotherapy for a head and neck malignancy or an individual who has recently started taking a tricyclic antidepressant. A recent survey found 1,500 drugs that are reported to have some incidence of dry mouth as a side effect. A complete history of all medications being taken (including over-the-counter medications, supplements, and herbal preparations) is critical. Often the temporal association of symptom onset with the treatment is a valuable clue. When the history does not suggest an obvious diagnosis, further detailed exploration of the symptomatic complaint should be undertaken. Unfortunately, the general complaint of oral dryness is not well correlated with decreased salivary function, but specific symptoms may be.[2] For example, while complaints of oral dryness at night or on awakening have not been found to be associated reliably with reduced salivary function, the complaints of oral dryness while eating, the need to sip liquids to swallow dry food, or difficulties in swallowing dry food have all been highly correlated with measured decreases in secretory capacity. These

complaints focus on oral activities (eg, swallowing and eating) that rely on stimulated salivary function. Patients should also be questioned concerning dryness at other body sites. A patient's report of eye, throat, nasal, skin, or vaginal dryness, in addition to xerostomia, may be a significant indication of a systemic condition, such as Sjögren's syndrome.[3,4]

CLINICAL EXAMINATION

Most patients with advanced salivary gland hypofunction have obvious signs of mucosal dryness. The lips are often cracked, peeling, and atrophic. The buccal mucosa may be pale and corrugated in appearance, and the tongue may be smooth and reddened, with loss of papillation. Patients may report that their lips stick to the teeth, and the oral mucosa may adhere to the dry enamel. There is often a marked increase in erosion and caries, particularly decay on root surfaces and even cusp tip involvement. The decay may be progressive, even in the presence of vigilant oral hygiene. One should look for active caries and determine whether the caries' history and current condition are consistent with the patient's oral hygiene. While caries are unquestionably increased, it has not been determined definitively whether increased prevalence or severity of periodontal pathology is associated with salivary gland hypofunction. Candidiasis, most commonly of the erythematous form, is frequent. Two additional indications of oral dryness that have been gleaned from clinical experience are the "lipstick" and "tongue blade" signs. In the former, the presence of lipstick or shed epithelial cells on the labial surfaces of the anterior maxillary teeth is indicative of reduced saliva (saliva would normally wet the mucosa and aid in cleansing the teeth). To test for the latter sign, the examiner can hold a tongue blade against the buccal mucosa; in a dry mouth, the tissue will adhere to the tongue blade as the blade is lifted away. Both signs suggest that the mucosa is not sufficiently moisturized by the saliva.

Enlargement of the salivary glands is seen frequently. In these cases, one must distinguish between inflammatory, infectious, or neoplastic etiologies. The major salivary glands should be palpated to detect masses and also to determine if saliva can be expressed via the main excretory ducts. Normally, saliva can be expressed from each major gland orifice by compressing the glands with bimanual palpation and by pushing towards the orifice. The consistency of the secretions should be examined. The expressed saliva should be clear, watery, and copious. Viscous or scant secretions suggest chronically reduced function. A cloudy exudate may be a sign of bacterial infection although some patients with very low salivary function will have hazy flocculated secretions that are sterile. In these cases, there may be mucoid accretions and clumped epithelial cells, which lend the saliva a cloudy appearance. The exudate should be cultured if it does not appear clear, particularly in the case of an enlarged gland. Palpation should be painless. Enlarged painful glands are indicative of infection or acute inflammation. The consistency of the gland should be slightly rubbery but not hard, and distinct masses within the body of the gland should not be present.[3–5]

SALIVA COLLECTION

Salivary flow rates provide essential information for diagnostic and research purposes. Salivary gland function should be determined by objective measurement techniques. Salivary flow rates can be calculated from the individual major salivary glands or from a mixed sample of the oral fluids, termed "whole saliva."

Whole saliva is the mixed fluid contents of the mouth. The main methods of whole saliva collection include the draining, spitting, suction, and absorbent (swab) methods. The draining method is passive and requires the patient to allow saliva to flow from the mouth into a preweighed test tube or graduated cylinder for a timed period. In the spitting method, the patient allows saliva to accumulate in the mouth and then expectorates into a preweighed graduated cylinder, usually every 60 seconds for 2 to 5 minutes. The suction method uses an aspirator or saliva ejector to draw saliva from the mouth into a test tube for a defined time period. The absorbent method uses a preweighed gauze sponge that is placed in the patient's mouth for a set amount of time. After collection, the sponge is weighed again, and the volume of saliva is determined gravimetrically.

The suction and absorbent (swab) methods give a variable degree of stimulation of secretion and are therefore less reproducible. The draining and the spitting methods are more reliable and reproducible for unstimulated whole saliva collection. If a stimulated whole saliva collection is desired, a standardized method of stimulation should be used. Chewing unflavored gum base or an inert material such as paraffin wax or a rubber band at a controlled rate is a reliable and reproducible means of inducing saliva secretion. One can also apply 2% citric acid to the tongue at regular intervals.[6,7]

It is difficult to determine a "normal" value for salivary output as there is a large amount of interindividual variability and consequently a large range of normal values. However, with the collection methods described above, most experts do agree on the minimal values necessary to consider salivary output normal. Unstimulated whole saliva flow rates of < 0.1 mL/min and stimulated whole saliva flow rate's of < 1.0 mL/min are considered abnormally low and indicative of marked salivary hypofunction. It is important to recognize that greater levels of output do not guarantee that function is normal. Indeed, they may represent marked hypofunction for some individuals. These values represent a lower limit of normal and a guide for the clinician.

Individual parotid gland saliva collection is performed by using Carlson-Crittenden collectors. The collectors are placed over the Stensen duct orifices and are held in place with gentle suction. Saliva from individual submandibular and sublingual glands is collected with an aspirating device or an alginate-held collector called a segregator. When using the suction device, gauze is placed sublingually to dry and isolate the sublingual region. The gauze and tongue are gently retracted away from the duct orifice. Gentle suction is used to collect the saliva as it is produced. The segregator is positioned over Wharton's ducts and is then held in place by alginate. As saliva is produced, it flows through tubing and is collected in a preweighed vessel.[6,8]

Stimulated saliva from individual glands is obtained by applying a sialagogue such as citric acid to the dorsal surface of the tongue. Preweighed tubes are used for individual salivary gland collections and for some of the whole saliva collection techniques, and flow rates are determined gravimetrically in milliliters per minute per gland, assuming that the specific gravity of saliva is 1 (ie, 1 g equals 1 mL of saliva). Samples to be retained for compositional analysis should be collected on ice and frozen until tested.[9–12]

Flow rates are affected by many factors. Patient position, hydration, diurnal variation, and time since stimulation can all affect salivary flow. Whichever technique is chosen for saliva collection, it is critical to use a well-defined, standardized, and clearly documented procedure. This allows meaningful comparisons to be made with other studies and with repeat measures in an individual over time. It is best to collect saliva in the morning. To insure an unstimulated sample, patients should refrain from eating, drinking, or smoking for 90 minutes prior to the collection.[9,12]

For a general assessment of salivary function, unstimulated whole saliva collection is the most valuable method of collection. It is easy to accomplish and is accurate and reproducible if carried out with a consistent and careful technique. Ideally, dentists would determine baseline values for unstimulated whole saliva output at an initial examination. This would allow later comparisons if patients begin to complain of oral dryness or present with other signs and symptoms of salivary dysfunction. For research purposes, or if more specific functional information is required for one particular gland, individual gland collection techniques should be used. These are not difficult but require specialized equipment and more time to accomplish.

SALIVARY GLAND IMAGING

A number of imaging techniques are useful in the evaluation of the salivary glands. For a full description of imaging techniques, see chapter 3, "Maxillofacial Imaging." The following describes specific techniques as they relate to the diagnosis of salivary gland disorders. Depending on the technique used, imaging can provide information on salivary function, anatomic alterations, and space-occupying lesions within the glands. This section discusses plain-film radiography, sialography, ultrasonography, radionuclide imaging, magnetic resonance imaging, and computed tomography (Table 9–1).

Plain-Film Radiography. Since the salivary glands are located relatively superficially, radiographic images may be obtained with standard dental radiographic techniques. Symptoms suggestive of salivary gland obstruction (swelling of the gland and pain) warrant plain-film radiography of the major salivary glands in order to visualize possible radiopaque sialoliths (stones) (Figure 9–1). Panoramic or lateral oblique and anteroposterior (AP) projections are used to visualize the parotid glands. Panoramic views overlap anatomic structures that can mask the presence of a salivary stone. A standard occlusal film can be placed intraorally adjacent to the parotid duct to visualize a stone close to the gland orifice. However, this technique will not capture the entire parotid gland. Sialoliths obstructing the submandibular gland can be visualized by panoramic, occlusal, or lateral oblique views.

Smaller stones or poorly calcified sialoliths may not be visible radiographically. If a stone is not evident with plain-film radiography but clinical evaluation and history are suggestive of salivary gland obstruction, then additional images are necessary.

Sialography. Sialography is the radiographic visualization of the salivary gland following retrograde instillation of soluble contrast material into the ducts (Figure 9–2). Sialography is one of the oldest imaging procedures and was first mentioned by Carpy in 1902. In 1925, Barsony and Uslenghi separately described sialography as a diagnostic tool. Sialography is the recommended method for evaluating intrinsic and acquired abnormalities of the ductal system because it provides the clearest visualization of the branching ducts and acinar end-

TABLE 9–1 Salivary Gland Imaging Modalities: Indications, Advantages, and Disadvantages

Imaging Modality	Indications	Advantages	Disadvantages
Ultrasonography	Biopsy guidance; mass detection	Noninvasive; cost-effective	No quantification of function; observer variability; limited visibility of deeper portions of gland; no morphologic information
Sialography	Stone, stricture; R/O autoimmune or radiation-induced sialadenitis	Visualizes ductal anatomy/ blockage	Invasive; requires iodine dye; no quantification
Radionuclide imaging	R/O autoimmune sialadenitis; sialosis, tumor	Quantification of function	Radiation exposure; no morphologic information
Computed tomography	R/O calcified structure; tumor	Differentiates osseous structures from soft tissue	No quantification; contrast dye injection; radiation exposure
Magnetic resonance imaging	R/O soft-tissue lesion	Soft-tissue resolution excellent, with ability to differentiate osseous structures from soft tissue; no radiation burden	Dental scatter; contraindicated with pacemaker or metal implant; no quantification

R/O = rule out

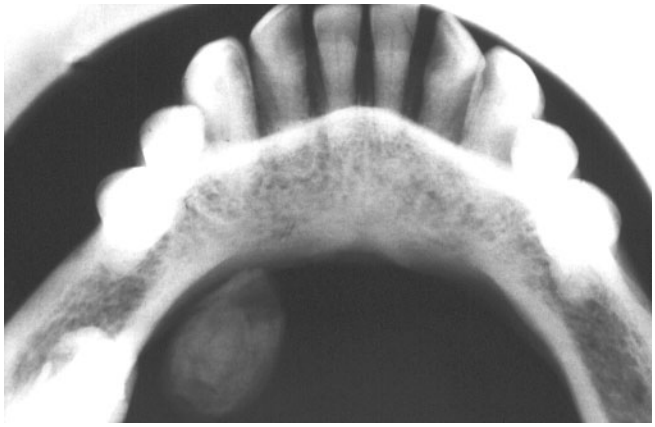

Figure 9–1 This roentgenogram occlusal view demonstrates a calcified deposit in Wharton's duct.

pieces. Salivary ductal obstruction, whether by a sialolith or stricture, can be easily recognized by sialography. When patients present with a history of rapid-onset, acute, painful swelling of a single gland (typically brought on by eating), sialography is the indicated imaging technique. Potential neoplasms are better visualized by cross-sectional imaging techniques such as computerized tomography or magnetic resonance imaging.

The two contraindications to sialography are active infection and allergy to contrast media. Sialography performed during active infection may further irritate and potentially rupture the already inflamed gland. Additionally, the injection of contrast material might force bacteria throughout the ductal structure and worsen the infection. The iodine in the contrast media may induce an allergic reaction and also can interfere with thyroid function tests and with thyroid cancer evaluation by nuclear medicine.

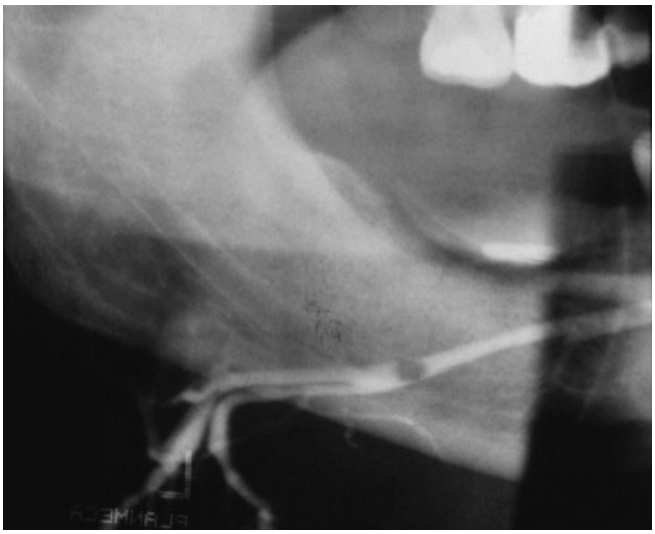

Figure 9–2 This is a sialogram of the submandibular gland demonstrating an uncalcified sialolithiasis in Wharton's duct, which can be visualized where the submandibular duct overlies the inferior alveolar canal. Courtesy of Dr. Eisa Mozaffari, University of Pennsylvania.

Sialography can be performed on both the submandibular and parotid glands. Initial plain-film radiography is recommended for visualizing radiopaque stones and potential bony destruction from malignant lesions, as well as for providing a background for interpreting the sialogram. Oil- and water-based contrast media are available. Both contain iodine and are therefore contraindicated in patients with iodine sensitivity.[13,14]

Oil-based contrast material is not diluted in saliva or absorbed across the mucosa, which allows for maximum opacificaton of the ductal and acinar structures. However, if extravasation into the glandular tissue occurs, the residual contrast material will remain at the site and may interfere with subsequent computed tomography (CT) images. Inflammatory responses and even the formation of granulomas have been reported following sialography using oil-based contrast. Injection of oil-based contrast medium requires more pressure because of its viscosity.

Water-based dyes are soluble in saliva and can diffuse into the glandular tissue, which can result in decreased radiographic density and poor visualization of peripheral ducts, compared to oil-based contrast. Higher-viscosity water-soluble contrast agents that allow better visualization of the ductal structures are available and are recommended.

Routine radiography includes panoramic, lateral oblique, AP, and "puffed-cheek" AP views. The normal ductal architecture has a "leafless tree" appearance. As the ductal structure branches through the major glands, the submandibular gland demonstrates a more abrupt transition in ductal diameter whereas the parotid gland demonstrates a gradual decrease in ductal diameter. Ductal stricture, obstruction, dilatation, ductal ruptures, and stones can be visualized by sialography. Nonopaque sialoliths appear as voids. Sialectasis is the appearance of focal collections of contrast medium within the gland, seen in cases of sialadenitis and Sjögren's syndrome. The progression of severity is classified as punctate, globular, and cavitary. Sialography is the imaging technique of choice for delineating ductal anatomy and for identifying and localizing sialoliths. It also may be a valuable tool in presurgical planning prior to the removal of salivary masses.[13,14]

Following the procedure, the patient should be encouraged to massage the gland and/or to suck on lemon drops to promote the flow of saliva and contrast material out of the gland. Postprocedure radiography is done approximately 1 hour later. If a substantial amount of contrast material remains in the salivary gland at that time, follow-up visits should be scheduled until the contrast material empties or is fully resorbed. Incomplete clearing can be due to obstruction of salivary outflow, extraductal or extravasated contrast, collection of contrast material in abscess cavities, or impaired secretory function.

