Salivary glands are subject to a variety of diseases, including inflammatory, infectious, obstructive, degenerative, and neoplastic processes. Many of these diseases culminate in salivary dysfunction, a problem seen frequently in oral medicine practice. In this chapter, emphasis is placed on xerostomia, followed by a discussion of infectious, obstructive, and neoplastic lesions.

**Salivary dysfunction and xerostomia**

Saliva plays an essential role in maintaining oral health. Alterations in salivary function lead to compromise of oral tissues and functions and have a large impact on a patient’s quality of life. Reductions in salivary flow most commonly manifest as symptoms of oral dryness. This subjective complaint of dry mouth is termed xerostomia, whereas objective alterations in salivary performance, quantitative or qualitative, are referred to as salivary gland dysfunction. This distinction, between symptoms and functional impairment, should be remembered when the evaluation of salivary gland disease is discussed. Although xerostomia is most often indicative of reduced salivary output, it is not invariably associated with objective salivary gland hypofunction. One cannot assume a diagnosis of salivary gland dysfunction based on reports of oral dryness alone. Conversely, the absence of symptoms of dry mouth is not a guarantee of adequate salivary function. Full and systematic evaluation is essential to determine if salivary gland dysfunction is present. This determination is important, as individuals who have true salivary gland hypofunction require aggressive management to prevent or minimize the deleterious effects of reduced salivary function.

Multiple functions of saliva have been recognized. Saliva is important for taste, mastication, deglutition, digestion, maintenance of oral hard and soft tissues, control of oral microbial populations, voice, and speech articulation (Table 26–1).

Saliva plays a role in taste perception by serving as a solute for tastants. Although taste can be maintained in the absence of major salivary gland function, complaints of dysgeusia and hypogeusia are increased in patients with decreased salivary gland function (see Chapter 27). Lubrication of the oral cavity is another important function of saliva. Adequate salivary flow enhances movement of the tongue and lips, which aids in cleansing the oral cavity of food debris and bacteria. This also allows for ease of proper tongue and lip movement necessary for clear articulation. The oral preparatory stage of swallowing requires the formation of a food bolus. Efficient chewing and bolus formation are dependent upon...
a moist, lubricated oral mucosa, an intact dentition and periodontium, and fluid to wet the food. Transport during swallowing requires the lubricating and wetting properties of salivary secretions. Saliva plays other roles in digestion beyond aiding in mastication. A variety of digestive enzymes, such as amylase and lipase, are present in saliva and initiate the process of food digestion. Saliva also helps protect the upper gastrointestinal tract by rinsing gastric secretions from the esophageal regions.

Saliva coats the oral mucosal tissues, helping maintain an effective barrier to external insults. Salivary constituents aid in maintaining mucosal integrity by binding to and hydrating the oral tissues. Saliva also contains factors that support tissue growth and differentiation.

Saliva contains numerous antimicrobial agents that help maintain a normal oral flora and control microbial overgrowth. These include both specific and nonspecific factors, such as secretory IgA, mucins, lactoferrin, lysozyme, and lactoperoxidase. The histatins, a family of histidine-rich proteins, have been shown to have potent antifungal properties and the proline-rich proteins influence bacterial colonization by modulating attachment. The combination of saliva’s cleansing properties and ability to influence microbial colonization helps prevent the establishment of pathogenic oral flora and decreases the chance of the oral cavity becoming a source of systemic infection.

The dentition is continuously undergoing a process of demineralization and remineralization. Saliva is critical to maintain tooth integrity. Salivary calcium and phosphorus, which are maintained at supersaturated concentrations, owing to specific salivary proteins, are important for remineralization of the teeth. Additionally, the buffering capacity of saliva helps maintain a neutral pH in the oral cavity. Acid production by bacteria at the tooth surface following ingestion of carbohydrates initiates the carious process. Saliva acts to return plaque pH rapidly toward neutrality. Patients who suffer from salivary gland hypofunction are prone to dental decay. Caries is often noted on dental examination, and the incisal and cervical aspects of the teeth are particularly susceptible to decay in these individuals. In spite of meticulous oral hygiene and frequent dental visits, patients with diminished salivary gland function may continue to have a high rate of caries.

As can be appreciated, normal salivary function is central to many aspects of oral health. Additionally, general health can be impacted when salivary function is affected. Altered salivary function has such a major impact on quality of life because saliva plays a critical role in two essential human needs: eating and communicating. Both are compromised when significant salivary gland dysfunction exists.

There are numerous causes of salivary gland dysfunction and xerostomia (Table 26–2). The most common cause of symptoms of oral dryness is therapeutic drug use. Over 500 agents have been associated with xerostomia symptoms. Interestingly, many of these have not been demonstrated to reduce secretory output quantitatively. Although there is no fully satisfactory explanation for this phenomenon, it may relate to qualitative alterations in saliva composition or to nonsalivary factors. Included among the agents that do directly affect salivary function are antidepressants, anticholinergics, antihypertensives (some), and antihistamines.

Radiotherapy that includes the salivary glands in the treatment fields leads to profound and permanent loss of secretory function at doses above approximately 40 Gy. Salivary function can also be diminished by radiiodine therapy for thyroid carcinoma, particularly if multiple doses are administered. Other cancer treatments may lead to salivary gland hypofunction. These include bone marrow transplantation, which can induce a salivary autoimmune reaction, and head and neck surgery, which can physically disrupt salivary output or secretory neural stimuli.

Many systemic conditions can affect salivary function. Perhaps most prominent is Sjögren syndrome, an autoimmune exocrinopathy. Sjögren syndrome is characterized by symptoms of oral and ocular dryness related to an autoimmune-mediated reduction in salivary and lacrimal function. A distinctive focal mononuclear inflammatory infiltrate can be seen in these glands (Figures 26–1 and 26–2). This condition can also affect other organ systems and, in approximately half of the cases, is associated with another autoimmune connective tissue disorder, such as rheumatoid arthritis or systemic lupus erythematosus. This is then termed secondary Sjögren syndrome. Sjögren syndrome also includes marked serologic autoimmune reactivity, with

<table>
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<th>Table 26–2 Causes of Salivary Gland Hypofunction</th>
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<td><strong>Pharmaceuticals</strong></td>
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<td>External beam irradiation to the head and neck and internal radionuclides (eg, 131I)</td>
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<tr>
<td><strong>Systemic diseases</strong></td>
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<td>Sjögren syndrome, primary and secondary</td>
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<td>Granulomatous diseases (sarcoidosis, tuberculosis)</td>
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<td>Graft-versus-host disease</td>
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<td>Cystic fibrosis</td>
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<td>Bell palsy</td>
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<td>Diabetes (uncontrolled)</td>
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<td>Amyloidosis</td>
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<td>Human immunodeficiency virus infection</td>
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<td>Thyroid disease (hypo- and hyperthyroidism)</td>
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<td>Late-stage liver disease</td>
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<td>Salivary gland disease (tumors)</td>
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<td>Psychologic factors (affective disorder)</td>
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<td>Malnutrition (anorexia, bulimia, dehydration)</td>
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<td>Idiopathic</td>
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**DISEASES OF THE SALIVARY GLANDS** 261
the majority of patients demonstrating autoantibodies against nuclei (antinuclear antibodies [ANA]) or extractable nuclear antigens (anti-SS-A/Ro and anti-SS-B/La). There is also a 40-fold increased risk for development of malignant lymphoma.

Other systemic conditions with associated salivary gland dysfunction include cystic fibrosis, poorly controlled diabetes, human immunodeficiency virus (HIV) and other viral infections, and thyroid disease (see Table 26–2). Nonsalivary factors that have been associated with xerostomia and salivary gland dysfunction include psychological disorders, malnutrition and eating disorders, and cognitive alterations. Since symptoms of xerostomia usually are not perceived until saliva output is reduced by 50% or more, dry mouth associated with secretory hypofunction is almost always related to involvement of multiple major salivary glands. This implies more generalized systemic involvement. Signs and symptoms of salivary gland hypofunction should prompt a full oral and medical evaluation to uncover potential underlying systemic disease.

There is continuing debate concerning the role of aging in salivary gland dysfunction. Symptoms of dryness and measurable reductions in salivary function are increased in an older population. However, most investigators believe that this can be explained by the increased incidence of medication use and systemic disease in this group. In healthy, nonmedicated subjects, there is no consistent reduction in salivary gland function with aging. Interestingly, this is true in spite of an approximately 30% decline in total salivary epithelial tissue with aging. For the clinician, the message is that one cannot dismiss symptoms of dryness and salivary gland dysfunction simply as a consequence of aging without a thorough search for other, more probable, causes.

**Molecular and pathologic correlates of disease**

Saliva is the product of three major salivary glands and the many minor glands dispersed throughout the oral cavity (Figure 26–3). It is a complex mixture of water, organic, and nonorganic components. Most constituents are produced locally within the glands; others are transported from the circulation. The three major salivary glands, the parotid, submandibular, and sublingual, are paired glands that share a basic anatomic structure (Figure 26–4). They are composed of acinar and ductal cells. The acinar cells are the secretory endpiece and are the site of fluid transport into the glands. The acinar cells of the parotid are serous, of the sublingual mucous, and of the submandibular, mixed mucous-serous. The duct cells form a branching system that transports the saliva 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. The excretory duct of the major glands is named as it enters the oral cavity. Stensen duct is the main duct of the parotid gland and enters the mouth in the buccal mucosa opposite the maxillary molar teeth. Wharton duct is the main duct of the submandibular gland, which runs along the floor of the mouth entering on either side of the lingual frenum. The main duct of the sublingual gland often joins Wharton duct and the secretions cannot be separated from it reliably.