Ultrasonography. Due to their superficial locations, the parotid and submandibular glands are easily visualized by ultrasonography although the deep portion of the parotid

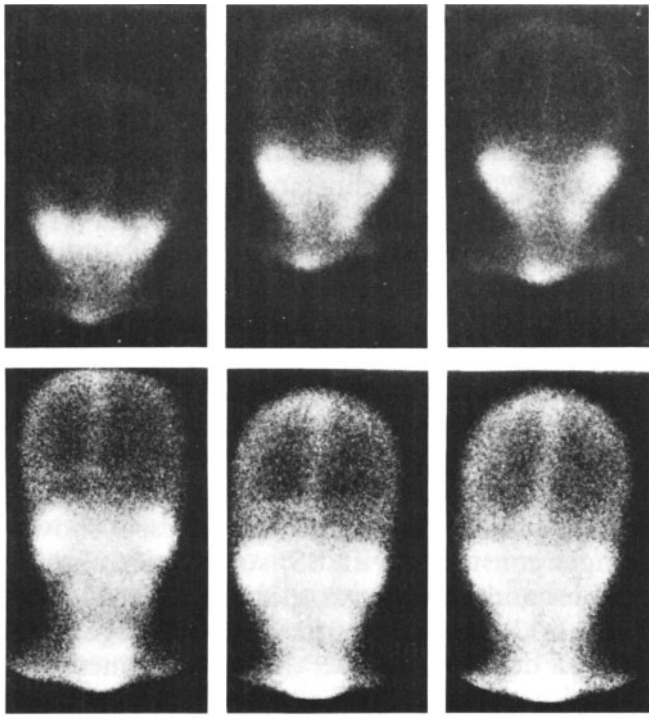

Figure 9–3 Anteroposterior view scintigrams developed during sequential salivary scintigraphy of the parotid gland for a normal patient (top row) and a patient with acute sialadenitis following administration of phenylbutazone (bottom row). Both illustrations on the left are at 10 minutes postintravenous injection of ^{99m}Tc pertechnetate, those in the middle at 30 minutes, and those on the right at 60 minutes. At 10 minutes, the isotope is already concentrated in the parotid and submandibular areas in contrast to that in the bloodstream, as reflected in the fainter outline of the cranium and sagittal venous sinuses. The thyroid gland, which also concentrated the isotope, also is intensely marked at the base of each scintigram. Normal and abnormal scintigrams show little difference at the time. In the normal scintigram at 30 minutes, an additional spot has appeared between the two parotid spots, corresponding to the secretion and accumulation of secreted isotope in the mouth and pharynx. By contrast, in the patient with acute sialadenitis who had markedly diminished salivary secretion, the parotid spots have intensified without development of a central spot. At 60 minutes, the xerostomia patient still retains a high level of radioactivity in the glands without a central secretory spot, whereas in the normal patient, the parotid spots are fading in contrast to the central spot. Because of the short half-life of this isotope of 6 hours, all radioactivity will have essentially disappeared from the scintigram by the next day, allowing the technique to be repeated if necessary. (Garfunkel AA, et al. Phenylbutazone-induced sialadenitis. Oral Surg. 1974; 38:223.)

gland is difficult to visualize because the mandibular ramus lies over the deep lobe. Ultrasonography is best at differentiating between intra- and extraglandular masses as well as between cystic and solid lesions. In general, solid benign lesions present as well-circumscribed hypoechoic intraglandular masses. Ultrasonography can demonstrate the presence of an abscess in an acutely inflamed gland, as well as the presence of sialoliths, which appear as echogenic densities that exhibit acoustic shadowing. Makula and colleagues studied a group of patients with Sjögren's syndrome and reported the appearance of parenchymal inhomogeneity. They also noted good agreement between ultrasonographic, sialographic, and scintigraphic results in this patient group. Ultrasonography is a noninvasive and cost-effective imaging modality that can be used in the evaluation of masses occurring in the submandibular gland and the superficial lobe of the parotid gland.[15–17]

Radionuclide Salivary Imaging. Scintigraphy with technetium (Tc) 99m pertechnetate is a dynamic and minimally invasive diagnostic test to assess salivary gland function and to determine abnormalities in gland uptake and excretion. Scintigraphy is the only salivary imaging technique that provides information on the functional capabilities of the glands (Figure 9–3). Technetium is a pure gamma ray–emitting radionuclide that is taken up by the salivary glands (following intravenous injection), transported through the glands, and then secreted into the oral cavity. Uptake and secretion phases can be recognized on the scans. Uptake of Tc 99m by a salivary gland indicates that there is functional epithelial tissue present. The Tc-99m scan can be used as a measure of secretory function as it has been shown to correlate well with salivary output. Tc 99m is capable of substituting for chloride (Cl^-) in the sodium-potasium (Na^+/K^+)/$2Cl^-$ salivary transport pump and serves as a measurement of fluid movement in the salivary acinar glands. Duct cells can also accumulate Tc 99m. Scintigraphy is indicated for the evaluation of patients when sialography is contraindicated or cannot be performed (such as in cases of acute gland infection or iodine allergy) or when the major duct cannot be cannulated successfully. It has also been used to aid in the diagnosis of ductal obstruction, sialolithiasis, gland aplasia, Bell's palsy and Sjögren's syndrome.[18–23]

Salivary imaging is performed following the injection of 10 to 20 mCi of Tc 99m pertechnetate. The uptake, concentration, and excretion of the pertechnetate anion by the major salivary glands and other organs is imaged with a gamma detector that records both the number and the location of gamma particles released in a given field during a period of time. This information can be stored in a computer for later analysis or recorded directly on film from the gamma detector, to give static images.

Several rating scales exist for the evaluation of salivary scintiscans; however, no standard rating method presently exists. Current approaches to functional assessment include visual interpretation, time-activity curve analysis, and numeric indices. Most radiologists read Tc 99m scans by using visual interpretation and clinical judgment. A semiquantitative

method exists in which Tc 99m uptake and secretion is calculated by computer analysis of a user-defined region of interest (ROI). Time-activity ROI studies are time-consuming and are more commonly used for research.

Radionuclide imaging can provide information regarding salivary gland function by generating a time-activity curve. A normal time-activity curve has three phases: flow, concentration, and washout. The flow phase is about 15 to 20 seconds in duration and represents the phase immediately following injection when the iostope is equilibrating in the blood and accumulating in the salivary gland at a submaximal rate. The concentration phase represents the accumulation of Tc 99m pertechnetate in the gland through active transport. This phase starts about 1 minute after administration of the tracer and increases over the next 10 minutes. With normal salivary function, tracer activity should be apparent in the oral cavity without stimulation after 10 to 15 minutes. Approximately 15 minutes after administration, tracer begins to increase in the oral cavity and decrease in the salivary glands. A normal image should demonstrate uptake of Tc 99m by both the parotid and submandibular glands, and the uptake should be symmetrical.

The last phase is the excretory or washout phase. During this phase, the patient is given a lemon drop, or citric acid is applied to the tongue to stimulate secretion. Normal clearing of Tc 99m should be prompt, uniform, and symmetrical. Activity remaining in the salivary glands after stimulation is suggestive of obstruction, certain tumors, and inflammation.

With few exceptions, neoplasms arising within the salivary glands do not concentrate Tc 99m. However, Warthin's tumor and oncocytomas, which arise from ductal tissue, are capable of concentrating the tracer. They retain Tc 99m because they do not communicate with the ductal system, and they appear as areas of increased activity on static images. The difference is accentuated during the washout phase, when normal tissue activity decreases with stimulation and activity is retained in the tumors. Other salivary tumors may appear as areas of decreased activity on scintiscans.[18–26]

Computed Tomography and Magnetic Resonance Imaging. Computed tomography (CT) images are produced by radiographic beams that penetrate the tissues (Figure 9–4). Computerized analysis of the variance of absorption produces a reconstructed image of the area. Coronal and axial images are usually obtained. The varying water content of tissues allows for magnetic resonance imaging (MRI) to distinguish tissue types. Tissues absorb and then re-emit electromagnetic energy when exposed to a strong electromagnetic field. Analysis of the net magnetization by radiofrequency is reconstructed to provide an image. Images are described as T1- or T2-weighted images, according to the rate constant with which magnetic polarization or relaxation occurs.

CT and MRI are useful for evaluating salivary gland pathology, adjacent structures, and the proximity of salivary lesions to the facial nerve. The retromandibular vein, carotid artery, and deep lymph nodes also can be noted on CT.

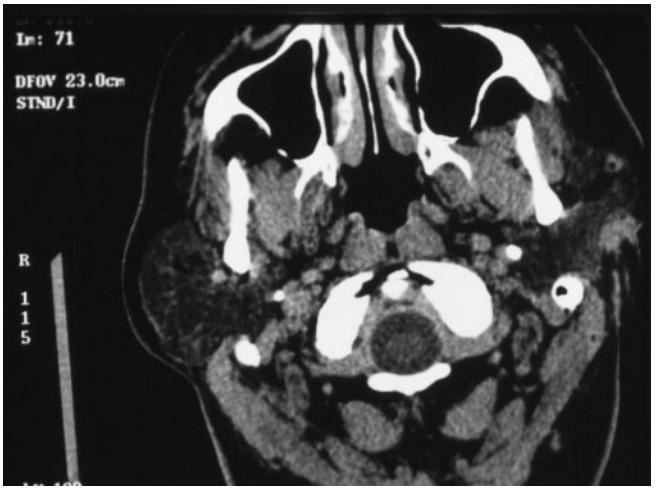

Figure 9–4 This is an axial view of a CT image soft tissue window demonstrating a tumor of the right parotid. Courtesy of Dr. Mel Mupparapu, University of Pennsylvania.

Osseous erosions and sclerosis are better visualized by CT than by MRI. Since calcified structures are better visualized by CT, this modality is especially useful for the evaluation of inflammatory conditions that are associated with sialoliths. Abscesses have a characteristic hypervascular wall that is evident with CT imaging. CT also provides definition of cystic walls, making it possible to distinguish fluid-filled masses (ie, cyst) from abscess.

CT images of salivary glands should be obtained by using continuous fine cuts through the involved gland. Axial-plane cuts should include the superior aspect of the salivary glands, continuing to the hyoid bone and visualizing potentially enlarged lymph nodes in the suprahyoid neck region. Dental restorations may interfere with CT imaging and may require repositioning the patient to a semiaxial position.

Non-enhanced and enhanced CT images are routinely obtained. The initial non-enhanced scans are reviewed for the presence of sialoliths, masses, glandular enlargement and/or asymmetry, nodal involvement, and loss of tissue planes. Glandular damage from chronic disease often alters the density of the salivary glands and makes the identification of masses more difficult. Contrast-enhanced images are more defined and accentuate pathology. Tumors, abscesses, and inflamed lymph nodes have abnormal enhancement compared to that of normal structures.

Ultrafast CT and three-dimensional–image CT sialography have been reported by Szolar and colleagues to be an effective method of visualizing masses that are poorly defined on MRI; they also advocate ultrafast CT for patients who are unable to lie still long enough for adequate MRI (pediatric, geriatric, claustrophobic, and mentally or physically challenged patients) and for patients for whom MRI is contraindicated. The disadvantages of CT include radiation exposure, administration of intravenous iodine-containing contrast media for enhancement, and potential scatter from dental restorations.

MRI has become the imaging modality of choice for preoperative evaluation of salivary gland tumors because of its excellent ability to differentiate soft tissues and its ability to provide multiplanar imaging. It provides images for evaluating salivary gland pathology, adjacent structures, and proximity to the facial nerve. In T1-weighted images, the normal parotid gland has greater intensity than muscle and lower intensity than fat or subcutaneous tissue. In T2-weighted images, the parotid has greater intensity than adjacent muscle and lower intensity than fat. Structures and conditions that are dark on both T1- and T2-weighted images include calcifications, rapid blood flow, and fibrous tissue. The use of intravenous MRI contrast can improve imaging and aid in defining neoplastic processes, but its uses are specific, and indications should be discussed with the radiologist.

MRI is preferred for salivary gland imaging because (a) patients are not exposed to radiation, (b) no intravenous contrast media are required routinely, and (c) there is minimal artifact from dental restorations. MRI is contraindicated for patients with pacemakers or metallic implants such as aneurysmal bone clips. Patients who have difficulty maintaining a still position or patients with claustrophobia may have difficulty tolerating the MRI procedure, which may result in poor image quality.[27–33]

The advantages and disadvantages of each method of imaging, as well as their indications for imaging the salivary glands, are listed in Table 9–1.

SALIVARY GLAND BIOPSY

Definitive diagnosis of salivary pathology may require tissue examination. When Sjögren's syndrome is suspected, the labial minor salivary gland is the most frequently sampled site. This procedure is considered to be the most accurate sole criterion for diagnosis of the salivary component of this disorder. Standardized histopathologic grading systems are used to assess the extent of changes (this is described in greater detail in the section of this chapter detailing Sjögren's syndrome). Biopsy of minor glands can also be used to diagnose amyloidosis. Biopsy of a minor gland of the lower lip is a minimal operative procedure that can be done with limited morbidity, using appropriate techniques. The incision is made on the inner aspect of the lower lip so that it is not externally visible. Six to ten minor gland lobules from just below the mucosal surface are removed and submitted for examination. The incision should be made through normal-appearing tissue, avoiding areas of trauma or inflammation of the lip that could influence the appearance of the underlying minor glands.

Biopsy of the major salivary glands requires an extraoral approach. There is increased morbidity, and major gland biopsy has not been shown to offer diagnostic superiority to the minor gland procedure in patients with Sjögren's syndrome. When major gland biopsy is indicated, such as for the evaluation of a distinct salivary mass, fine-needle aspiration can be attempted. If this does not yield an adequate sample for diagnosis, an open biopsy procedure should be done. In cases of suspected lymphoma, immunophenotyping of the tissue is essential for diagnosis.[34–36]

SEROLOGIC EVALUATION

Laboratory blood studies are helpful in the evaluation of dry mouth, particularly in suspected cases of Sjögren's syndrome. The presence of nonspecific markers of autoimmunity, such as antinuclear antibodies, rheumatoid factors, elevated immunoglobulins (particularly immunoglobulin G [IgG]), and erythrocyte sedimentation rate, or the presence of antibodies directed against the more specific extractable nuclear antigens SS-A/Ro or SS-B/La are important contributors to the definitive diagnosis of Sjögren's syndrome. Approximately 80% of patients with Sjögren's syndrome will display antinuclear antibodies, and about 60% will have antibodies against anti-SS-A/Ro. This latter autoantibody is considered the most specific marker for Sjögren's syndrome although it may be found in a small percentage of patients with systemic lupus erythematosus or other autoimmune connective-tissue disorders.[37,38] Another serologic marker that may prove useful for the diagnosis of salivary gland disorders is serum amylase. This is frequently elevated in cases of salivary gland inflammation. Determination of amylase isoenzymes (pancreatic and salivary) will allow the recognition of salivary contributions to the total serum amylase concentration.

Evaluation of a Salivary Mass or Enlarged Salivary Gland

PRESENTATION

Salivary gland tumors most commonly present as an asymptomatic mass. Pain is not a reliable indicator of malignancy. Cystic enlargement, hemorrhage, or infection can cause pain in benign tumors. Malignant tumors often enlarge without symptoms, but when pain occurs, it is often the result of neural involvement and carries a worse prognosis. If nasal obstruction is also present, the clinician should suspect a tumor in the nasal or paranasal sinuses, possibly arising from a minor salivary gland.

PHYSICAL EXAMINATION OF THE SALIVARY GLANDS

The major salivary glands are palpated, and the orifices of the ducts are observed for saliva output. Normally, clear saliva should be expressed when the gland is pressed and "milked." The facial nerve is assessed for any decrease in motor function, and regional lymph nodes are palpated. Intraorally, any masses noted on the soft or hard palate are evaluated for ulceration of mucosa and invasion of associated structures.

Tumors of the parotid gland will typically present as solitary painless mobile masses, most often located at the tail of the gland. It is important to document function of the facial nerve when evaluating parotid tumors, because the nerve runs through the gland, and evidence of decreased motor function of the nerve thus has diagnostic significance. Facial nerve paralysis is usually indicative of malignancy. Rarely, benign tumors may cause paralysis by either sudden rapid growth or the presence of an infection. Other findings suggesting malignancy include multiple masses, a fixed mass with invasion of surrounding tissue, and the presence of cervical lymphadenopathy.

Tumors in the submandibular or sublingual glands usually present as painless solitary slow-growing mobile masses. Bimanual palpation, with one hand intraorally on the floor of the mouth and the other extraorally below the mandible, is necessary to evaluate the glands adequately. Tumors of the minor salivary glands are usually smooth masses located on the hard or soft palate. Ulceration of the overlying mucosa should raise suspicion of malignancy.

Other lesions may mimic the presentation of salivary gland tumors. Inflammatory diseases, infections, and nutritional deficiencies may present as diffuse glandular enlargement (usually of the parotid gland). Patients who are seropositive for human immunodeficiency virus (HIV) may develop cystic lymphoepithelial lesions that may be confused with tumors. Both melanoma and squamous cell carcinoma can metastasize to the parotid gland and appear similar to a primary salivary tumor. Chronic sialadenitis in the submandibular glands can commonly be confused with a tumor. In the minor salivary glands, necrotizing sialometaplasia can be confused with squamous cell carcinoma. This can have significant adverse consequences since the treatments for these two lesions are so different.

IMAGING

Plain-film radiography of the mandible or maxilla may be performed as a rapid and inexpensive way to determine if salivary tumors involve adjacent bony structures. The bone is assessed for compression by slow expansion or erosion by aggressive invasion.

CT and MRI both image the salivary glands well, but they do not differentiate reliably between benign and malignant tumors. These modalities are not cost-effective for the initial evaluation of salivary gland lesions and are not recommended for the routine evaluation of salivary gland masses. Frequently, these imaging techniques are reserved for presurgical treatment planning, and initial evaluation is plain-film radiography followed by biopsy. If malignancy is known or suspected, scans can provide useful information about nodal involvement. Central necrosis of a lymph node is indicative of metastatic involvement.

Technetium scanning is useful for diagnosing salivary gland tumors containing oncocytes, such as Warthin's tumor and oncocytoma. These lesions appear as bright masses on the scan, indicating active uptake and retention of the radionuclide. Technetium scanning also provides information on the functional capabilities of the major salivary glands.

FINE-NEEDLE ASPIRATION BIOPSY

Fine-needle aspiration (FNA) biopsy is a simple and effective technique that aids the diagnosis of solid lesions. It may be particularly useful for elderly patients who can not tolerate an excisional biopsy because of medical considerations. A syringe is used to aspirate cells from the lesion for cytologic examination. To establish a diagnosis accurately, it is important to have a well-trained cytopathologist who is familiar with salivary cytology read the specimen. FNA biopsies do not provide a specimen with anatomic structure. The cytologist will examine the individual cells aspirated from the lesion and will offer a diagnosis based on the cellular characteristics of different lesions. Even if an exact diagnosis is not made, it may be possible to determine if a lesion is benign or malignant. Knowing the biologic aggressiveness of the tumor prior to definitive surgery is helpful in planning optimal treatment.[39]

OPEN SURGICAL BIOPSY

A preoperative surgical biopsy is rarely indicated for salivary masses. In almost all salivary gland tumors, the treatment of choice is an excisional biopsy. In the parotid gland, this most often consists of a superficial parotidectomy, with careful preservation of the facial nerve. In small well-localized tumors of the parotid gland, local excision may be performed. Enucleation of tumors or local excision, however, is associated with a high recurrence rate in the parotid gland and is infrequently recommended. Tumors in the submandibular gland require the total removal of the gland. For tumors in the minor salivary glands, total excision with a margin of normal tissue is required. This approach is both diagnostic and curative in the majority of salivary gland tumors.

Analysis of frozen sections should be performed at the time of surgery, to establish a diagnosis and guide the surgical approach. More than 80% of the time, the diagnosis based on the frozen section agrees with the final pathologic diagnosis from fixed and stained tissue. Most errors involve a failure to recognize malignant lesions. Malignant tumors are incorrectly called benign 5 to 24% of the time, but benign tumors are incorrectly diagnosed as malignant only 0 to 2% of the time. If frozen sections reveal a malignant tumor, the surgical margins may require extension.[40,41]

STAGING OF SALIVARY GLAND TUMORS

A single tumor-node-metastasis (TNM) staging system (Table 9–2) is used for tumors of the parotid and submandibular glands. The letter "T" denotes tumor size as well as extension into adjacent tissue; the letter "N" indicates nodal involvement. Local lymph nodes that are commonly involved by tumors of the parotid gland include the intraparotid, intraauricular, and preauricular nodes. The submandibular gland drains locally to the submandibular, upper cervical, and internal jugular lymph nodes. The letter "M" signifies metastases. Any nodal involvement other those mentioned above is considered a distant metastasis.

▼ SPECIFIC DISEASES AND DISORDERS OF THE SALIVARY GLANDS

Developmental Abnormalities

The absence of salivary glands is rare although it may occur together with other developmental defects, especially malformations of the first brachial arch, which manifest with various craniofacial anomalies. Patients with salivary gland aplasia

Table 9–2 Staging for Major Salivary Gland Cancer

T_x	Primary tumor can not be assessed
T_o	No evidence of primary tumor
T_1	Tumor < 2 cm in greatest dimension
T_2	Tumor 2–4 cm in greatest dimension
T_3	Tumor 4–6 cm in greatest dimension
T_4	Tumor >6 cm in greatest dimension

All categories are subdivided: (a) no local extension, (b) local extension. Local extension is clinical/macroscopic invasion of skin, soft tissue, bone or nerve. Microscopic evidence alone is not considered local extension for classification purposes.

N_x	Regional nodes cannot be assessed
N_0	No regional lymph node metastases
N_1	Single ipsilateral node < 3 cm in diameter
N_{2a}	Single ipsilateral node 3–6 cm in diameter
N_{2b}	Multiple ipsilateral node, none > 6 cm
N_{2C}	Bilateral or contralateral nodes, none > 6 cm
N_3	Metastasis in a lymph node > 6 cm
M_x	Presence of distant metastases cannot be assessed
M_0	No distant metastases
M_1	Distant metastases

Stage I	T_{1a}	N_0	M_0
	T_{2a}	N_0	M_0
Stage II	T_{1b}	N_0	M_0
	T_{2b}	N_0	M_0
	T_{3a}	N_0	M_0
Stage III	T_{3b}	N_0	M_0
	T_{4a}	N_0	M_0
	Any T (except T_{4b})	NI	M_0
Stage IV	T_{4b}	Any N	M_0
	Any T	N_2N_3	M_0
	Any T	Any N	M_1

Adapted from the American Joint Committee for Cancer Staging and End Results Reporting: manual staging of cancer. Chicago 1988

experience xerostomia and increased dental caries. Indeed, rampant dental caries in children who have no other symptoms has led to the diagnosis of congenitally missing salivary glands. Enamel hypoplasia, congenital absence of teeth, and extensive occlusal wear are other oral manifestations of salivary agenesis.[42,43]

Parotid gland agenesis has been reported in conjunction with several congenital conditions, including hemifacial microstomia, mandibulofacial dysostosis, cleft palate, lacrimoauriculodentodigital syndrome, Treacher Collins syndrome, and anophthalmia. Hypoplasia of the parotid gland has been associated with Melkersson-Rosenthal syndrome. Congenital fistula formation within the ductal system has been associated with brachial cleft abnormalities, accessory parotid ducts, and diverticuli.[43–51]

"Aberrant" salivary glands are salivary tissues that develop at unusual anatomic sites. Aberrant salivary glands have been reported in a variety of locations, including the middle-ear cleft, external auditory canal, neck, posterior mandible, anterior mandible, pituitary, and cerebellopontine angle. These are usually incidental findings and do not require intervention.[52-56]

When the submandibular salivary gland sits within a depression on the lingual posterior surface of the mandible, it is referred to as Staphne's cyst. Staphne's cyst is usually located between the angle of the mandible and the first molar below the level of the inferior alveolar nerve. The gland is usually asymptomatic and appears on radiographs as a round unilocular well-circumscribed radiolucency. The characteristic location and radiographic appearance make Staphne's cyst easily recognized. Palpation of the salivary gland is possible sometimes, and sialography has been used to aid in diagnosis. Surgical intervention is recommended only in atypical situations in which the diagnosis is unclear and a tumor is suspected. Less commonly, anterior lingual submandibular salivary glands have been reported.[56–60]

Aberrant salivary glands occur rarely in the anterior mandible and are difficult to diagnose. They may give rise to radiolucent lesions at the apex of teeth, at extraction sites, and below and between the roots of teeth. The differential diagnosis includes the numerous unilocular radiolucent lesions of the mandible, and definitive diagnosis usually requires surgical intervention. FNA biopsy may be attempted and can yield sufficient tissue for diagnosis.[60–61]

Accessory Salivary Ducts

Accessory ducts are common and do not require treatment. In a study of 450 parotid glands by Rauch and Gorlin, half of the patients had accessory parotid ducts. The most frequent location was superior and anterior to the normal location of Stenson's duct.[42]

Diverticuli

By definition, a diverticulum is a pouch or sac protruding from the wall of a duct. Diverticuli in the ducts of the major salivary glands often lead to pooling of saliva and recurrent sialadenitis. Diagnosis is made by sialography. Patients are encouraged to regularly milk the involved salivary gland and to promote salivary flow through the duct.[63–64]

Darier's Disease

Salivary duct abnormalities have been reported in Darier's disease. Sialography of parotid glands in this condition revealed duct dilation, with periodic stricture affecting the main ducts. Symptoms of occasional obstructive sialadenitis have been reported. Progressive involvement of the salivary ducts in Darier's disease may be more common than previously reported.[63,64]

Sialolithiasis (Salivary Stones)

The true prevalence of sialolithiasis is difficult to determine since many cases are asymptomatic. Sialoliths are calcified and organic matter that form within the secretory system of the major salivary glands. The etiology of sialolith formation is still unknown; however, there are several factors that contribute to stone formation. Inflammation, irregularities in the duct system, local irritants, and anticholinergic medications may cause pooling of saliva within the duct, which is thought to pro-

TABLE 9–3 Causes of Salivary Gland Hypofunction

Pharmaceuticals
Radiation therapy
External-beam radiation
Internal radionuclide therapy
Oncologic chemotherapy
Systemic diseases
Sjögren's syndrome (primary and secondary)
Granulomatous diseases (sarcoidosis, tuberculosis)
Graft-versus-host disease
Cystic fibrosis
Bell's palsy
Diabetes
Amyloidosis
Human immunodeficiency virus infection
Thyroid disease (hyper- and hypofunction)
Late-stage liver disease
Psychological factors (affective disorder)
Malnutrition (anorexia, bulimia, dehydration)
Idiopathic disorders

mote stone formation. It is believed that a nidus of salivary organic material becomes calcified and gradually forms a sialolith. Researchers have investigated the possibility of altered salivary hydrogen ion concentration (pH), abnormal serum calcium and phosphorous levels, and diet as causes of sialolith formation, but consistent alterations have not been detected. Frequently, there is no clear explanation for stone formation. Since the underlying cause is unknown and uncorrected in most patients, the recurrence rate is ≈20%.[65–67]

It is known that the structure of sialoliths is crystalline and that sialoliths are primarily composed of hydroxyapatite. The chemical composition is calcium phosphate and carbon, with trace amounts of magnesium, potassium chloride, and ammonium. Fifty percent of parotid gland sialoliths and 20% of submandibular gland sialoliths are poorly calcified. This is clinically significant because such sialoliths are not radiographically detectable.[66–69]

The submandibular gland is the most common site of involvement, and 80 to 90% of sialoliths occur in this gland. The parotid gland is involved in 5 to 15% of cases, and 2 to 5% of cases occur in the sublingual or minor salivary glands. It is believed that the higher rate of sialolith formation in the submandibular gland is due to (1) the torturous course of Wharton's duct, (2) higher calcium and phosphate levels, and (3) the dependent position of the submandibular glands, which leave them prone to stasis.[65–67]

Gout can cause salivary calculi composed of uric acid. However, patients with a history of renal stone formation do not have an increased incidence of salivary gland stone formation. There is one report of obstructive sialadenitis by intraparotid deposits of gold salts in a patient receiving sodium aurothiomalate (gold salt compound) treatment for rheumatoid arthritis.[70]

CLINICAL PRESENTATION AND EVALUATION

Patients with sialoliths most commonly present with a history of acute, painful, and intermittent swelling of the affected major salivary gland. The degree of symptoms is dependent on the extent of salivary duct obstruction and the presence of secondary infection. Typically, eating will initiate the salivary gland swelling. The stone totally or partially blocks the flow of saliva, causing salivary pooling within the ducts and gland body. Since the glands are encapsulated, there is little space for expansion, and enlargement causes pain. If the calculus partially blocks the duct, then the swelling subsides as salivary stimulation is removed and output decreases, and saliva seeps past the partial obstruction.[71,72]

The involved gland is usually enlarged and tender. Stasis of the saliva may lead to infection, fibrosis, and gland atrophy. Fistulae, a sinus tract, or ulceration may occur over the stone in chronic cases. An examination of the soft tissue surrounding the duct may show a severe inflammatory reaction. Palpation along the pathway of the duct may confirm the presence of a stone. Bacterial infections may or may not be superimposed and are more common with chronic obstructions. Other complications from sialoliths include acute sialadenitis, ductal stricture, and ductal dilatation.[72]

Radiographic examination is often necessary since the stone may not be accessible to bimanual palpation. However, as stated earlier, poorly calcified sialoliths will not be visible radiographically (see Figure 9–1). An occlusal view is the recommended view for radiography of submandibular glands. Stones in the parotid gland can be more difficult to visualize due to the superimposition of other anatomic structures; therefore, requesting proper radiographic views is important. An anteroposterior view of the face is useful for visualization of a parotid stone. One can also place an occlusal film intraorally adjacent to the duct. CT may be used for the detection of sialoliths and has 10 times the sensitivity of plain-film radiography for detecting calcifications.

Calcified phleboliths are stones that lie within a blood vessel; they can be easily mistaken radiographically for sialoliths. Phleboliths occur outside the ductal structure, and sialography can therefore aid in differentiating these lesions.

Stanley and colleagues reported using FNA of the submandibular gland as a diagnostic tool in 5 patients who did not present with classic symptoms of sialolithiasis. In 3 of the 5 cases, stone fragments were identified, and the patients were diagnosed with sialolithiasis. In the other 2 patients, FNA samples did not reveal stone fragments but showed foam cells and metaplastic squamous cells in a mucoid background that resembled low-grade mucoepidermoid carcinoma. Surgical excision of the glands was performed, and stones were found, which emphasizes that FNA cytology should be interpreted cautiously in this situation.[72]

TREATMENT

During the acute phase, therapy is primarily supportive. Standard care includes analgesics, hydration, antibiotics, and antipyretics, as necessary. In pronounced exacerbations, sur-

gical intervention for drainage is sometimes required. Stones at or near the orifice of the duct can often be removed transorally by milking the gland, but deeper stones require surgery. Once the acute phase subsides, surgical treatment can be performed. Location within the duct determines the type of surgery required for removal of the stone. If the stone lies in the intraglandular portion of the duct, it is recommended that the entire gland be removed. As much as 75% of normal function can return if the stone can be removed from within the duct, without entering the body of the gland.

Lithotripsy is gaining popularity because it offers a noninvasive treatment for sialoliths. Current protocols use ultrasonography to detect the stone and extracorporeal lithotripsy to fragment the stone. Several treatments may be needed, and a stone with a diameter of > 2 mm is required for detection with ultrasonography. Reported complications associated with this procedure include transient hearing changes, hematoma at the site, and pain. There have been initial reports of intraductal lithotripsy, but this technique requires specialized equipment and has been performed at only a few centers.[73–76]

Mucoceles

"Mucocele" is a clinical term that describes swelling caused by the accumulation of saliva at the site of a traumatized or obstructed minor salivary gland duct. Mucoceles are classified as extravasation types and retention types. A large form of mucocele located in the floor of the mouth is known as a ranula[77] (Figure 9–5).

EXTRAVASATION AND RETENTION MUCOCELES

Etiology. The formation of an extravasation mucocele is believed to be the result of trauma to a minor salivary gland excretory duct. Laceration of the duct results in the pooling of saliva in the adjacent submucosal tissue and consequent swelling. The extravasation type of mucocele is more common than the retention form. Although often termed a cyst, the extravasation mucocele does not have an epithelial cyst wall or a distinct border. In contrast, the retention mucocele is caused by obstruction of a minor salivary gland duct by calculus or possibly by the contraction of scar tissue around an injured minor salivary gland duct. The blockage of salivary flow causes the accumulation of saliva and dilation of the duct. Eventually, an aneurysm-like lesion forms, which can be lined by the epithelium of the dilated duct.

Clinical Presentation. Extravasation mucoceles most frequently occur on the lower lip, where trauma is common. The buccal mucosa, tongue, floor of the mouth, and retromolar region are other commonly traumatized areas where mucous extravasation may be found. Mucous retention cysts are more commonly located on the palate or the floor of the mouth.

A common clinical sequence is a history of a traumatic event, followed by the development of the lesion. Mucoceles often present as discrete painless smooth-surfaced swellings that can range from a few millimeters to a few centimeters in diameter. Superficial lesions frequently have a characteristic blue hue. Deeper lesions can be more diffuse and can be covered by normal-appearing mucosa without the distinctive blue color. The lesions may vary in size over time. Patients will frequently traumatize a superficial mucocele, allowing it to drain and deflate. In these circumstances, the mucocele will recur (see Figure 9–5; Figure 9–6).

Although the development of a bluish lesion after trauma is highly suggestive of a mucocele, other lesions (including salivary gland neoplasms, soft-tissue neoplasms, vascular malformation, and vesiculobullous diseases) should be considered.

Treatment. The treatment of choice for mucoceles is surgical excision. Removal of the associated salivary glands is essential to prevent recurrence. Aspiration of the fluid only does not provide long-term benefit. Managing of mucoceles can be difficult because surgical removal may cause trauma to other adjacent minor salivary glands and lead to the development of a new mucocele. Intralesional injections of corticosteroids have been used successfully to treat mucoceles.

RANULAS

A ranula is a large mucocele located on the floor of the mouth. Ranulas may be either mucous extravasation phenomena or

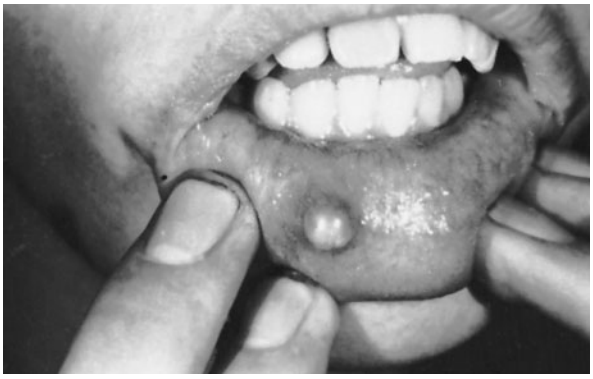

Figure 9–5 Mucocele. Mucous extravasation phenomenon involving the lower lip.

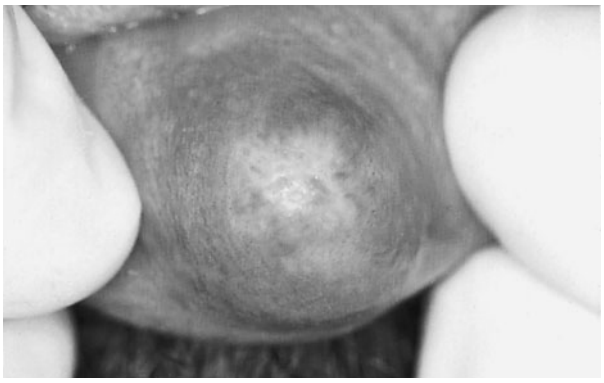

Figure 9–6 With time, fibrosis occurs, replacing the acinar functional cells with connective tissues. The inflammatory components disappear, and a sessile, firm mass is observed on the lower lip with normal mucous membrane.

mucous retention cysts and are most commonly associated with the sublingual salivary gland duct (Figure 9–7).

Etiology. The most common cause of ranula formation is trauma. Other causes include an obstructed salivary gland or a ductal aneurysm. A sarcoid-associated ranula also has been reported.

Clinical Presentation. The term "ranula" is used because this lesion often resembles the swollen abdomen of a frog. The lesion most commonly presents as a painless, slow growing, soft, and movable mass located in the floor of the mouth. Usually, the lesion forms to one side of the lingual frenum; however, if the lesion extends deep into the soft tissue, it can cross the midline. Like mucoceles, superficial ranulas can have a typical bluish hue, but when the lesion is deeply seated, the mucosa may have a normal appearance. The size of the lesions can vary, and larger lesions can cause deviation of the tongue. A deep lesion that herniates through the mylohyoid muscle and extends along the fascial planes is referred to as a plunging ranula and may become large, extending into the neck. Radiography should be performed to rule out a sialolith as a cause of duct obstruction. Radiopaque material instilled into the ranula cavity may be helpful in delineating the borders and full extent of the lesion.

Treatment. Ranulas are usually treated sugically. A marsupialization procedure that unroofs the lesion is the initial treatment of choice, especially for smaller lesions. Recurrences have been noted with the marsupialization technique alone, and in these cases, excision of the lesion (including the gland) is recommended. Intralesional injections of corticosteroids have been used succsessfully in the treatment of ranulas.

Inflammatory and Reactive Lesions

NECROTIZING SIALOMETAPLASIA

Etiology. Necrotizing sialometaplasia is a benign self-limiting reactive inflammatory disorder of the salivary tissue. Clinically, this lesion mimics a malignancy, and failure to recognize this lesion has resulted in unnecessary radical surgery. It is widely accepted that necrotizing sialometaplasia is initiated by a local ischemic event.

Clinical Presentation. Necrotizing sialometaplasia has a rapid onset. Lesions occur predominately on the palate; however, lesions can occur anywhere salivary gland tissue exists, including the lips and the retromolar pad region. Lesions initially present as a tender erythematous nodule. Once the mucosa breaks down, a deep ulceration with a yellowish base forms. Even though lesions can be large and deep, patients often describe only a moderate degree of dull pain.