Although 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 minor sali-
may be progressive even in the presence of excellent and vigilant oral hygiene. Whereas caries is unquestionably increased, it is unclear if there is an increased prevalence or severity of periodontal pathology associated with salivary gland hypofunction. Candidiasis is frequent, most commonly of the erythematous form. Other oral microbial infections are increased as well. Enlargement of the salivary glands is seen with some frequency. In these cases, one must distinguish between inflammatory, infectious, or neoplastic etiologies (Figure 26–6).

Symptoms in the patient with salivary gland hypofunction are related to decreased fluid in the oral cavity. Patients complain predominantly of dryness of all the mucosal surfaces, including the throat, and also of difficulties chewing, swallowing, and speaking. Many patients report a need to drink fluids while eating to help swallowing, or an inability to swallow dry foods. Most 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 enjoyment of meals.

Clinical features

Most patients with salivary gland hypofunction have obvious signs of mucosal dryness. The lips are often cracked, peeling, and may be atrophic. The buccal mucosa may be pale and corrugated in appearance. The tongue is often smooth and reddened, with loss of papillation (Figure 26–5). Patients may report that their lips stick to the teeth and one may see shed epithelial cells adhering 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
Diagnosis

The differential diagnosis of xerostomia and salivary gland dysfunction is a lengthy process. The optimal approach to diagnosis is a coherent, sequential plan that should first establish the cause of the complaint, then determine the extent of salivary gland hypofunction that is present, and finally assess the potential for treatment. The goal is to identify patients who require treatment and to recognize associated systemic conditions.

A critical first step is a thorough history. If the past and present medical history reveal medical conditions or medications that are known to be associated with salivary gland dysfunction, the diagnosis may be obvious. Examples would be the patient who has received radiotherapy for a head and neck malignancy or an individual who has recently started a prescription for a tricyclic antidepressant. 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. Particular attention should be paid to the specific dryness symptoms. Unfortunately, the general complaint of oral dryness is not well correlated with decreased salivary function; however, specific symptoms may be. For example, whereas complaints of dryness at night or on awakening have not been found to be associated with reduced salivary function, complaints of oral dryness while eating, the need to sip liquids to swallow dry food, or reports of difficulties in swallowing dry food all are highly correlated positively with measured decreases in secretory capacity (Table 26–3). Patient responses to questions that focus on oral activities (eg, swallowing, eating) that rely on stimulated salivary function, when combined with the clinical signs of salivary hypofunction, are highly predictive of reduced secretory performance and help identify an individual who requires further evaluation and treatment. Therefore, the patient who presents with a complaint of “dry mouth” should be asked specific questions, to help determine whether salivary gland hypofunction exists. Patients should also be questioned concerning dryness at other body sites. It may be a significant indication of a systemic condition, such as Sjögren syndrome, if a patient reports eye, throat, nasal, skin, or vaginal dryness, in addition to xerostomia.

Signs of salivary gland dysfunction should be sought through careful examination. As noted above, dryness of

Table 26–3 Questions Helpful in Evaluating Patients with Complaints of Dry Mouth

1. Do you have difficulty swallowing dry foods?
2. Does your mouth feel dry while eating a meal?
3. Do you sip liquids to aid in swallowing dry food?
4. Does the amount of saliva in your mouth most of the time seem to be too little, too much, or do you not notice it?

Positive responses to questions 1 to 3, or the perception of too little saliva (question 4), are significantly associated with reduced salivary gland function.

the mucosal surfaces with erythematous or atrophic changes can be seen. Partial or total papillary atrophy may be present on the tongue. Fissuring of the tongue may also occur. One should look for active caries and may be present on the tongue. Fissuring of the tongue changes can be seen. Partial or total papillary atrophy

Fin wax, unflavored gum base, or a rubber band. Dur-

Salivary output can be measured as well. One can

Stimulated saliva is secreted in response to a stimulus,

The expressed saliva should be clear, watery, and copi-

Salivary output can be measured as well. One can

Whole saliva can be collected easily by the spitting

DISEASES OF THE SALIVARY GLANDS

265

ing stimulated collection, patients are usually asked to

Parotid gland collection is performed with Carlson-

Although definitive guidelines are not available, pri-

There are numerous salivary gland imaging tech-

Technetium scintigraphy uses 99mTc pertechnetate, a

radionuclide with affinity for salivary, thyroid, and gas-

Technetium 99m is injected intravenously, and the uptake into the major salivary glands and subsequent secretion into the oral cavity are imaged (Figure 26–7). The Tc scan is a dynamic test of salivary activity. Scintigraphy can serve as a measure of the amount of functional water-transporting acinar tissue remaining in the glands. This is useful in determining the potential benefit from the use of sialagogues in a patient with markedly reduced function. However, this technique does not indicate the cause of gland destruction.