Lesions often occur shortly after oral surgical procedures, restorative dentistry, or administration of local anesthesia although lesions also may develop weeks after a dental procedure or trauma. It is not uncommon for lesions to develop in

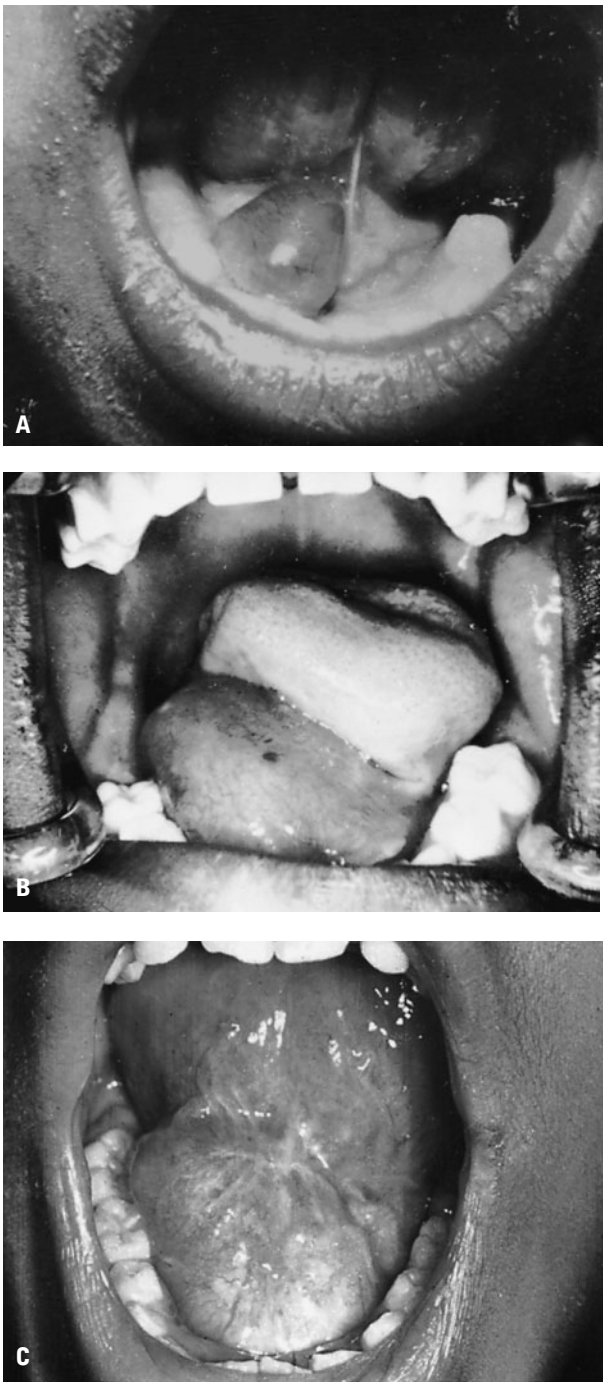

Figure 9–7 **A,** Blockage of Wharton's duct at the salivary orifice on the lingual frenum induces acute cystic dilation of the proximal portion of the duct as the secretory pressure from a functional gland is directed at the point of blockage. The ranula may be caused by blockage of this duct and is manifested by acute swelling in the floor of the mouth. **B,** When blockage is extensive and complete, the swollen mass extends posteriorly throughout the course of the submandibular salivary duct. The tongue may be elevated by this fluctuant mass, with associated pain and discomfort. Note the prominent vasculature, indicating the stretching of the sublingual tissues. **C,** Frequently some form of drainage is spontaneously achieved, but the cystic enlargement of the distal section of duct proximal to the blockage persists, with changes in the tissue architecture of the entire sublingual space.

an individual with no obvious history of trauma or oral habit. Necrotizing sialometaplasia has been reported along with induced vomiting practiced by patients suffering from bulimia.[78–83]

Treatment. It is important for the clinician to understand the etiology and biologic behavior of this lesion and for the pathologist to have expertise on oral lesions. In addition to the specimen, a complete clinical history should be provided to the pathologist to aid in distinguishing this lesion from squamous cell carcinoma.

An adequate biopsy specimen is essential since the histologic features of this lesion are unique. Necrosis of the salivary gland, pseudoepitheliomatous hyperplasia of the mucosal epithelium, and squamous metaplasia of the salivary ducts are seen. Histopathologic examination will reveal that there are no malignant cells and that the lobular architecture is preserved even though necrosis is present.[74–77]

Necrotizing sialometaplasia is self-limiting, lasts approximately 6 weeks, and heals by secondary intention. No specific treatment is required, but débridement and saline rinses may help the healing process. Recurrence and impairment are not usually encountered.

RADIATION-INDUCED PATHOLOGY

Effects of External-Beam Radiation. External-beam radiation is standard treatment for head and neck tumors, and the salivary glands are often within the field of radiation. Doses of ≥ 50 Gy will result in permanent salivary gland damage and symptoms of oral dryness. The exact mechanism of the destruction of salivary gland tissue by radiation is not fully understood.

Clinical Presentation. Radiotherapy is usually delivered in fractionated doses 5 days per week for 6 to 8 weeks. Acute effects on salivary function can be recognized within a week of beginning treatments at doses of approximately 2 Gy daily and patients will often voice complaints of oral dryness by the end of the second week. Mucositis is a very common consequence of treatment and can become severe enough to alter the radiation therapy regimen. If permanent salivary dysfunction develops, patients are at risk of the full range of associated oral complications. Typically, at doses > 50 Gy, salivary dysfunction is severe and permanent. Difficulty in speaking, dysphagia, and increased dental caries are common complaints that dramatically affect the quality of life for patients with radiation-induced salivary gland dysfunction. Saliva is minimal, and the saliva that is present tends to be thick and ropy.[84–86]

"Radiation caries" is the term commonly used to describe these patients' rapidly advancing caries, which characteristically occur at the incisal or cervical aspect of the teeth and wrap around the teeth in an "apple core" fashion. In spite of meticulous oral hygiene, the caries rate is often difficult to control and poses a challenge to even the experienced restorative dentist.

This patient population is susceptible to other oral complications, including candidiasis and sialadenitis. Clinicians should always be aware of the risk of osteonecrosis and the increased incidence of salivary gland neoplasms in postradiation patients. Osteonecrosis is a lifelong risk due to the decreased vascularity following the exposure of bone to radiation. There is also an increased incidence of second primary tumors involving the radiated tissues.

Treatment. Radiation planning is key to the effective preservation of salivary gland tissue. Eisbrush and colleagues reported that when three-dimensional comformal radiation therapy was used in patients receiving bilateral head and neck radiation with the goal of limiting salivary exposure, 50% of salivary gland function was preserved. Tumor control and complications are still being assessed, but this technique appears to offer real benefit.[86,87]

In addition to improvements in the planning and delivery of radiation therapy, radioprotective agents may help limit radiation therapy–induced salivary gland damage. Starting in the 1970s, studies have investigated the radioprotective properties of amifostine; however, not until 1999 was amifostine approved as a radioprotective agent by the Food and Drug Administration. This agent is useful for the preservation of salivary function and for the reduction of dry mouth in patients undergoing radiation treatment for head and neck cancer when the radiation port includes a substantial portion of the parotid glands. The proposed mechanism of action involves the scavenging of free oxygen radicals. Following administration, amifostine is dephosphorylated in the circulation by alkaline phosphatase to a pharmacologically active free thiol metabolite. The thiol metabolite scavenges free oxygen species generated by radiation. Normal tissue is more vascular than the tumor and has higher capillary levels of alkaline phosphatase. Therefore, the concentration of the active thiol metabolite is higher in normal tissue and thus will protect the normal tissue but not the cancer. Amifostine is administered intravenously 15 to 30 minutes prior to each fractionated radiation treatment. Major side effects include hypotension, hypocalemia, nausea, and vomiting. Reversible episodes of loss of consciousness and rare incidences of seizures have been reported. This drug should be used with close supervision in patients taking hypertension medications. Its safety for patients with cardiovascular disease or cerebrovascular conditions has not been studied.[88–92]

Since patients undergoing radiation therapy have reduced salivary flow, they are susceptible to oral fungal and bacterial infections. Candidal infections can be difficult to treat and resistant to therapy. Due to the increased risk of caries, antifungal agents should be free of sugar. Vaginal clotrimazole troches and dissolved nystatin powder may be used orally as sugar-free antifungal agents. Since xerostomic patients may have too little saliva to dissolve troches, antifungal oral rinses are preferred. Daily prescription-strength topical fluoride (which can be brushed on or administered in trays) is recommended to help control caries.

Symptomatic treatment for postradiation patients is discussed in detail later in this chapter, in the section on the treatment of xerostomia. Alternative medicine is gaining popular-

ity in Western culture and medical curricula. Studies investigating acupuncture treatment for radiation-induced xerostomia have reported varying results. Chi gong and herbal medications are alternative therapies that are reported to increase salivary flow. More controlled trials of these therapeutic modalities are needed.[93]

Effects of Internal Radiation Therapy. *Etiology.* Disseminated thyroid cancer (DTC) is treated by the removal of the thyroid gland. To insure that all remnants of thyroid tissue are destroyed, patients are given radioactive iodine 131 (^{131}I) after surgery. Radioactive iodine is taken up not only by thyroid tissue but also by the oncocytes in salivary gland tissue. Radioactive iodine can cause permanent salivary gland damage and fibrosis resulting in salivary gland hypofunction. Mandel and colleagues recently reported changes in saliva composition following ^{131}I therapy. It is believed that salivary gland damage is related to the dose of ^{131}I administered.[94,95]

Clinical Presentation. Patients with DTC treated with^{131}I may experience xerostomia and decreased salivary gland function. However,^{131}I treatment is less caustic than external-beam radiation therapy and generally causes less destruction to the salivary glands.

Treatment. Following administration of ^{131}I, patients should suck on lemon drops or chew gum to stimulate salivary flow. This will aid in clearing the radioactive iodine from the salivary glands and will potentially decrease salivary gland damage. Patients with ^{131}I-induced salivary gland hypofunction should be treated with the same measures as patients who have salivary gland damage from other causes.

ALLERGIC SIALADENITIS

Enlargement of the salivary glands has been associated with exposure to various pharmaceutical agents and allergens. Cases that are without rash or other signs of allergy have been reported. The characteristic feature of such an allergic reaction is acute salivary gland enlargement, often accompanied by itching over the gland. It is unclear whether all of the reported cases are true allergic reactions or some represent secondary infections resulting from medications that reduced salivary flow. Compounds have salivary gland enlargement as a potential side effect include phenobarbital, phenothiazine, ethambutol, sulfisoxazole, iodine compounds, isoproterenol, and heavy metals. The diagnosis of allergic reaction should be made judiciously, especially when salivary gland enlargement is not accompanied by other signs of an allergic reaction. The possibility of infection or autoimmune disease should be considered. Allergic sialadenitis is self-limiting. Avoiding the allergen, maintaining hydration, and monitoring for secondary infection are recommended.[96]

Viral Diseases

Viruses have been associated with acute nonsuppurative salivary gland enlargement. This section focuses on the viruses responsible for the majority of cases of virally induced salivary gland enlargement: *Paramyxovirus*, *Cytomegalovirus* (CMV), HIV, and hepatitis C virus (HCV). Echoviruses, Epstein-Barr virus, parainfluenza virus, and choriomeningitis virus infections have been linked to occasional reports of nonsuppurative salivary gland enlargement.

MUMPS (EPIDEMIC PAROTITIS)

Etiology. Mumps is caused by a ribonucleic acid (RNA) *Paramyxovirus* and is transmitted by direct contact with salivary droplets. The United States and Canada have recommended the mumps vaccine since the 1970s and monitor vaccinations at school admission. An attenuated live vaccine is available and is indicated for immunization against mumps in children aged 12 months or older. The incidence of mumps in developed countries has significantly decreased; in the United States, 906 cases were reported in 1995.[97] The Centers for Disease Control and Prevention (CDC) published modifications to the Recommended Childhood Immunization Schedule in 1998. The CDC currently recommends an initial vaccination at 12 to 18 months of age and a second dose at 4 to 6 years of age. Mumps virus vaccine is not recommended for severely immunocompromised children because the protective immune response often does not develop, and risk of complications exists.[97,98] There has been speculation that the measles-mumps-rubella (MMR) vaccine might be linked to autism and inflammatory bowel disease, which raised parental concern. Although epidemiologic studies demonstrate no evidence for a causal association between MMR administration and these conditions, many parents have refused vaccination for their children.[99–102] This raises public health concerns as it results in a susceptible population and the possibility of the re-emergence of mumps in the United States. International travelers who have not had mumps or been vaccinated can import the virus. In 1997, an outbreak of mumps among adults (ages 17 to 40 years) attending "rave" parties was reported in Vancouver, British Columbia.[100–102] Therefore, this infection must be considered in cases of acute nonsuppurative salivary gland inflammation in unvaccinated patients who have not had mumps.

Clinical Presentation. Ordinarily, mumps occurs in children between the ages of 4 and 6 years. The diagnosis of mumps in adults can be more difficult. The incubation period is 2 to 3 weeks; this is followed by salivary gland inflammation and enlargement, preauricular pain, fever, malaise, headache, and myalgia. The majority of cases involve the parotid glands, but 10% of the cases involve the submandibular glands alone. The skin over the involved glands is edematous. The salivary gland enlargement is sudden and painful to palpation. The salivary gland ducts are inflammed but without purulent discharge. If partial duct obstruction occurs, the patient may experience pain when eating. One gland can become symptomatic 24 to 48 hours before another gland does so. Swelling is usually bilateral and lasts approximately 7 days[99–102] (Figure 9–8).

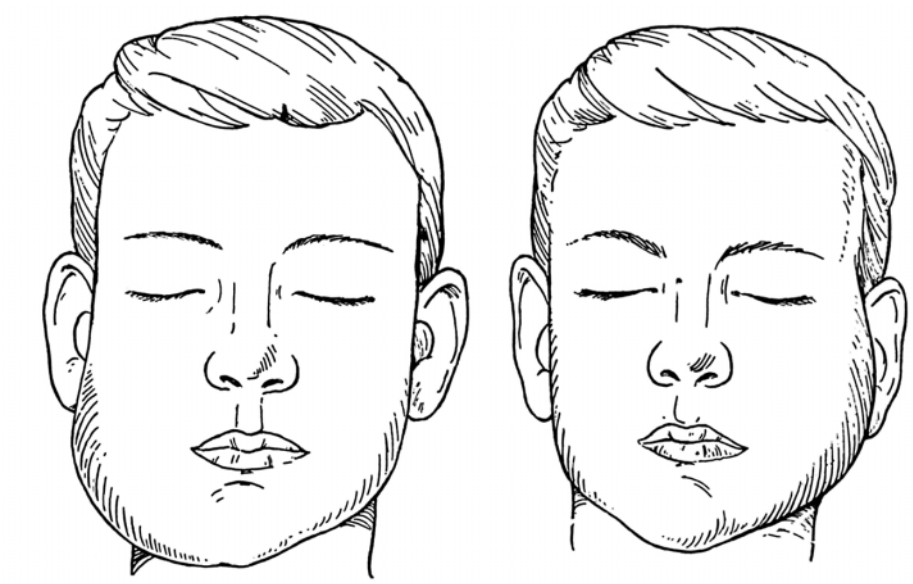

Figure 9–8 *Left,* Typical location and configuration of swelling associated with mumps. *Right,* Usual location and configuration of swelling associated with abscessed mandibular molars.

The diagnosis is made by the demonstration of antibodies to the mumps S and V antigens and to the hemagglutination antigen. Serum amylase levels may be elevated.

Complications of mumps include mild meningitis and encephalitis. Deafness, myocarditis, thyroiditis, pancreatitis, and oophoritis occur less frequently. Males can experience epididymitis and orchitis, resulting in testicular atrophy and infertility if the disease occurs in adolescence or later.

Treatment. The treatment of mumps is symptomatic, and vaccination is important for prevention. Rare fatalities have occurred from viral encephalitis, myocarditis, and neuritis.

CYTOMEGALOVIRUS INFECTION

Etiology. Human CMV is a beta herpesvirus that infects only humans. CMV may remain latent after initial exposure and infection. Although its reactivation can occur in healthy individuals without clinical illness, reactivation in immunocompromised individuals can be life threatening.[103–104]

CMV can be cultured from blood, saliva, feces, respiratory secretions, urine, and other body fluids. A large percentage of healthy adults have serum antibodies to the virus. CMV is the major cause of non-Epstein-Barr virus infectious mononucleosis in the general population. Horizontal transmission can occur through blood transfusion, allograft transplants, and sexual contact. Particularly high rates of seropositivity are found in homosexual males, intravenous drug users, prostitutes, and individuals who have undergone multiple transfusions.[108–111]

Transmission from children to adults or between children is more common through fomites, urine, and respiratory secretions. Transplacental spread of CMV may result in congenital infection and malformations. Perinatal infection occurs in 3% of all live births and is thought to be due to transmission from breast milk, saliva, fomites, or urine. Infection in newborns and young children can be fatal.[110,111]

Clinical Presentation. CMV mononucleosis often occurs in the young adult population and presents as an acute febrile illness that includes salivary gland enlargement. Diagnosis is based on an elevated titer of antibody to CMV, and the prognosis for healthy adults is excellent. There is one report (by Guntinas-Lichius and colleagues) of acute severe CMV sialadenititis in a 57-year-old immunocompetent male who required hospitalization for 30 days.[106]

It is important to detect CMV infections in pregnant women. Transplacental transmission of CMV can result in prematurity, low birth weight, and various congenital malformations. Infected newborns and young children suffer from hepatitis, myocarditis, hematologic abnormalities, pneumonitis, and nervous system damage. The infection is often fatal; those children who do survive frequently experience permanent nerve damage resulting in mental retardation and seizure disorders.[108–112]

Infection in adults can occur by reactivation of the latent virus or by primary infection. An impaired immune system allows the virus to replicate and allows disseminated infection to occur. Patients taking immunosuppressive medications and patients with hematologic abnormalities or HIV infection are susceptible to severe CMV infections. In fact, CMV is considered a clinical marker for acquired immunodeficiency syndrome (AIDS). The CDC's surveillance case definition for AIDS includes CMV infection of the salivary glands that lasts longer than 1 month in adult patients. CMV infection also is strongly associated with an increased incidence of fungal and bacterial infections, particularly from gram-negative organisms.

The advent of highly active antiretroviral therapy (HAART) for treating HIV infection has resulted in a decline of CMV end-organ damage. Deayton and colleagues reported that HAART (including a protease inhibitor) suppresses CMV viremia in HIV-infected patients who are not receiving specific anti-CMV therapy. There are no published reports

addressing the incidence of CMV-related salivary gland pathology in HIV-infected patients since the widespread adoption of HAART.[102]

The diagnosis of CMV infection may be difficult because of the issues of viral latency in many individuals, past virus infection versus acute clinical disease, and reactivation. The classic method for detection is histologic examination of infected tissue. CMV-infected tissue contains large atypical cells with inclusion bodies. These cells can be two times the normal size and have eccentrically placed nuclei, resulting in an "owl-like" appearance. Tissue necrosis and nonspecific inflammation may also be seen histologically.