Sialography involves cannulation of the main duct of a major salivary gland and retrograde instillation of
radiographic contrast material into the body of the gland, followed by radiographic visualization. The contrast material fills the ductal tree of the gland and shows the main excretory duct and branching into the secondary and terminal ductules (Figure 26–8). Sialography is useful to detect disruption of the gland architecture, either by demonstrating the absence of contrast material within the ducts (as is seen with salivary stones) or the abnormal distribution or displacement of the ducts (as might be seen with a salivary tumor). This technique is also useful for detection of fistulas and duct strictures. The procedure is contraindicated in patients with acute salivary gland inflammation, as the procedure may cause retrograde spread of infection. Since the contrast material contains iodine, this technique should be avoided in patients allergic to this halide.

The boundaries of the salivary glands and the quality of the parenchyma are well delineated by both CT and MRI. The retromandibular vein, the external carotid artery, and intraglandular lymph nodes are well visualized. Volumetric determinations of the major glands also may be obtained.

Computed tomography images transverse planes of tissue. Dental amalgam produces scatter and can obstruct the image. Coronal and axial images are usually viewed. Iodinated contrast can be used to enhance imaging. Computed tomography is most useful in detecting and localizing tumors in the body of the glands.

Magnetic resonance imaging is dependent on the varying water content to distinguish different tissue types. It is predominantly used for imaging soft tissues, and is useful in the salivary glands to distinguish the location, size, and quality of masses and their relation to surrounding structures (Figure 26–9). The differentiation of cystic versus solid masses is particularly accurate. Visualization of the facial nerve within the parotid gland has been reported by MRI. Advantages of MRI as an imaging modality include (1) the patient is not exposed to ionizing radiation, (2) intravenous iodine-containing contrast media is not required, and (3) there is minimal artifact from dental restorations. Magnetic resonance imaging is contraindicated in patients with pacemakers or any metallic implants, such as aneurysmal bone clips.

Ultrasonography of the major salivary glands has been recommended primarily for visualization of cystic masses. Resolution is often low and diagnostic specificity is lacking.

More definitive diagnosis can be obtained with tissue biopsy. A minor salivary gland biopsy is the most accurate sole diagnostic criterion available for diagnosis of the salivary component of Sjögren syndrome. Histologic examination of labial minor glands demonstrates a characteristic focal, periductal, mononuclear cell infiltrate with acinar cell loss (see Figure 26–2). Ductal

Figure 26–7 Technetium scintiscan of the salivary glands using technetium 99m (99mTc) pertechnetate. The timed sequence shows the initial uptake of tracer into the parotid glands. A, Prompt uptake is seen in both the parotid and submandibular glands in this healthy individual. Appearance of tracer in the oral cavity is seen in the final frame. B, The submandibular glands are not seen in this patient, owing to gland dysfunction. The uptake is slowed in this patient with dry mouth, and release of tracer into the oral cavity is not apparent. The thyroid gland can be visualized at the inferior of the frame.
aspirates are effective in sampling tissue to examine the infiltrate for monoclonality, a sign of lymphoma. An additional advantage to use of fine-needle aspiration is that there is less disruption of the field for subsequent surgery or radiotherapy.

A final diagnostic procedure is examination of peripheral blood. Serologic markers of autoimmunity can be found in patients with Sjögren syndrome and can aid in diagnosis, but a lack of abnormal findings does not exclude the diagnosis of Sjögren syndrome. Antinuclear antibodies (ANA) are present in 80% of patients with Sjögren syndrome. The two most specific autoantibodies in Sjögren syndrome are anti-SS-A/Ro and anti-SS-B/La, found in approximately 60% and 40% of patients, respectively. Rheumatoid factors (RF) are also found in Sjögren syndrome. Other autoantibodies, such as anti-SM, anti-DNA, and anti-RNP (ribonuclear proteins) are rarely found. Patients with Sjögren syndrome often demonstrate elevated total serum protein and marked hypergammaglobulinemia, with one or all (IgG, IgM, IgA) of the immunoglobulin subtypes elevated. The sedimentation rate may be elevated, and the white blood cell count decreased. In cases of salivary gland enlargement or inflammation, the serum amylase is often increased.

At the conclusion of the diagnostic evaluation, one should have a clear indication of the adequacy of salivary function, a possible cause for salivary gland dysfunction (if it exists), and a plan for management based on the diagnosis and the extent of the dysfunction present.

Minor salivary glands are easily accessible and biopsy can be obtained with minimal morbidity. Procedures to biopsy the major salivary glands are more invasive, requiring an external incision in the orofacial region, and have higher morbidity. Parotid biopsy carries a risk of damage to the facial nerve and formation of postoperative fistula. Minimally invasive procedures sampling tissue from the parotid tail region are less hazardous and may be performed in an outpatient setting. The choice of biopsy site—major versus minor gland—is determined by the diagnostic requirements in each case.