Current methods for diagnosis include culture, antigen detection, and CMV deoxyribonucleic acid (DNA) detection. Diagnosis of primary infection in an immunocompetent patient uses a combination of immunoglobulin M (IgM) anti-CMV antibody seropositivity, IgG seroconversion, and viral culture. Antibodies to CMV are less useful diagnostically in immunocompromised individuals. Anti-CMV antibodies can be falsely negative in transplantation patients and falsely positive in patients with autoimmune disease. The virus can be detected directly in body fluids or tissue by culture, antigen assay, or CMV DNA assay. The presence of IgG antibodies against CMV is used to detect past CMV infection in immunocompetent patients who are being screened for blood or organ donation.[108–110]

Treatment. Immunocompetent patients are treated symptomatically. Immunocompromised patients require aggressive management and may be treated with intravenous ganciclovir, foscarnet, or cidofovir. A live attenuated vaccine is in clinical trials and has demonstrated partial protection in seronegative women exposed to seropositive infants and in seronegative kidney transplant recipients who received organs from seropositive donors. It is speculated that vaccine-induced immunity will be less effective against sexually transmitted CMV infection, in which re-infection with wild virus strains occurs.[108–112]

HIV INFECTION

Etiology. Neoplastic and non-neoplastic salivary gland lesions occur with increased frequency in HIV-infected patients. Clinicians should consider AIDS-related tumors such as Kaposi's sarcoma and lymphoma. A Sjögren's syndrome–like phenomenon is also seen in HIV-infected patients. A variety of terms have been used to describe this condition; "HIV salivary gland disease" (HIV-SGD) is the preferred term. HIV-SGD describes xerostomia and benign (unilateral or bilateral) salivary gland enlargement in HIV-positive patients. The prevalence of HIV-SGD is ≈1.0% in adult HIV-infected patients but has been reported to be as high as 19% in pediatric patients. Adult African Americans experience lesions more frequently than Caucasians based on data in the US. Homosexual persons and intravenous drug users experience gland enlargement more frequently than patients infected by other routes of transmission. The etiology of HIV-SGD is not understood, but the reactivation of a latent virus has been hypothesized. Changes in the incidence of parotid hypertrophy since the advent of HAART have not been reported.[115–119]

HIV-SGD is associated with a cluster designation 8 (CD8) cell lymphocytosis of the salivary glands and with the diffuse infiltrative lymphocytosis syndrome (DILS). In this condition, lymphocytic infiltration is found in the salivary glands, lungs, gastrointestinal tract, and liver.

Modest changes in salivary function without enlargement have also been reported. Greenberg and colleagues studied two groups of HIV-infected patients: one group with xerostomia and one group without xerostomia. Both groups were evaluated for the presence of CMV in saliva, blood, labial minor salivary glands, and peripheral blood mononuclear cells.[115] Xerostomia and reduced salivary flow were associated with the presence of CMV. These results suggest a potential link between CMV in saliva and salivary gland dysfunction in HIV-infected patients.[120]

Clinical Manifestations. The most notable symptom of HIV-SGD is salivary gland swelling, which may or may not be accompanied by xerostomia. The parotid glands are involved in 98% of reported cases, and 60% of patients have bilateral enlargement[115–117] (Figure 9–9).

HIV-SGD frequently resembles Sjögren's syndrome and must be distinguished from this disorder by appropriate evaluation including salivary flow rates, ophthalmologic evaluation (with assessments of lacrimal function and the tear film), and autoimmune serologies. Ten percent of HIV-infected patients have a reduced lacrimal flow. Salivary flow rates may be reduced, and salivary immunoglobulin A (IgA) may be elevated both in patients with Sjögren's syndrome and in patients with HIV-SGD. Peripheral blood changes can resemble the changes seen in cases of Sjögren's syndrome and include hypergammaglobulinemia, circulating immune complexes, and rheumatoid factors. However, anti-SS-A and anti-SS-B autoantibodies are usually negative in the HIV-SGD population. A minor salivary gland biopsy may be indicated, and histologic findings resemble changes seen in cases of Sjögren's syndrome (including focal mononuclear cell infiltration) with routine tissue examination. Using immunohistochemical stains to differentiate the infiltrating cells, one finds a preponderance of CD8-positive (+) cells in HIV-SGD, as compared to the CD4+ infiltrates that predominate in Sjögren's syndrome. If there is involvement of the major salivary glands, they can be imaged with ultrasonography, CT, or MRI. Multiple cystic masses are characteristic of HIV-associated benign lymphoepithelial hypertrophy. With persistent enlargement of a major gland, a biopsy of the affected tissue may be necessary to exclude neoplasia. Of particular concern are lymphoma and Kaposi's sarcoma, both of which have been reported in the salivary glands of HIV-infected individuals. A biopsy specimen from an HIV-SGD–involved major gland demonstrates hyperplastic lymph nodes, lymphocytic infiltrates, and cystic cavities.[115–118]

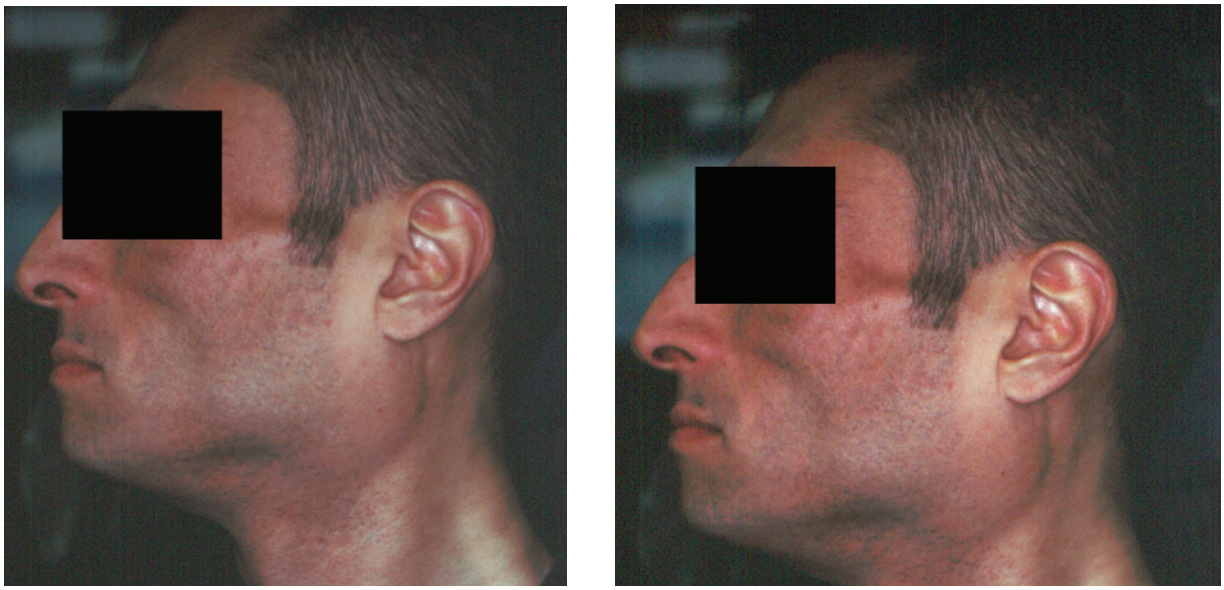

Figure 9–9 The patient demonstrates the bilateral salivary gland enlargement often associated with HIV. Courtesy of Dr. Michael Glick, University Medicine and Dentistry, New Jersey.

When assessing the HIV infected patient who has salivary complaints, it is important to consider that this patient group also frequently experiences medication-induced xerostomia. When salivary gland enlargement is present, bacterial infection should also be considered.

Treatment. Treatment of neoplastic lesions is addressed below, under "Salivary Gland Tumors." Treatment for HIV-SGD is primarily symptomatic. Xerostomia may be relieved by sipping water, using saliva substitutes, chewing sugar-free gum, or sucking sugar-free candy. Topical fluoride is suggested for control of caries. (For a fuller discussion, see the section "Treatment of Xerostomia," below.)

Benign parotid enlargement is an esthetic concern for some patients, and surgery has been performed for cosmetic reasons. Treatment of the enlargement with external radiation therapy has also been attempted, but only 1 of 12 HIV-infected patients with parotid hypertrophy who were treated with 8 to 10 Gy of radiotherapy to the affected gland had a reduction in gland size. In 68% of patients, 24 Gy delivered in 1.5 Gy doses was effective, and 70% of those cases had a clinical benefit lasting 2 years. The potential for radiation-induced malignancy does exist, and clinicians must schedule regular follow-up visits to monitor for malignant changes. Radiation therapy also may increase the degree of xerostomia. It is speculated that systemic anti-HIV treatment may augment radiation therapy. However, antiretroviral treatments alone have shown minimal effects on enlarged parotid glands.[121,122]

Two other methods of treatment include the aspiration of cysts and tetracycline sclerosis. The injection of a tetracycline solution into cystic areas will sometimes induce an inflammatory reaction and eventual sclerosis. Formal studies with long-term follow-up have not been reported for these methods.[123]

HEPATITIS C VIRUS INFECTION

Etiology. Viruses have been considered potential triggers of autoimmune diseases for many years. Retroviruses are known to infect cells of the immune system and to disrupt immunoregulation. Sicca symptoms mimicking Sjögren's syndrome have been described in diseases caused by retroviruses (see discussion of HIV-SGD, above). Hepatitis C virus (HCV) DNA has been detected in the saliva of patients with chronic hepatitis C infection, and it has been demonstrated that the saliva of HCV carriers is infective. A number of reports from European centers have suggested an association between HCV and Sjögren's syndrome.[124–128] Subsequent investigations reported conflicting results. King and colleagues examined 48 Sjögren's syndrome patients and reported them negative for HCV.[122] Marrone and colleagues found that none of their 100 well-characterized Sjögren's syndrome patients had evidence of acute or chronic HCV infection.[127] In contrast, Pawlotsky and colleagues looked at a series of HCV-infected patients and found that 14% had a salivary gland pathology that resembled Sjögren's syndrome.[129]

These differences in results may be due to population variability and differing case definitions. The prevalence of asymptomatic HCV infection is higher in Europe than in the United States. Also, different authors have used less stringent diagnostic criteria for Sjögren's syndrome. When stringent diagnostic criteria have been applied and studies have been done in populations with relatively low endemic HCV infection, an increase of HCV infection in Sjögren's syndrome has not been found. However, the potential relationship between HCV and autoimmune disease remains an area of continuing debate.

Although a causal relationship between autoimmune disease and HCV is unlikely, salivary gland pathology can be

noted in HCV-infected patients. Haddad and colleagues reported that 16 of 28 HCV-infected patients in their study had sialadenitis resembling Sjögren's syndrome.[130] Scott and colleagues performed biopsies of labial minor salivary glands in HCV-infected patients and found lymphoid aggregates, duct ectasia, lymphocytic infiltrates, and acinar depletion.[131] Pirisi and colleagues reported that specimens from lip biopsies from 17 of 22 HCV-positive patients demonstrated inflammatory changes similar to those seen in patients with Sjögren's syndrome. The inflammation seen in the HCV-infected population was described as mild compared to that seen in Sjögren's syndrome patients.[132]

Clinical Manifestations. HCV infection has many extrahepatic manifestations, including salivary gland enlargement. Patients may report xerostomia along with chronic major salivary gland enlargement.[133–141] Both Scott and colleagues and Haddad and colleagues reported that females with chronic HCV infection had a greater tendency for sialadenitis.[130,131] Clinical manifestations and salivary histologic lesions generally are significantly milder in patients with chronic HCV infection than in patients with Sjögren's syndrome.[135,136] It is worth noting that HCV-infected patients do not commonly experience dry eyes along with xerostomia. The diagnosis of HCV infection is made by the detection of anti-HCV antibodies and HCV DNA.[133,134]

Treatment. Hepatitis-associated sialadenitis is treated symptomatically.

BACTERIAL SIALADENITIS

Etiology. Bacterial infections of the salivary glands are most commonly seen in patients with reduced salivary gland function(Figure 9–10 and 9–11). This condition was formerly referred to as "surgical parotitis" because postsurgery patients often experienced gland enlargement from ascending bacterial infections. This was thought to relate to the markedly decreased salivary flow during anesthesia, often as the result of administered anticholinergic drugs and relative dehydration due to restricted fluids. With the administration of prophylactic antibiotics and routine perioperative hydration, this condition now occurs much less frequently.[142] Raad and colleagues reported only three instances in 300,000 cases occurring postoperatively.[143]

Today, the majority of bacterial infections occur in patients with disease- or medication-induced salivary gland hypofunction. The reduction of salivary flow results in diminished mechanical flushing, which allows bacteria to colonize the oral cavity and then to invade the salivary duct and cause acute bacterial infection. Studies have shown that poor oral hygiene contributes to salivary gland bacterial infections. The geriatric population is particularly suseptible to bacterial sialadenitis due to the frequent combination of medication-induced xerostomia and poor oral hygiene (Figure 9–12). The habit of fecal ingestion also has been associated with sialadenitis.[142–144]

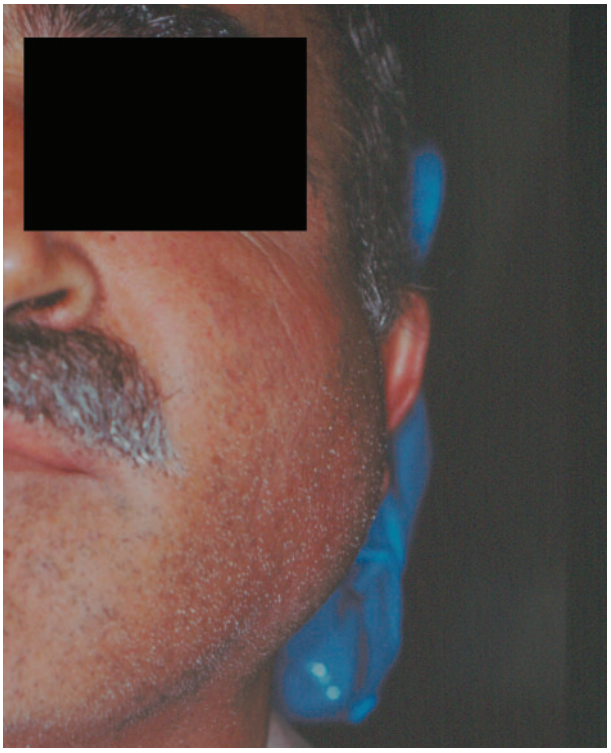

Figure 9–10 This patient demonstrates parotid swelling due to a bacterial infection.

Although sialoliths occur more frequently in the submandibular glands, bacterial sialadenitis occurs more frequently in the parotid glands. It is theorized that the submandibular glands may be protected by the high level of mucin in the saliva, which has potent antimicrobial activity. Anatomy may also play a protective role; tongue movements tend to clear the floor of the mouth and protect Wharton's duct. In contrast, the orifice of Stenson's duct is located adjacent to the molars, where heavy bacterial colonization occurs.[142–144]

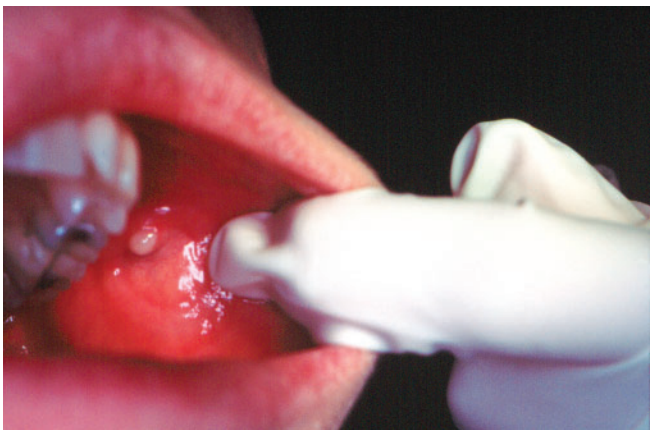

Figure 9–11 The expression of purulence from Stenson's duct seen in this patient is one of the signs of acute parotitis. Culture and sensitivity testing will produce guidance to appropriate antibiotics.

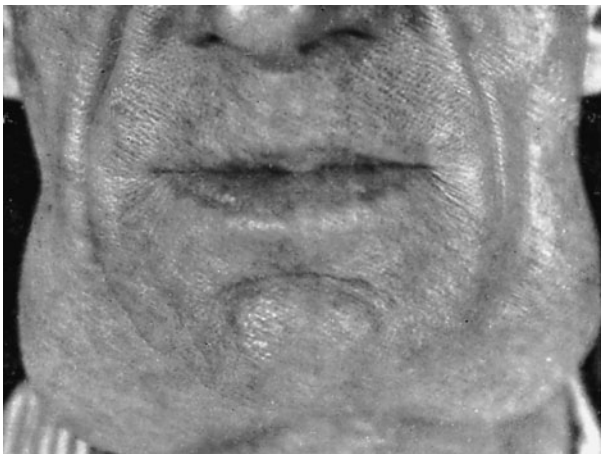

Figure 9-12 Bilateral chronic submaxillary sialadenitis in a dehydrated patient. (King HA, Koerner TA. JAMMA. 167:1813.)

Clinical Presentation. Patients usually present with a sudden onset of unilateral or bilateral salivary gland enlargement. Approximately 20% of the cases present as bilateral infections. The involved gland is painful, indurated, and tender to palpation. The overlying skin may be erythematous. A purulent discharge may be expressed from the duct orifice, and samples of this exudate should be cultured for aerobes and anaerobes (Figure 9–11). A second specimen should be sent for testing with Gram's stain.

The most commonly cultured organisms include coagulase-positive *Staphylococcus aureus, Streptococcus viridans, Streptococcus pneumoniae, Escherichia coli,* and *Haemophilus influenzae*. Institutionalized individuals are particularly susceptible to infections caused by methicillin-resistant *Staphylococcus aureus*.

Due to the dense capsule surrounding the salivary glands, it is difficult to determine, based on physical examination alone, whether an abscess has formed. Ultrasonography or CT is recommended for visualizing possible cystic areas.[142–144]

Treatment. If a purulent discharge is present, empiric intravenous administration of a penicillinase- resistant antistaphylococcal antibiotic is indicated. Patients should be instructed to "milk" the involved gland several times throughout the day. Increased hydration and improved oral hygiene are required. With these measures, significant improvement should be noted within 24 to 48 hours. If this does not occur, then incision and drainage should be considered. The mortality rate for bacterial sialadenitis was once high, but the availability of a selection of broad-spectrum antibiotics has eliminated mortality in noncritically ill patients.