Parotid gland biopsy is not more accurate than minor gland biopsy for routine diagnostic evaluation of Sjögren syndrome and has given false-negative results. However, major salivary gland biopsy is indicated when tissue must be examined to evaluate an enlarged gland. Patients with Sjögren syndrome often have chronic major salivary gland enlargement. If persistent unilateral enlargement exists or changes in an enlarged region are noted, one should be suspicious of malignant lymphoma and biopsy the affected gland. An open biopsy provides a larger tissue sample than a fine-needle biopsy. It allows one to view a lesion in context of surrounding tissue and indicates if a mass has a distinct margin. However, fine-needle aspiration is useful for repeat biopsies to monitor lesions that have been reported to be benign. In Sjögren syndrome there may be progression of the so-called benign lymphoepithelial lesion to a malignancy. Needle aspirates are effective in sampling tissue to examine the infiltrate for monoclonality, a sign of lymphoma. An additional advantage to use of fine-needle aspiration is that there is less disruption of the field for subsequent surgery or radiotherapy.

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At the conclusion of the diagnostic evaluation, one should have a clear indication of the adequacy of salivary function, a possible cause for salivary gland dysfunction (if it exists), and a plan for management based on the diagnosis and the extent of the dysfunction present.
Treatment

Management of the patient with dry mouth can be characterized as symptomatic, preventive, or curative. Symptomatic treatment is directed at alleviating or minimizing the complaints associated with decreased salivation. These range from simple methods of hydration and lubrication, to use of systemic secretagogues to stimulate salivary function. The goal of preventive treatments is to limit the consequences of salivary gland hypofunction on the oral hard and soft tissues. Curative approaches address the underlying cause of the symptoms.

The use of water cannot be overemphasized for the patient with dry mouth. Patients should be encouraged to carry non-sugar-containing fluids with them and take frequent small sips. This helps hydrate the oral mucosa and also rinses retained debris. The patient must be counseled specifically to avoid fluids that contain sugar, which exacerbate caries problems. Sugar-free soft drinks can be used, but one must be aware of the caffeine-content of these beverages, as caffeine can contribute to the feeling of oral dryness. Patients may benefit from use of humidifiers, particularly placed near the bed at night. Moisturizers and emollients applied to the lips are essential. Although many patients find that petrolatum-based products give relief, more penetrating creams may be preferable. Products containing lanolin and vitamin E seem to be especially well tolerated.

Sensitivity of the mucosal surfaces is a common complaint in patients with dry mouth. Avoiding spicy foods, alcohol, and strong flavorings may limit this symptom. Many dental products have flavorings that can irritate dry tissues. Also, patients should be cautioned to avoid mouthrinses with high alcohol content that can induce mucosal irritation and sensitivity.

Many saliva-replacement products are available. There are a number of oral rinses and gels that may be used to cleanse the mouth and wet the mucosa. Some have gained moderate patient acceptance, but controlled studies have not demonstrated superiority to regular use of sips of water. Often patients prefer sipping water or sucking on ice chips. The taste and mechanical stimulation of salivation from chewing sugarless candy and gum can increase saliva output and provide relief for some patients.

Several systemic sialogogues have been investigated. These agents are only useful for patients who have remaining salivary gland function that can be stimulated. Anethole-trithione has been found to be helpful for mild medication-induced xerostomia in limited clinical studies. It is not available in the United States. Clinical trials have also been conducted with the mucolytic agent bromhexine, but objective evidence of enhanced salivary function is lacking. Pilocarpine hydrochloride is a parasympathomimetic agonist that increases exocrine output. It is the most widely tested secretagogue and has been shown to be effective in relieving symptoms of oral dryness in both radiation and Sjögren syndrome-induced salivary hypofunction. Side effects are common but tolerable. Recommended doses are 5 mg given three or four times daily. Recently (January 2000) a new secretagogue, cevimeline hydrochloride, has been approved for use in the United States for relief of symptoms of dry mouth in patients with Sjögren syndrome. There is limited published information on this compound. It is also a parasympathomimetic agonist and appears to have an activity and adverse event profile similar to that of pilocarpine, based on the prescribing information provided by the manufacturer. The recommended dose is 30 mg three times daily.

Patients with dry mouth have increased susceptibility to dental caries. Oral applications of topical fluorides have been shown to reduce caries and to help preserve the dentition. The fluoride is incorporated into the enamel of the teeth during the demineralization-remineralization process and increases resistance to decay. Fluorides are available as rinses and as higher-concentration gels. The latter can be applied by brush or in custom-made carriers that hold the material against the teeth. The frequency and mode of application must be determined for each patient based on the extent of salivary hypofunction and caries activity. When coupled with increased attention to dental hygiene and frequent professional dental care, supplemental fluoride can protect against the rampant dental decay that can accompany salivary dysfunction. However, sometimes even with daily topical fluoride and meticulous oral hygiene, patients may continue to have increased caries.

There has been research with use of rinse solutions high in calcium and phosphate to help prevent loss of tooth structure in patients with dry mouth. These preparations appear to be helpful, replacing the important function of saliva in promoting remineralization of the teeth. None is presently available commercially in the United States.

If salivary gland hypofunction is related to medication use, it may be possible to stop or change the offending pharmaceutical. The issue should be explored with the prescribing physician. Often patients may have fewer side effects with a different drug of the same class. If possible, a trial with an alternative medication should be done.