As salivary gland enlargement may be nonbacterial in origin, such as in virally induced swelling or in Sjögren's syndrome, antibiotics should not be started routinely unless bacterial infection is clinically obvious. In any case, purulent discharge from the salivary gland should be cultured to confirm the diagnosis and determine antibiotic sensitivity.[142–144]

Systemic Conditions with Salivary Gland Involvement

Many systemic diseases are manifested by salivary gland dysfunction. Systemic conditions with associated salivary gland involvement are listed in Table 9–4. The most prominent example is Sjögren's syndrome. Xerostomia, the symptom of oral dryness, has been reported in association with many additional systemic conditions. In some instances, it is unclear whether these symptoms and the salivary gland changes are part of the disease process or whether they result from treatment of the disease.

Metabolic Conditions

Sialadenitis most often involves the parotid gland. The underlying systemic metabolic disorders that are commonly associated with salivary gland disease include diabetes, anorexia nervosa, bulimia, and alcoholism.[145–147] The parotid gland is not often involved.

DIABETES

Diabetes mellitus is a common endocrine disease, especially in the geriatric population. Multiple metabolic abnormalities take place, and long-term complications such as renal hypertension, neuropathies, and ophthalmic disease can occur.

TABLE 9–4 Systemic Conditions with Salivary Gland Involvement

Infectious disorders
Actinomycosis
Grandulomatous disease (sarcoidosis, tuberculosis)
Tuberculosis
Viral infection
HIV-SGD
Hepatitis
CMV infection
Metabolic disorders
Sjögren's syndrome
Thyroid disease
Granulomatous disease (sarcoidosis, tuberculosis)
Alcoholism
Malnutrition
Eating disorders (anorexia, bulimia)
Diabetes (uncontrolled)
Neoplasms
Benign
Pleomorphic adenoma
Monomorphic adenoma
Ductal papilloma
Malignant
Lymphoma
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Acinic cell carcinoma
Squamous cell carcinoma
Adenocarcinoma

CMV = *Cytomegalovirus*; HIV-SGD = human immunodeficiency syndrome salivary gland disease.

Patients with uncontrolled diabetes often report dry mouth, which is believed to be due to polyuria and poor hydration. Research results regarding salivary flow and compositional changes in diabetic patients are contradictory. One study reported that salivary flow rates in children with poorly controlled diabetes mellitus were decreased when compared to flow rates in well-controlled pediatric diabetic patients and normal controls.[148] However, other investigators found that salivary flow rates were normal but that salivary compositional changes occurred in pediatric diabetic patients.[149] Ship and colleagues[150] conducted a clinical trial comparing adult diabetes type 2 patients with normal controls. They found that patients with poorly controlled diabetes had lower salivary flow rates when compared to patients with well-controlled diabetes and to normal controls. Of interest, these investigators also found that there was no difference between these populations in the frequency of xerostomic complaints, and further, that salivary dysfunction may be present in older diabetic patients who do not complaint of xerostomia.[150–152]

The etiology of diabetic salivary gland dysfunction is unclear.[153–155] (Figure 9–13). Sreebny and colleagues suggested that poor glycemic control directly effects salivary gland metabolism.[146] It has also been suggested that autonomic nervous system dysfunction may play a role. Meurman and colleagues reported no change in flow rates between non-insulin-dependent diabetic patients and normal controls.[154] However, they found the effects of xerostomic medications on salivary flow rates to be stronger in the diabetic patients. They postulated that this was due to documented autonomic nervous system dysfunction in the diabetic population.

ANOREXIA NERVOSA/BULIMIA

Salivary gland enlargement and dysfunction can occur in patients with anorexia nervosa and bulimia.[156] The enlargement appears to be related to nutritional deficiencies and to the habit of induced vomiting. One case study reported that histologic examination of the involved salivary gland revealed acinar enlargement and reduced interstitial fat. Salivary gland enlargement usually resolves when patients return to normal weight and discontinue unhealthy eating habits. However, benign hypertrophy may persist and be a cosmetic concern. While superficial parotidectomy will reduce salivary hypertrophy, some surgeons believe that surgical management is contraindicated for a patient with an eating disorder, because of the increased risk associated with the patient's metabolic imbalance and psychological profile.

Total and salivary specific amylase levels are increased with bulimia. Salivary amylase tends to increase with the frequency of binge eating, but the correlation is not strong enough to include salivary amylase levels as an index of disease severity.[157,158]

Eating disorders are difficult to diagnose because of the secretive nature of the condition. To facilitate early diagnosis and treatment, dentists should be aware of the common oral findings (enamel erosion, xerostomia, salivary gland enlargement, mucosal erythema, and cheilitis). Patients should be questioned directly if an eating disorder is suspected. Eating disorders must be considered in the differential diagnosis of salivary gland dysfunction and hypertrophy.

CHRONIC ALCOHOLISM

Chronic alcoholism is associated with salivary gland dysfunction and bilateral salivary (usually parotid) gland enlargement. The exact etiology is unclear, but the decreased salivary flow is believed to be due to dehydration and poor nutrition. Enlarged salivary glands in alcoholic patients demonstrate fatty-tissue changes on histologic examination.[159,160] (Figure 9–14).

Medication-Induced Salivary Dysfunction

There are over 400 medications that are listed as having dry mouth as an adverse event. However, there are relatively few drugs that have been shown objectively to reduce salivary function. The reason for this disparity is unclear. It may be due to unrecognized alterations in saliva composition that lead to the perception of oral dryness in spite of an apparently unchanged volume of saliva. Drugs that have been shown to result in sali-

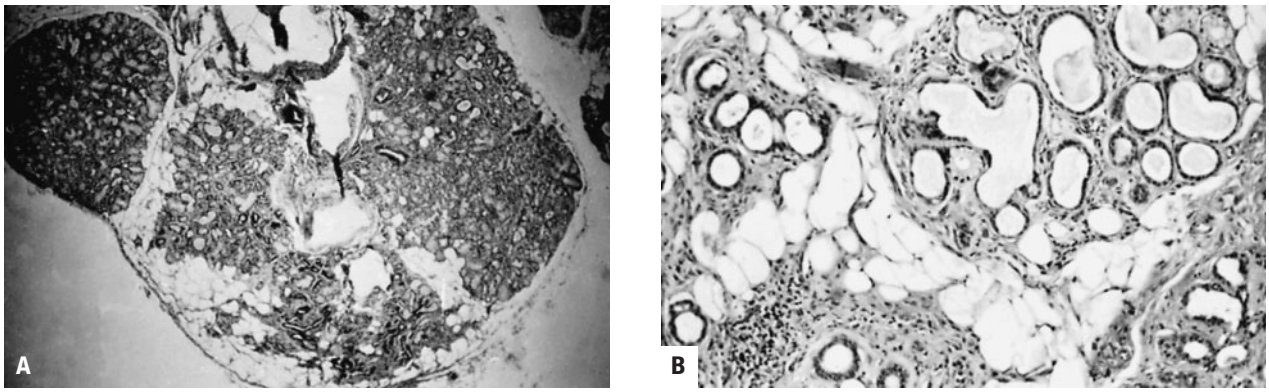

Figure 9-13 Histologic section of biopsy of minor salivary gland from lip of patient with complaints of dry, sore mouth; persistent salty taste; and evidence of chronic pansialadenitis, diabetes mellitus, and type II hyperlipoproteinemia, H & E stain. **A,** Low-power view showing chronic sialadenitis affecting entire gland with fatty replacement of some area fibrosis and atrophy of the gland parenchyma and cystic dilation of ducts. **B,** High-power view to illustrate the same features.

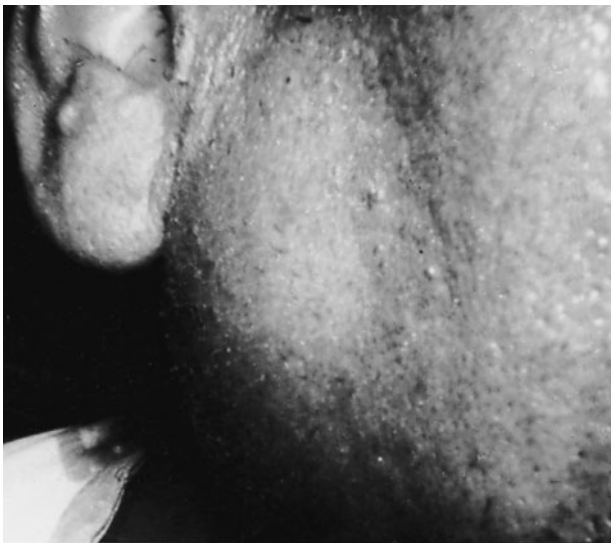

Figure 9-14 Sialadenosis. Asymptomatic parotid swelling in an alcoholic. Salivary secretion is normal.

vary dysfunction include anticholinergics, antidepressants (particularly tricyclics), antihypertensives, and antihistaminics. Medication-induced salivary hypofunction usually affects the unstimulated output, leaving stimulated function intact. When the causative drug is withdrawn, function often returns to normal.[12,65,85]

Immune Conditions

BENIGN LYMPHOEPITHELIAL LESION (MIKULICZ'S DISEASE)

The etiology of benign lymphoepithelial lesion is unknown. It has been speculated that autoimmune, viral, or genetic factors are the trigger. This condition predominantly affects middle-aged women.

Patients present with unilateral or bilateral salivary gland swelling due to a benign lymphoid infiltration. Reduced salivary flow makes these patients susceptible to salivary gland infections. The differential diagnosis includes Sjögren's syndrome, lymphoma, sarcoidosis, and other diseases associated with salivary gland enlargement. Diagnosis is based on findings of salivary gland biopsy and the absence of the abnormalities in peripheral blood counts and autoimmune serologies seen in Sjögren's syndrome.[161, 162]

Treatment is palliative. The possibility of neoplastic transformation is a concern. The detection of a monoclonal lymphocytic infiltrate is thought to be suggestive of a low-grade lymphoma. Treatment is controversial; some clinicians advocate irradiation therapy whereas others recommend monitoring when the disease is limited to the salivary glands.

SJÖGREN'S SYNDROME (PRIMARY AND SECONDARY)

Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by symptoms of oral and ocular dryness and lymphocytic infiltration and destruction of the exocrine glands. The etiology of SS is unknown, and there is no cure. The salivary and lacrimal glands are primarily affected, but other exocrine tissues, including the thyroid, lungs, and kidney, may also be involved. SS patients also frequently experience arthralgias, myalgias, peripheral neuropathies, and rashes. Autoimmune-associated anemia, hypergammaglobulinemia, and other serologic abnormalities are frequent in this patient population.[163,164]

SS primarily affects postmenopausal women (the female-to-male ratio is 9:1) and is classified as primary or secondary. Patients with secondary SS have salivary and/or lacrimal gland dysfunction in the setting of another connective-tissue disease. Primary SS is a systemic disorder that includes both lacrimal and salivary gland dysfunctions without another autoimmune condition.

Clinical Manifestations. Patients with SS experience the full spectrum of oral complications that result from decreased salivary function. Virtually all patients complain of dry mouth and the need to sip liquids throughout the day. Oral dryness causes difficulty with chewing, swallowing, and speaking without additional fluids. Patients often have dry cracked lips and angular cheilitis. Intraorally, the mucosa is pale and dry, minimal salivary pooling is noted, and the saliva that is present tends to be thick and ropy. Mucocutaneous candidal infections are common in this patient population. As noted previously, decreased salivary flow results in increased dental caries and erosion of the enamel structure.[165]

Patients with SS can experience chronic salivary gland enlargement. (Figure 9–15). They are also susceptible to salivary gland infections and/or gland obstructions that present as acute exacerbations of chronically enlarged glands.[164,165] (Figure 9–16).

Diagnosis. There are no universally accepted diagnostic criteria for SS, and multiple criteria sets have been published.[164–169] The strictest criteria include objective measurement of decreased salivary and lacrimal gland function, positive autoimmune serologies, and a minor salivary gland biopsy specimen that demonstrates focal mononuclear cell infiltration in a periductal pattern (focus score > 1 [see below]). Less stringent criteria, which rely partly on symptomatic reports, exist and are commonly used by clinicians.[166] At present, a criteria set created by a European Community SS multicenter study group and validated by large-scale clinical testing is gaining wider acceptance.[167] Efforts are being made to establish an internationally accepted diagnostic criteria set for SS. Most investigators accept the premise that a definitive diagnosis of primary SS requires either the presence of a salivary gland biopsy specimen demonstrating characteristic histopathologic findings or the presence of autoantibodies against the extractable nuclear antigens SS-A/Ro or SS-B/La, in addition to objective evidence of lacrimal dysfunction.

The minor salivary gland biopsy specimen finding is considered to be the best sole diagnostic criterion for the salivary

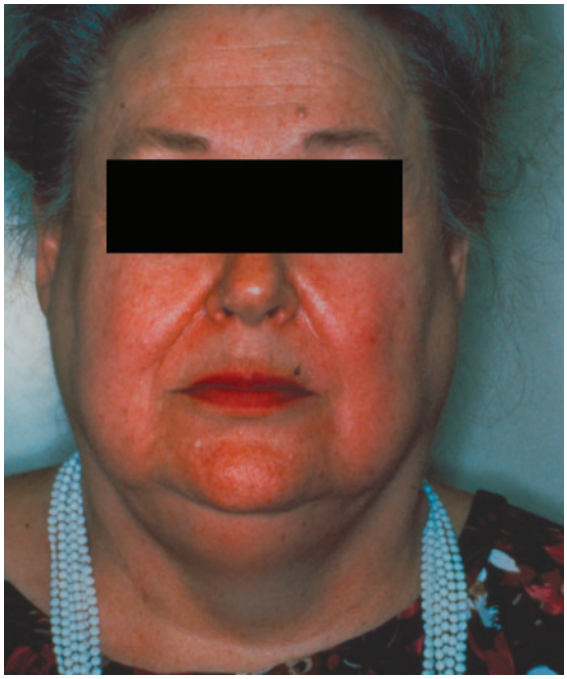

Figure 9-15 This patient demonstrates bilateral parotid enlargement secondary to Sjögren's syndrome.

component of SS. A grading system exists for quantifying the salivary histologic changes seen in the minor glands in SS, as follows: (1) the numbers of infiltrating mononuclear cells are determined, with an aggregate of 50 or more cells being termed a focus; (2) the total number of foci and the surface area of the specimen are measured; and (3) the number of foci per 4 mm^2 is calculated. This constitutes the focus score. The range is from 0 to 12, with 12 denoting confluent infiltrates. A focus score of 1 is considered positive for SS in some criteria although others require the score to be > 1. Acinar degeneration, with the relative preservation of ductal structures, is also noted[157] (Figure 9–17).

Imaging of the salivary glands is discussed earlier in this chapter. Sialography shows characteristic changes and may be useful in the evaluation of SS. MRI or CT can be helpful also, particularly in the assessment of enlarged glands and potential lymphadenopathies. MRI is preferable to CT, unless a stone or other calcified structure requires visualization as MRI provides better resolution of soft tissue. Some clinicians use Tc-99m radionuclide studies to determine salivary gland function.

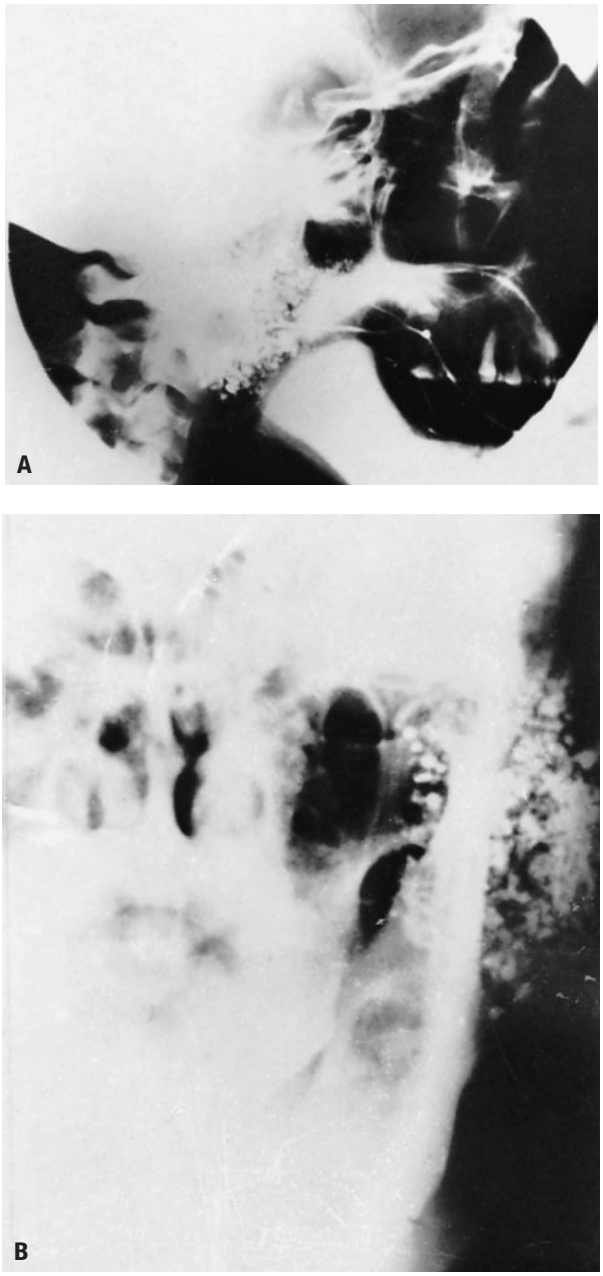

Figure 9–16 Retrograde sialogram of patient with Sjögren's syndrome. **A,** Lateral view; **B**, Anteroposterior view. Note the absence of fine arborization and the presence of many larger dye-filled spaces (sialectasis) on the posterior view. Also note dilatation of major intraglandular duct in lateral view. (Nichols CN, Brightman VJ. Parotid calcifications and cementomas in a patient with Sjögren's syndrome and idiopathic thrombocytopenic purpura. J Oral Pathol 1977; 6:51.)