If a bacterial infection is identified, appropriate antibiotics should be prescribed. Salivary gland infections often can require prolonged therapy to eradicate an infection completely. Use of sensitivity testing is recommended to select the appropriate medication. Patients should maintain high fluid intake and use a strong secretagogue, such as sour lemon candies, at least three times daily to promote fluid flow. If there is enlargement caused by an inflammatory (and not an
infectious) cause, such as in Sjögren syndrome, antibiotics are not indicated. In these cases, short courses of systemically administered corticosteroids, may be beneficial. In general, the nonsteroidal anti-inflammatory drugs have not been useful in this setting.

As noted previously, owing to the loss of the anti-fungal activity of saliva, candidal and other fungal infections are a common and recurrent problem for patients with dry mouth. Treatment with topical or systemic antifungal agents may be prolonged. A particular concern is that most topical preparations (troches or lozenges) sold for treatment of oral fungal infections contain high concentrations of sugar. Although this improves the taste, it creates a problem for patients with salivary dysfunction who may need to be treated for several weeks to resolve a fungal infection completely. Non-sugar-containing antifungal rinse solutions can be formulated with nystatin powder or a nonflavored vaginal troche can be used orally.

Although secretagogues can provide transient relief of oral dryness, a limitation is that they are directed at the symptoms but fail to address the underlying causes of the gland dysfunction. In conditions such as Sjögren syndrome, patients are left with a gradual decline in function over time, worsening symptoms, and functional deficits.

Since the changes that take place in the salivary glands in Sjögren syndrome are of a chronic, inflammatory nature, the agents that have been tested have been primarily anti-inflammatory drugs used in other connective tissue diseases: nonsteroidal agents, steroids, or members of a large group of more potent drugs known as disease-modifying antirheumatic drugs.

The nonsteroidal anti-inflammatory drug (NSAID) piroxicam was tested in a placebo-controlled, double-masked, randomized clinical trial and was not beneficial in improving either the salivary or the lacrimal component in patients with primary Sjögren syndrome, based on objective and subjective criteria. In the same study, the steroid prednisone was effective in improving the serologic alterations found in Sjögren syndrome and in relieving symptoms of oral and ocular dryness. However, there was not significant improvement in major salivary gland function. More critically, there was no change in the extent of mononuclear cell infiltration of the labial minor salivary glands or of the proportion of individual glandular cellular elements (acinii, ducts, other). Therefore, steroids were not helpful in addressing the underlying pathologic tissue changes. Steroids may be used in selected cases of Sjögren syndrome, particularly in managing acute inflammatory swelling of the glands, but cannot be recommended routinely for treatment.

A number of other disease-modifying antirheumatic drugs have been proposed or tested for treatment of Sjögren syndrome. Most have either been ineffective or have had unacceptable risk:benefit ratios. Currently, there is a great deal of interest in hydroxychloroquine. This drug was originally developed as an antimalarial, as an alternative to chloroquine, with fewer adverse effects. It has been used for many years in systemic lupus erythematosus and rheumatoid arthritis, two autoimmune connective tissue diseases with many similarities, histopathologically and serologically, to Sjögren syndrome. There were initial uncontrolled studies suggesting benefit in certain aspects of Sjögren syndrome; however, in later controlled trials the results were not positive. The beneficial effects of hydroxychloroquine on salivary and lacrimal functions in Sjögren syndrome remain unproven.

A series of studies have demonstrated beneficial effects of alpha interferon (IFN-α) on salivary function in Sjögren syndrome. Trials have been conducted with both high-dose injectable formulations and a low-dose oral lozenge form of the drug. In addition to significant increases in salivary output, improvement has been shown in exocrine histopathology. A reduction in inflammatory infiltrating cells and an increase in normal-apparing salivary epithelial tissue have been demonstrated following 6 months of low-dose IFN-α therapy. If confirmed in additional studies, this represents the first disease-modifying therapeutic for Sjögren syndrome.

**Infectious, obstructive, and neoplastic salivary diseases**

Infections of the salivary gland are not common, with the exception of endemic parotitis, or mumps. Bacterial sialadenitis is usually a complication of obstructive disease and evolves as a consequence of retrograde extension through ducts that no longer transmit salivary secretions. Obstructions can occur from tumors and other inflammatory lesions that encroach upon and compress major salivary gland ducts; however, the most common cause is sialolithiasis (intraductal calcific masses, salivary stones). The submandibular gland is affected more often than the parotid, and occasionally, sialoliths evolve within the ducts of minor salivary glands.

Neoplastic lesions of the salivary glands occur most frequently in the parotid, less frequently in the submandibular gland, and are extremely rare in the sublingual gland. The minor glands of the oral cavity are a common site for salivary tumors, the palate, buccal mucosa, and labial mucosa glands being involved most frequently.

**Molecular and pathologic correlates of disease**

The histologic compartments of the salivary glands are illustrated in Figure 26–10. The individual components...
include the ductal orifice leading down into the extra-lobular duct that then branches into smaller extralobular ducts before entering the salivary parenchyma. These ducts are lined by stratified squamous epithelium. Once in the gland proper, the ductal lining becomes high, columnar, and oncocytic, a region referred to as the striated duct zone. These ducts branch further into terminal or intercalated ducts that then enter the acini. Myoepithelial cells encircle these ducts as well as the acini. These contractile cells expel saliva into the lumens, propelling the secretions out through the ductal tree. Recall that acini may be serous, mucous, or seromucous.

The mumps virus, which causes endemic parotitis, is an organism that shows tropism for salivary tissue yet can also infect the testes, pancreas, and central nervous system. The virus is a member of the paramyxovirus family, and its surface is occupied by large glycoproteins with neuraminidase and hemagglutinin activities. The virus is transmitted by aerosol droplets and can propagate in salivary epithelium as well as T lymphocytes. Following infection of the parotid glands, it can be disseminated to other sites via a transient viremia.

Sialolithiasis occurs in the absence of hypercalcemia; rather, the process is a local one whereby detritus accumulates within the ductal lumen. This material forms a mucinous plug that is comprised of viscous glycoproteins, bacteria, and epithelial debris. Theropy and viscous saliva of the submandibular duct appears to be more prone to be associated with stone formation. Upon this organic matrix, calcium salts become precipitated in an accretional, laminated manner such that, microscopically, concentric layering is encountered in decalcified specimens. Small stones may continue to be only partially obstructive, whereas larger sialoliths can cause total blockage (Figure 26–11). Once complete obstruction ensues, the parenchyma continues to function, secreting saliva into a closed space, which then becomes distended with elevated intraluminal pressure that causes atrophy and, ultimately, necrosis of acini. Whereas ductal conduits are preserved, the lobules show mononuclear infiltrates with fibrosis, a process referred to as chronic sclerosing sialadenitis. Other forms of obstruction include mucous plugs, which can be dislodged, and mucous extravasation.

Microscopically, the vast majority of salivary tumors derive from parenchyma and are either adenomas, if benign, or adenocarcinomas, if malignant. In children, some parotid region tumors originate from the fibrovascular supportive tissues of the gland, and in adults, a salivary mass may in actuality represent malignant lymphoma. The nosology of salivary tumors is based exclusively on tumor cell differentiation. Recall that salivary tissue is comprised of three major cellular compartments: acini, ducts, and myoepithelium. The diagnosis is rendered by histopathologic examination. The pathologist bases the diagnosis on two major features: (1) tumor margin characteristics, and (2) resemblance of tumor cells to normal glandular components. With regard to the first feature, encapsulation is perhaps the most important criterion for arriving at a diagnosis of adenoma, whereas invasion of contiguous tissues is the hallmark of adenocarcinomas. The second feature refers to the differentiation of the tumor with respect to ductal, acinar, and myoepithelial components. In most salivary tumors, the differentiation of the cells and their pattern of growth constitute the criteria for establishing a diagnosis.

Clinical features of infectious diseases

Endemic parotitis is a viral infection of the parotid glands that may also infect the submandibular gland. The patient complains of malaise and fever, accompanied by painful bilateral parotid enlargement. The
swollen glands typically cause the lobe of the ear to project upward and outward. The glands are extremely tender to palpation and milking them produces a thick white secretion from the parotid ducts. Histologically there is an interstitial infiltrate of mononuclear cells, although neutrophils are often seen within ductal lumens. As acinar cells undergo lysis, the amylase stored in secretory granules is liberated and results in serum elevations of this enzyme. In prepubertal males, the risk of testicular infection is extremely low, yet in postpubertal males, orchitis develops in 20% of cases. Testicular infection follows parotid infection by 1 week and is more often unilateral. Because of the interstitial nature of the inflammatory response in the testes, sterility is rare. There are no effective antiviral agents for mumps.

In rare instances, bacterial sialadenitis develops following extensive or prolonged abdominal surgery. The etiopathogenesis for this complication is unknown, yet may be the consequence of prolonged xerostomia during anesthesia. Patients are febrile and lethargic. The glands swell bilaterally and purulent exudate may be expressed from the duct orifices. This material should be subjected to culture and sensitivity, to allow selection of the appropriate antibiotic. Healing is usually uneventful.

Clinical features of obstructive salivary disease

Obstruction of the salivary ducts is usually attributable to calculus (sialolithiasis). Mucous plugs may congeal within salivary ducts, particularly those of the minor glands and cause intraoral swellings, owing to ductal ectasia. Neoplasms can also compress major ducts and cause the symptoms indicative of obstructive salivary disease; importantly, the gland should be palpated and imaged, to be certain that a neoplastic process is not present, since most instances of obstruction are not related to tumor compression. Magnetic resonance imaging is the preferred modality of imaging in these instances.