Treatment. Treatment for SS is limited. As the causes of SS and the mechanisms of salivary damage are not fully understood, available treatment modalities are primarily symptomatic. Management of the oral consequences of salivary dysfunction in SS is not different than in other causes of secretory damage. Symptomatic therapies include artificial saliva, oral rinses and gels, and water sipping (see "Treatment of Xerostomia," below). Patients with remaining salivary function can also stimulate salivary flow by chewing sugarfree gum or by sucking on sugarfree candies. Corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) have not been shown to improve salivary flow in SS patients.[170–172] Systemic cholinergic medications that stimulate salivary flow in functioning salivary glands include pilocarpine and cevimeline.[173,174] Multicenter clinical trials of interferon-α

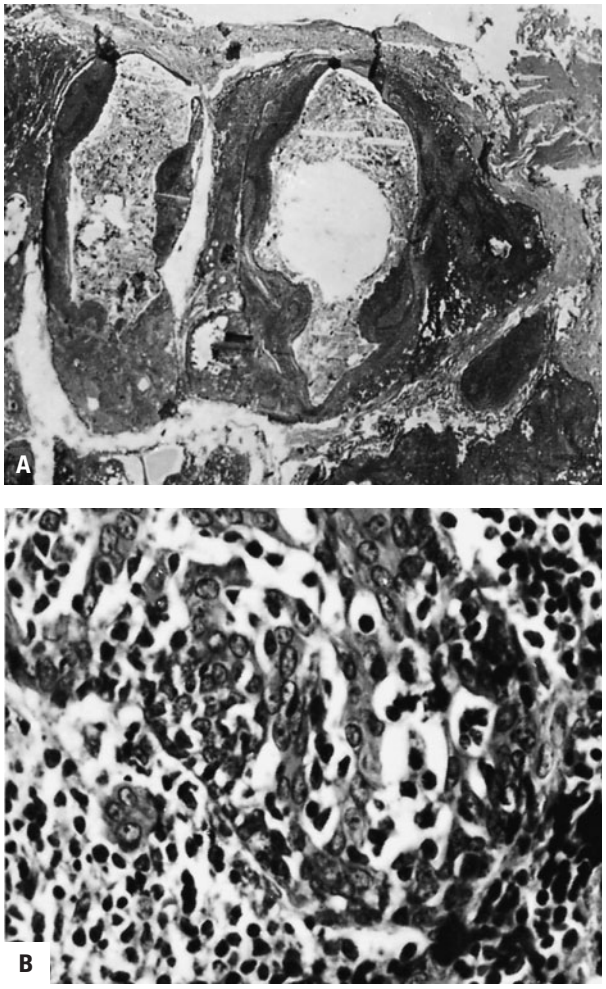

Figure 9–17 Histologic section of excised parotid gland from patient with Sjögren's syndrome, H & E stain. **A,** Low-power view of two cystlike spaces with development of lymphoid follicles in their walls. Elsewhere parotid gland parenchyema is obliterated and replaced by lymphoid tissue. **B,** High-power view of lymphoepithelial proliferation within an area of lymphoid infiltration. (Nichols CN, Brightman VJ. Parotid calcifications and cementomas in a patient with Sjögren's syndrome and idiopathic thrombocytopenia purpura. J Oral Pathol 1977; 6:51.)

lozenges as a treatment for the salivary component of SS are taking place.[175] Other biologics are also being investigated as possible therapeutic agents. The role of sex hormones in SS is an area of active research, and there is an ongoing clinical trial investigating the use of dehydroepiandrosterone (DHEA), a systemically administered nonvirilizing androgen, as a therapy for SS.

There is a recognized increased incidence of malignant lymphomas in SS.[176,177] These tumors often involve the salivary glands. It has been hypothesized that salivary gland enlargement in SS may progress from a benign sialadenitis with polyclonal lymphocytic infiltration to an oligoclonal infiltration and that monoclonal lymphoid malignancy may later develop. Chronic salivary gland enlargement or any lymphadenopathy in SS patients should be viewed with caution. Routine monitoring is required and should include regular physical evaluation and assessment of immunoglobulin levels. Laboratory studies should determine if a monoclonal gammopathy is present. Suspicious lesions can be assessed by cytologic examination of FNA biopsy specimens for clonality of lymphoid cells. Histologic findings dictate the degree of intervention. An oncologist should be consulted when lymphoma or a monoclonal gammopathy is detected. Often, salivary lymphomas in SS are indolent and progress very slowly, and the recommended treatment is close monitoring. However, lesions can be aggressive, and this must be considered when exploring treatment options.

Granulomatous Conditions

TUBERCULOSIS

Tuberculosis (TB) is a chronic bacterial infection, caused by *Mycobacterium tuberculosis*, that leads to the formation of granulomas in the infected tissues. The lungs are most commonly affected, but other tissues, including the salivary glands, may be involved. Patients with TB may experience xerostomia and/or salivary gland swelling, with granuloma or cyst formation within the affected glands. Salivary gland enlargement usually presents as part of a characteristic symptom complex; however, salivary gland changes have been reported in the absence of systemic symptoms.

The worldwide increase in mycobacterial diseases and their association with immunocompromised patients must be considered when developing a differential diagnosis. Diagnosis depends on the identification of *Mycobacterium*. Treatment of the salivary involvement is encompassed in standard multidrug anti-TB chemotherapy. Patients who have not responded to appropriate chemotherapy regimens have required surgical intervention to address persistent salivary gland pathology.[178,179]

SARCOIDOSIS

Sarcoidosis is a chronic condition in which T lymphocytes, mononuclear phagocytes, and granulomas cause destruction of involved tissue. The etiology of the disease is unknown. Onset primarily occurs in the third or fourth decades of life. Women are affected more often than men, and African Americans are affected more often than Caucasians. Heerfordt's syndrome (uveoparotid fever) is a form of sarcoid that can occur in the presence or absence of systemic sarcoidosis. The syndrome is defined by the triad of inflammation of the uveal tract of the eye, parotid swelling, and facial palsy.[180]

Sarcoidosis affects the salivary glands in 1 of 20 cases. Patients usually present with bilateral, painless, and firm salivary gland enlargement. Unilateral salivary gland enlargement has been reported. Decreased salivary function is usually noted in the involved glands. Examination of a minor salivary gland biopsy specimen can confirm the diagnosis of sarcoidosis. Serum laboratory chemistries including calcium level, autoim-

mune serologies, and angiotensin I–converting enzyme concentration aid in the diagnosis.[180–182]

The treatment of the salivary component of sarcoidosis is primarily palliative. Depending on the extent of disease affecting other tissues or during exacerbations, corticosteroids may be administered. Chloroquine has also been used, alone or in combination with corticosteroids. Immunosuppressive and immunomodulatory medications have been administered to patients who failed to respond to corticosteroids.[180,181]

▼TREATMENT OF XEROSTOMIA

Treatment that is available for the dry mouth patient can be divided into four main categories: (1) preventive therapy, (2) symptomatic treatment, (3) local or topical salivary stimulation, and (4) systemic salivary stimulation. Effective treatment of an underlying systemic disorder associated with salivary gland dysfunction may correct the salivary complaint as well.

Preventive Therapy

The use of topical fluorides in a patient with salivary gland hypofunction is absolutely critical to control dental caries. There are many different fluoride therapies available (eg, over-the-counter fluoride rinses, brush-on forms, and highly concentrated prescription fluorides that can be applied by brush or in a custom carrier). The frequency of application (from daily to once per week) should be modified, depending on the severity of the salivary dysfunction and the rate of caries development.

It is essential that patients maintain meticulous oral hygiene. Patients will require more frequent dental visits (usually every 4 months) and must work closely with the dentist to maintain good dental health. When salivary function is compromised, there may be an increase in demineralization, speeding the loss of tooth structure. Remineralizing solutions may be used to alleviate some of the effects of the loss of normal salivation.

Patients with dry mouth also experience an increase in oral infections, particularly mucosal candidiasis. This may take an erythematous form (without the easily recognized pseudomembranous plaques), and the patient may present with redness of the mucosa and complaints of a burning sensation of the tongue or other intraoral soft tissues. A high index of suspicion should be maintained, and appropriate antifungal therapies should be instituted as necessary. Patients with salivary gland dysfunction may require prolonged treatment periods and re-treatment to eradicate oral fungal infections.[171]

Symptomatic Treatment

Several symptomatic treatments are available. Water is by far the most important. Patients should be encouraged to sip water throughout the day; this will help to moisten the oral cavity, hydrate the mucosa, and clear debris from the mouth. The use of water with meals can make chewing and forming the food bolus easier, will ease swallowing, and will improve taste perception. An increase in environmental humidity is exceedingly important. The use of room humidifiers, particularly at night, may lessen discomfort markedly. As part of the normal diurnal variation, salivary flow drops almost to zero during rest. In individuals who have any degree of secretory hypofunction, the dessication of the mucosa is particularly troublesome at night and may interfere with restorative sleep.

There are a number of oral rinses and gels available. Patients should be cautioned to avoid products containing alcohol, sugar, or strong flavorings that may irritate sensitive dry mucosa. Moisturizing creams are important. The frequent use of products containing aloe vera or vitamin E should be encouraged. Persistent cracking and erythema at the corners of the mouth should be investigated for a fungal cause.

There are many commercially available salivary substitutes. However, saliva replacements (artificial salivas) are not well accepted by most patients. While there is clearly a role for the use of saliva replacements, particularly in individuals who have no residual salivary gland function, it must be recognized that this is not a highly effective symptomatic therapy.[170,171]

Salivary Stimulation

LOCAL OR TOPICAL STIMULATION

Several approaches are available for stimulating salivary flow. Chewing will stimulate salivary flow effectively, as will sour and sweet tastes. The combination of chewing and taste, as provided by gums or mints, can be very effective in relieving symptoms for patients who have remaining salivary function. Patients with dry mouth must be told not to use products that contain sugar as a sweetener, due to the increased risk for dental caries in this group. Electrical stimulation has also been used as a therapy for salivary hypofunction but has been inadequately investigated clinically. A device that delivers a very-low-voltage electrical charge to the tongue and palate has been described although its effect was modest in patients with dry mouth.

SYSTEMIC STIMULATION

The use of systemic secretogogues for salivary stimulation has also been examined, with mixed results. More than 24 agents have been proposed as means of stimulating salivary output systemically. Four have been examined extensively in controlled clinical trials; these are bromhexine, anetholetrithione, pilocarpine hydrochloride (HCl), and cevimeline HCl.

Bromhexine is a mucolytic agent used in Europe and the Middle East. The proposed mechanism of action for salivary stimulation is unknown. No proven benefit to salivary function has been shown by objective and controlled clinical trials. Bromhexine may stimulate lacrimal function in patients with Sjögren's syndrome although this is controversial.[183,184]

Anetholetrithione is a mucolytic agent that has been shown to increase salivary output in clinical trials. The mechanism of action is not definitively known, but it has been suggested that anetholetrithione may up-regulate muscarinic receptors. In patients with mild salivary gland hypofunction, anetholetrithione significantly increased saliva flow. However, it was ineffective in patients with marked salivary gland hypofunc-

tion. The adverse effects are mild. One study suggested a possible synergistic effect of anetholetrithione in combination with pilocarpine.[185,186]

Pilocarpine HCL is approved specifically for the relief of xerostomia. Current indications are for patients with dryness following radiotherapy for head and neck cancers and for those with Sjögren's syndrome. Pilocarpine HCL is a parasympathomimetic drug, functioning as a muscarinic cholinergic agonist. Pilocarpine increases salivary output, stimulating any remaining gland function. The adverse effects of pilocarpine in human studies are very common and are usually mild. They are consistent with the known mechanism of action of the drug. Sweating is the most common side effect. Other frequently reported side effects are hot flashes, urinary frequency, diarrhea, and blurred vision.[172,173,187,188]

After the administration of pilocarpine, salivary output increases fairly rapidly, usually reaching a maximum within 1 hour. The best-tolerated doses are those of 5.0 to 7.5 mg, given three or four times daily. The duration of action is approximately 2 to 3 hours. Pilocarpine is contraindicated for patients with pulmonary disease, asthma, cardiovascular disease, glaucoma, or urethral reflux. Patients do not appear to develop tolerance to pilocarpine following prolonged use. Pilocarpine has been shown to be a safe and effective therapy for patients with diminished salivation but who have some remaining secretory function that can be stimulated.[172,173,187,188]

Cevimeline HCl is another parasympathomimetic agonist that has been recently approved for the treatment of symptoms of oral dryness in Sjögren's syndrome. This medication reportedly specifically targets the muscarinic receptors of the salivary and lacrimal glands. It still must be used with caution in patients with a history of glaucoma or cardiovascular, respiratory, or gall bladder disease and in patients who use various medications. Its side effects are similar to those of pilocarpine. To date, there have been few published reports of clinical trials with cevimeline.[174,189]

Pilocarpine HCl and cevimeline HCl are the only systemic sialagogues that are available in the United States. Medical consultation prior to prescribing these drugs for patients with significant medical conditions may be indicated. Increased understanding of the causes of xerostomia and salivary gland hypofunction undoubtedly will lead to improvement in the available treatments through the design and testing of more rational and specific therapies.

▼SIALORRHEA

"Sialorrhea" refers to excess saliva production. Medications (eg, pilocarpine and cevimeline) can cause increased salivation. Often, the report of increased salivation is due to changes in oral perception or decreased swallowing efficiency rather than to an increase in salivation. Patients with neurologic changes may note an onset of sialorrhea. This commonly occurs after a cerebral vascular accident or in various neuromuscular diseases (eg, Parkinson's disease). Patients who have undergone extensive oral surgical procedures (eg, for oral cancer) may also report changes in salivary flow. A patient with a severe neurologic deficit may experience drooling due to the inability to swallow effectively. Drooling can be socially akward and can affect the patient's quality of life.

A complete past medical history and a history of present illness are important for determining the etiology of sialorrhea. Saliva collection is helpful in diagnosing hypersalivation and gives an objective measurement of salivary flow. The complaint of increased salivation can be due to decreased swallowing efficiency. Swallowing studies aid in diagnosis and evaluate the risk of aspiration.

The treatment of sialorrhea varies. If the patient is experiencing difficulty in swallowing, speech pathology study and therapy are recommended. Informing the patient about oral perception changes and therapy often provide sufficient relief. Depending on the patient's medical condition and the severity of the problem, a mild xerostomia-inducing medication (such as an antihistamine) may be helpful. A temporary reduction in salivary flow has been reported after the injection of botulinum toxin into the parotid glands of patients with neurologic disease. Injection of botulinum toxin should be done by experienced clinicians who are familiar with the side effects of botulinum toxin.[190]

▼SALIVARY GLAND TUMORS

The majority of salivary gland tumors (about 80%) arise in the parotid glands. The submandibular glands account for 10 to 15% of tumors, and the remaining tumors develop in the sublingual or minor salivary glands. Approximately 80% of parotid gland tumors and 50% of submandibular gland tumors are benign. In contrast, more than 60% of tumors in the sublingual and minor salivary glands are malignant. The risk of malignancy increases as the size of the tumor decreases. Over 85% of salivary gland tumors occur in adults. Salivary tumors in children are most often located in the parotid glands, and about 65% of all salivary tumors found in children are benign.[191–198]

Benign Tumors

PLEOMORPHIC ADENOMA

Etiology. The pleomorphic adenoma is the most common tumor of the salivary glands; overall, it accounts for about 60% of all salivary gland tumors. It is often called a mixed tumor because it consists of both epithelial and mesenchymal elements. About 85% of these tumors are found in the parotid glands, 8% are found in the submandibular glands, and the remaining tumors are found in the sublingual and minor salivary glands. This tumor represents the most common neoplasm in each of the salivary glands and accounts for about 50% of salivary tumors in the minor salivary glands.[192,193]

Pleomorphic adenomas may occur at any age, but the highest incidence is in the fourth to sixth decades of life. It also represents the most common salivary neoplasm in children. There is a slight predilection for female gender.[194]

Clinical Presentation. On clinical examination, these tumors will appear as painless, firm, and mobile masses that rarely ulcerate the overlying skin or mucosa. In the parotid gland, these neoplasms are slow growing and usually occur in the posterior inferior aspect of the superficial lobe. Mixed tumors in the submandibular glands present as well-defined palpable masses. It is difficult to distinguish these tumors from malignant neoplasms and indurated lymph nodes. Intraorally, the mixed tumor most often occurs on the palate, followed by the upper lip and buccal mucosa.

Pleomorphic adenomas can vary in size, depending on the gland in which they are located. In the parotid gland, the tumors are usually several centimeters in diameter but can reach much larger sizes if left untreated. When observed in situ, the tumors are encased in a pseudocapsule and exhibit a lobulated appearance.[194–196]

Pathology. The gross appearance of pleomorphic adenoma is that of a firm smooth mass within a pseudocapsule. Histologically, the lesion demonstrates both epithelial and mesenchymal elements. The epithelial cells make up a trabecular pattern that is contained within a stroma. The stroma may be chondroid, myxoid, osteoid, or fibroid. The presence of these different elements accounts for the name pleomorphic tumor or mixed tumor. Myoepithelial cells are also present in this tumor and add to its histopathologic complexity. One characteristic of a pleomorphic adenoma is the presence of microscopic projections of tumor outside of the capsule. If these projections are not removed with the tumor, the lesion will recur.

Treatment. The treatment of this lesion consists of surgical removal with adequate margins. Because of its microscopic projections, this tumor requires a wide resection to avoid recurrence. In spite of the capsule, close excision should not be attempted. A superficial parotidectomy is sufficient for the majority of these lesions. A small tumor in the tail of the parotid gland may be removed with a wide margin of normal tissue, sparing the remainder of the superficial lobe. Lesions that occur in the submandibular gland are treated by the removal of the entire gland.[194–196]

MONOMORPHIC ADENOMA

A monomorphic adenoma is a tumor that is composed predominantly of one cell type, as opposed to a mixed tumor (pleomorphic adenoma), in which different elements are present.[196] Management is the same as pleomorphic adenoma.

PAPILLARY CYSTADENOMA LYMPHOMATOSUM

Papillary cystadenoma lymphomatosum, also known as Warthin's tumor, is the second most common benign tumor of the parotid gland. It represents about 6 to 10% of all parotid tumors and is almost always located in the parotid gland, most commonly in the inferior pole of the gland, posterior to the angle of the mandible. The tumor demonstrates a slight predilection toward males, and it usually occurs between the fifth and eighth decades. These tumors occur bilaterally in about 6 to 12% of patients.[192–194,197]

Clinical Presentation. This tumor presents as a well-defined slow growing mass in the tail of the parotid gland. It is usually painless unless it becomes superinfected. Because this tumor contains oncocytes, it will take up technetium and will be visible on technetium scintiscans.

Pathology. The gross appearance of this tumor is smooth, with a well-defined capsule. Cutting a specimen reveals cystic spaces filled with thick mucinous material. Histologically, the tumor consists of papillary projections lined with eosinophilic cells that project into cystic spaces. The projections are characterized by a lymphocytic infiltrate. Oncocytes are present within this tumor, and because they can concentrate technetium, these tumors are visible with Tc-99m nuclear imaging.

Treatment. Papillary cytadenoma lymphomatosum is most often located in the tail of the parotid gland and is easily removed with a margin of normal tissue. Larger tumors that involve a significant amount of the superficial lobe of the parotid gland are best treated by a superficial parotidectomy. Recurrences and malignant degeneration of this tumor are rare.[192,193,197]

ONCOCYTOMA

Oncocytomas are less common benign tumors that make up less than 1% of all salivary gland neoplasms. The name of the tumor is derived from the fact that it contains oncocytes, which are large granular acidophilic cells. This tumor occurs almost exclusively in the parotid glands and is equally distributed in both men and women. The sixth decade is the most common time of presentation.[199–202]

Clinical Presentation. Oncocytomas are usually solid round tumors that can be seen in any of the major salivary glands but that are extremely rare intraorally. These lesions can be found commonly in the superficial lobe of the parotid gland. Bilateral presentation of this tumor can occur, and it is the second most common salivary gland tumor that occurs bilaterally (after Warthin's tumor).

Pathology. On gross examination, these tumors appear noncystic and firm. Histologically, they consist of brown granular eosinophilic cells. The oncocytes within this tumor concentrate technetium, and this tumor can be visualized by Tc-99m scintigraphy. Malignant oncocytomas can occur, and these are aggressive lesions.

Treatment. Oncocytomas demonstrate a very slow growth rate and a benign course. Superficial parotidectomy with preservation of the facial nerve is the treatment of choice for parotid gland tumors. Removal of the gland is the treatment of choice for tumors in the submandibular gland, and gland removal with a normal cuff of tissue is the treatment of choice for oncocytomas of the minor salivary glands. Recurrence is rare.[195,196,199–202]

BASAL CELL ADENOMAS

Basal cell adenomas are slow growing and painless masses and account for approximately 1 to 2% of salivary gland adenomas. This lesion has a male predilection (the male-to-female ratio is 5:1). Seventy percent of basal cell adenomas occur in the parotid gland, and the upper lip is the most common site for basal cell adenomas of the minor salivary glands.

Pathology. Histologically, three varieties of basal cell adenomas exist: solid, trabecular-tubular, and membranous. The solid form consists of islands or sheets of basaloid cells. Nuclei have a normal size and are basophilic, with minimal cytoplasmic material. The trabecular-tubular form consists of trabecular cords of epithelium. The membranous form is multilocular, and 50% of the lesions are encapsulated. The membranous form tends to grow in clusters interspersed between normal salivary tissue.

Treatment. Lesions are removed, with conservative surgical excision extending to normal tissue. In general, lesions do not recur; however, the membranous form has a higher recurrence rate.[200]

CANALICULAR ADENOMA

Canalicular adenomas predominantly occur in persons older than 50 years of age and occur mostly in women. Eighty percent of cases occur in the upper lip. The lesions are slow growing, movable, and asymptomatic.

Pathology. This lesion is composed of long strands of basaloid tissue, usually arranged in a double row. The supporting stroma is loose, fibrillar, and highly vascular.

Treatment. Treatment is surgical excision with a margin of normal tissue. Recurrence is rare but has been reported; thus, patients should be monitored periodically.[195,196,200,201]

MYOEPITHELIOMA

Most myoepitheliomas occur in the parotid gland; the palate is the most common intraoral site. No gender predeliction exists, and lesions tend to occur in adults, with the average age being 53 years. Lesions present as a well-circumscribed asymptomatic slow-growing mass.

Pathology. Myoepitheliomas consist of spindle-shaped cells, plasmacytoid cells, or a combination of the two. Diagnosis is based on the identification of myoepithelial cells. Growth patterns vary from a solid to a loose stroma formation with myoepithelial cells. This tumor is epithelial in origin; however, it functionally resembles smooth muscle and is demonstrated by immunohistochemical staining for actin, cytokeratin, and S-100 protein.

Treatment. Standard surgical excision, including a border of normal tissue, is recommended. Recurrence is uncommon.[195,196,198,200,201]

SEBACEOUS ADENOMA

Sebaceous adenomas are rare. These lesions are derived from sebaceous glands located within salivary gland tissue. The parotid gland is the most commonly involved gland.

Pathology. Cells derived from sebaceous glands are present. Benign forms contain well-differentiated sebaceous cells whereas malignant forms consist of more poorly differentiated cells.

Treatment. Removal of the involved gland is the treatment of choice. Intraoral lesions are surgically removed with a border of normal tissue.[195,196,200,201]

DUCTAL PAPILLOMA

Ductal papillomas form a subset of benign salivary gland tumors that arise from the excretory ducts, predominantly of the minor salivary glands. The three forms of ductal papillomas are simple ductal papilloma (intraductal papilloma), inverted ductal papilloma, and sialadenoma papilliferum.

Simple Ductal Papilloma. The simple ductal papilloma presents as an exophytic lesion with a pedunculated base. The lesion often has a reddish color. Microscopic examination reveals epithelium-lined papillary fronds projecting into a cystic cavity without proliferating into the wall of the cyst. Local surgical excision is the recommended treatment. A minimal recurrence rate is reported.[188,186,190–191]

Inverted Ductal Papilloma. The inverted ductal papilloma occurs in the minor salivary glands. It presents clinically as a submucosal nodule that is similar to a fibroma or lipoma. The inverted ductal papilloma histologically resembles the sialadenoma. This form of ductal papilloma also consists of projections of ductal epithelium that proliferate into surrounding stromal tissue, forming clefts. The lesion is treated by surgical excision. A low recurrence rate is reported.[195,196,200–204]

Sialadenoma Papilliferum. The sialadenoma papilliferum form of ductal papilloma is analogous to the syringocystadenoma papilliferum of the skin. An adult male predeliction exists, and most lesions occur between the fifth and eighth decades of life. This lesion occurs primarily on the palate and buccal mucosa and presents as a painless exophytic mass. Clinically, the lesion resembles a papilloma. Microscopic examination shows epithelium-lined papillary projections supported by fibrovascular connective tissue, forming a series of clefts within the lesion. Local surgical excision is the recommended treatment. Recurrence is rare.[195,196,200–202]

Malignant Tumors

MUCOEPIDERMOID CARCINOMA

Mucoepidermoid carcinoma is the most common malignant tumor of the salivary glands. It is the most common malignant tumor of the parotid gland and the second most common malignant tumor of the submandibular gland, after adenoid cystic

carcinoma. Approximately 60 to 90% of these lesions occur in the parotid gland; the palate is the second most common site. Men and women are affected equally by this tumor, and the highest incidence occurs in the third to fifth decades of life.

As its name suggests, mucoepidermoid carcinoma consists of both epidermal and mucous cells. The tumor is classified as of either a high grade or a low grade, depending on the ratio of epidermal cells to mucous cells. The low-grade tumor has a higher ratio and is a less aggressive lesion. Although low-grade tumors have the ability for metastasis and local invasion, they behave more like benign tumors. The high-grade form is considered to be a more malignant tumor and has a poorer prognosis.[195,196,202–204]

Clinical Presentation. The clinical course of this lesion depends on its grade. It is not uncommon for low-grade tumors to undergo a long period of painless enlargement. In contrast, high-grade mucoepidermoid carcinomas often demonstrate rapid growth and a higher likelihood for metastasis. Pain and ulceration of overlying tissue are occasionally associated with this tumor. If the facial nerve is involved, the patient may exhibit a facial palsy.

Pathology. Macroscopically, low-grade mucoepidermoid carcinomas are usually small and partially encapsulated. The high-grade tumors are less likely to demonstrate a capsule because of the more rapid growth and local tissue invasion. After sectioning, the low-grade tumors usually demonstrate a mucinous fluid, but the high-grade lesions are usually solid in appearance.

Microscopically, the low-grade lesions consist of regions of mucoid cells with interspersed epithelial strands. The high-grade tumors consist primarily of epithelial cells, with very few mucinous cells. In fact, special stains are necessary to differentiate between high-grade mucoepidermoid carcinoma and squamous cell carcinoma.

Treatment. A low-grade mucoepidermoid carcinoma can be treated with a superficial parotidectomy if it involves only the superficial lobe. Usually, the facial nerve can be spared. High-grade lesions should be treated aggressively to avoid recurrence. A total parotidectomy is performed, with facial nerve preservation if possible. If there is any possibility that the tumor involves the facial nerve, the nerve is resected with the tumor. Immediate nerve reconstruction can be performed at the time of tumor extirpation. Neck dissections may be performed for lymph node removal and staging in high-grade lesions. Postoperative radiation therapy has been shown to be a useful adjunct in treating the high-grade tumor. With high-grade lesions, recurrence with metastases can occur in up to 60% of patients. The survival rate for patients with low-grade lesions is about 95% at 5 years; for patients with high-grade lesions, this rate drops to approximately 40%.[195,196,198–204]

ADENOID CYSTIC CARCINOMA

Adenoid cystic carcinomas make up about 6% of all salivary gland tumors and are the most common malignant tumors of the submandibular and minor salivary glands. They make up 15 to 30% of submandibular gland tumors, 30% of minor salivary gland tumors, and 2 to 15% of parotid gland tumors. Approximately 50% of adenoid cystic carcinomas occur in the minor salivary glands. The tumor affects men and women equally and usually occurs in the fifth decade of life.[195,196,198,204–207]

Clinical Presentation. Adenoid cystic carcinoma usually presents as a firm unilobular mass in the gland. Occasionally, the tumor is painful, and parotid tumors may cause facial nerve paralysis in a small number of patients. This tumor has a propensity for perineural invasion; thus, tumor tissue often can extend far beyond the obvious tumor margin. Unfortunately, the tumor's slow growth may delay diagnosis for several years, allowing perineural invasion to be advanced at the time of surgical extirpation. An intraoral adenoid cystic carcinoma may exhibit mucosal ulceration, a feature that helps distinguish it from a benign mixed tumor. Radiographically, the tumor reveals extension into adjacent bone. Metastases into the lung are more common than regional lymph node metastasis.

Pathology. On gross examination, the tumor is unilobular and either partially encapsulated or non-encapsulated. There is often evidence of invasion into adjacent normal tissue. Microscopically, the individual cells are small and cuboidal. Nuclear atypia and mitotic figures are not seen, but chromatin aggregation is dense. Pseudocystic spaces filled with acellular material are a characteristic feature of this tumor. Also, microscopic evidence of perineural or intraneural invasion is a distinguishing feature of adenoid cystic carcinoma.

Treatment. Because of the ability of this lesion to spread along the nerve sheaths, radical surgical excision of the lesion is the appropriate treatment. Even with aggressive surgical margins, tumor cells can remain, leading to long-term recurrence. Frozen pathologic sections of the nerve sheath can help the surgeon achieve a clear margin. Some clinicians feel that a more conservative surgical resection and radiation therapy can provide adequate treatment. Neutron beam radiation has been shown to be more effective than photon beam therapy for the treatment of this tumor. Because of this tumor's capability for long-term recurrence, patients need to be observed indefinitely. Factors affecting the long-term prognosis are the size of the primary lesion, its anatomic location, the presence of metastases at the time of surgery, and facial nerve involvement.[195,196,198,204–211]

ACINIC CELL CARCINOMA

Acinic cell carcinoma represents about 1% of all salivary gland tumors. About 90 to 95% of these tumors are found in the parotid gland; almost all of the remaining tumors are located in the submandibular gland. The distribution of acinic cell carcinoma reflects the location of acinar cells within the different glands. This tumor occurs with a higher frequency in

women and is usually found in the fifth decade of life. It is the second most common malignant salivary gland tumor in children, second only to mucoepidermoid carcinoma.

Clinical Presentation. These lesions often present as slow-growing masses. Pain may be associated with the lesion but is not indicative of the prognosis. The superficial lobe and the inferior pole of the parotid gland are common sites of occurrence. Bilateral involvement of the parotid gland has been reported in approximately 3% of cases.

Pathology. The gross specimen is a well-defined mass that is often encapsulated. Microscopically, two types of cells are present; cells similar to acinar cells in the serous glands are seen adjacent to cells with a clear cytoplasm. These cells are positive on periodic acid–Schiff (PAS) staining. Lymphocytic infiltration is often found.

Treatment. Acinic cell carcinomas initially undergo a relatively benign course. Unfortunately, long-term survival is not as favorable, and the 20-year survival rate is about 50%. Treatment consists of superficial parotidectomy, with facial nerve preservation if possible. When these tumors are found in the submandibular gland, total gland removal is the treatment of choice.[205-208]

CARCINOMA EX PLEOMORPHIC ADENOMA

Carcinoma ex pleomorphic adenoma is a malignant tumor that arises within a pre-existing pleomorphic adenoma. The malignant cells in this tumor are epithelial in origin. This tumor represents 2 to 5% of all salivary gland tumors.

Clinical Presentation. These tumors are slow growing and have usually been present for 15 to 20 years before they suddenly increase in size and become clinically apparent. Carcinoma ex pleomorphic adenoma occurs more often in pleomorphic adenomas that have been left untreated for long periods of time (It is for this reason that early removal of pleomorphic adenomas is recommended).

Pathology. Macroscopically, these tumors are nodular or cystic, without encapsulation. The sectioned tumor appears similar to pleomorphic adenoma except for the presence of necrosis and hemorrhage associated with the malignant tumor.

Histologically, the tumor appears as a squamous cell carcinoma, adenocarcinoma, or undifferentiated carcinoma located within a benign mixed tumor. It may appear as a small focus of malignancy within the pleomorphic adenoma, or the malignant cells can almost completely replace the mixed tumor, making its appearance similar to that of a primary malignant tumor. Destructive infiltrative growth is usually seen around the malignancy.

Treatment. This is a malignant salivary gland tumor that has an aggressive course and that carries a very poor prognosis. Local and distant metastases are common. Surgical removal with postoperative radiation therapy is the recommended treatment. Early removal of benign parotid gland tumors is recommended to avoid the development of this lesion.[195,196,202,204,208]

ADENOCARCINOMA

Any tumors arising from salivary duct epithelium are, by definition, adenocarcinomas. This group of neoplasms has been divided into discrete entities based on structure and behavior. The term "adenocarcinoma" is often used as a catchphrase to refer to lesions that do not meet the specific criteria for other lesions (such as polymorphous low-grade adenocarcinoma, epimyoepithelial carcinoma, or salivary duct carcinoma). Clarification of the type of adenocarcinoma with a histologic description should be obtained in order to determine an appropriate treatment approach.[195,196,204,208]

LYMPHOMA

By definition, "primary lymphoma" describes a situation in which a salivary gland is the first clinical manifestation of the disease. Primary lymphoma of the salivary glands probably arises from lymph tissue within the glands. However, primary lymphoma of the salivary glands is rare.

The major forms of lymphoma are non-Hodgkin's lymphoma (NHL) and Hodgkin's disease. NHL is less curable and is often disseminated at diagnosis. There is an increased incidence of NHL in patients with autoimmune disease, as was described earlier in this chapter (see section on Sjögren's syndrome). The parotid gland is the most commonly involved gland, followed by the submandibular gland.

Clinical Presentation. This lesion commonly presents as painless gland enlargement or adenopathy.

Treatment. Superficial parotidectomy is recommended for isolated asymptomatic parotid gland masses. A staging work-up is required to determine treatment. An initial phase of observation is not uncommon for patients with asymptomatic low-grade disease. Appropriate treatment includes radiation therapy, chemotherapy, or a combination of the two, depending on the staging of the lymphoma.[208,212]

Surgical Treatment

PAROTIDECTOMY

Since most tumors of the parotid gland occur in the tail region, superficial to the facial nerve, surgical treatment most commonly consists of superficial parotidectomy. The facial nerve is identified at surgery in order to avoid damage. If a tumor is very small, it may be excised with an adequate margin of tissue, leaving the remainder of the superficial lobe. Superficial parotidectomy is also the treatment of choice in cases of low-grade malignant salivary tumors.

For high-grade malignant salivary tumors, a total parotidectomy is performed. Unless there is intimate involve-

ment of the tumor with the facial nerve, the nerve may be spared. If the tumor does invade the nerve, resection of the nerve is performed, with immediate reconstruction. Biopsies of any suspicious regional lymph nodes are performed; if the results are positive for malignancy, a modified neck dissection is performed immediately. There is no evidence to support prophylactic neck dissection for malignant tumors of the salivary glands.[198,202,204,208,213]

Complications can occur after parotidectomy. Permanent partial or total facial nerve paralysis occurs in less than 3% of patients, and temporary nerve palsies can occur in 10 to 30% of patients. A salivary fistula or sialocele is a relatively common complication after parotid gland surgery. A sialocele occurs when an edge of the parotid gland capsule is cut and the gland continues to leak fluid, leading to a palpable collection. Pressure dressings can be applied, and an antisialagogue such as glycopyrolate can be given if there are no contraindications. In cases of chronic sialoceles, serial aspirations or drain placement may be carried out in an attempt to expedite resolution.[213]

Frey's syndrome is a relatively common complication of parotidectomy. This syndrome presents as gustatory sweating. When regenerating postganglionic secretory parasympathetic fibers from the parotid gland become mixed with the postganglionic sympathetic fibers to the sweat glands, a condition in which a patient will flush or sweat with salivary stimulation results. Minor's starch-iodine test can be used to demonstrate the area of gustatory sweating. Iodine is applied to the patient's face and is allowed to dry. Starch is then lightly applied to the regions of interest. After a sialagogue is administered, the patient will begin to sweat in the areas of involvement. Wetting the starch and iodine, the sweat will turn the involved areas black. This test aids in delineating the distribution of affected area. Frey's syndrome can occur in as many as 30 to 60% of patients who have undergone parotidectomy. The treatment of this disorder consists of the topical application of antiperspirants or anticholinergics. Botulinum toxin injections have been used to treat Frey's syndrome. However, it is recommended that only experienced clinicians attempt this treatment.[214]

SUBMANDIBULAR, SUBLINGUAL, AND MINOR SALIVARY GLAND SURGERY

Tumors of the submandibular and sublingual glands are treated by total removal of the gland. The loss of salivary flow from a single submandibular gland is negligible, and patients tolerate this procedure well. The risks associated with the removal of the submandibular gland include hemorrhage, infection, and injury to the hypoglossal, lingual, or marginal mandibular nerves.

The treatment of tumors of the minor salivary glands depends on the location and extent of disease. Complete excision is usually sufficient for benign tumors. Complications from the treatment of benign lesions are few.[200,202,208,209,211] In contrast, the treatment of malignant tumors may involve maxillectomy or composite resection.

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