The classic clinical findings include episodic glandular enlargement secondary to distention by retained mucus (Figure 26–12, A). This enlargement is accompanied by pain, particularly during eating. The pain is stated to be “drawing” or of a stretching or stinging nature. When these symptoms appear, selected radiographs should be obtained, to explore for the presence of a sialolith. When the symptoms are referable to the submandibular gland, a mandibular occlusal film should be taken (Figure 26–12, B). If no opacity in the vicinity of the course of the submandibular duct can be detected, a panoramic and submental vertex plain film should be taken. Ultrasonography is also a useful imaging technique for discovery of salivary calculi. The more rare occurrence of parotid stones usually requires that a panoramic film be obtained, in which the sialolith can be visualized anterior to the overlying ramus of the mandible. When radiographs fail to reveal any evidence of sialolithiasis, lacrimal probe progressive ductal dilatation is indicated, to open any strictures or remove mucinous plugs. Sialography is also a useful diagnostic tool when no reason can be found for obstructive disease.

Mucous extravasation occurs when a salivary duct is severed, usually as a consequence of trauma, and mucus escapes into the connective tissue. The resulting mucocèle is soft and fluctuant and is walled-off by a rim of connective tissue yielding a cystic appearance. Most mucocèles are located on the lower lip, yet they may be found anywhere in the mouth where minor salivary glands are located. The buccal mucosa and ventral tongue are other areas where mucocèles are seen. Clinically, they appear as bluish dome-shaped elevations of the mucosa (Figure 26–13).

Clinical features of salivary neoplasms

As mentioned previously, salivary tumors are either benign or malignant with variability in clinical behavior for both groups of neoplasms (Table 26–4). Benign tumors, because of their encapsulation are typically freely movable, except in the hard palate, and are soft or firm, yet not indurated (Figure 26–14). The overlying skin or mucous membrane is unremarkable, ulceration being extremely rare. There are some general principles to be remembered when considering a salivary tumor in
the differential diagnosis. In general, all salivary tumors present as visual and palpable masses, with one exception: the deep lobe of the parotid, where the tumor is within the pharyngeal space and small neoplasms may go unnoticed. Parotid gland tumors are more often benign, whereas oral cavity tumors have a 1:1 ratio for benign versus malignant. Unlike other malignancies, malignant parotid tumors are not always indurated and fixed; they may be soft and well defined on palpation, masquerading as a benign tumor. Importantly, malignancy in the parotid often is attended by facial nerve weakness. Oral mucosal malignant salivary tumors often show surface ulceration or overlying telangiectasia.

Adenomas are histopathologically subdivided into monomorphic and pleomorphic subtypes. There are numerous monomorphic adenoma subtypes that vary in their site of occurrence. The monomorphic adenomas share the common feature of having a single cell type. Most are comprised of ductal cells that resemble either the striated ducts or the intercalated ducts. In the parotid gland, oncocyroma, papillary cystadenoma lymphomatosum (PCL), and basal cell adenoma are the more commonly encountered types. All are encapsulated and relatively soft to palpation. Oncocyroma is a tumor of ductal cells that are enriched with mitochondria, giving the cell a swollen eosinophilic appearance, a feature in common with normally occurring oncocyes within the glands of elderly individuals (Figure 26–15, A). Likewise, oncocyromas are usually encountered in elderly females. Males are more often affected by PCL (Warthin tumor), a lesion that feels like dough on palpation. This characteristic is the result of the histologic pattern of growth. The tumor is well encapsulated and the striated duct-like cells surround cystic spaces into which they project as papillary fronds (Figure 26–15,
Within the cystic zones are mucinous secretions. The intervening stroma, unlike in most tumors, is comprised of lymphoid tissue rather than fibrous tissue. Some cases are bilateral. Basal cell adenomas tend to occur at a younger age and are firmer to palpation. They are comprised of monomorphic islands of basilar-appearing cells and may have only occasional duct-like structures (Figure 26–15, C).

In the minor glands of the oral cavity, the monomorphic adenomas are subdivided into basal cell adenoma and a unique variant known as canalicular adenoma. These are moveable nodules found in the lip and buccal mucosa. Canalicular adenoma, so-named because of the anastomosing ductal strands that form canal-like structures, is found almost exclusively in the upper lip (Figure 26–15, D). Multicentricity is occasionally seen, presenting as multiple small submucosal nodules.

The most common benign salivary neoplasm is pleomorphic adenoma or mixed tumor. The term pleomorphic is applied, not in the sense of cytologic atypia, but rather as a descriptor that defines the diversity of histologic cell types seen in these lesions. There are ductal structures with circumferential myoepithelial cells that fan out into a myxomatous component. Cartilage, fat, and bone may also be seen in the stroma (Figure 26–15, E). There is a well-defined capsule that surrounds mixed tumors; however, a feature that accounts for recurrences after enucleation is the extention of satellite tumor nodules beyond the capsule. When these nodules remain behind, particularly in the parotid gland, they tend to recur as multinodular tumor masses. In the oral cavity, the palate is the most common site, followed by the buccal mucosa and lips. Most mixed tumors occur during midlife.

Adenocarcinomas of salivary origin are varied in their histologic appearance and behavior. Some are low-grade with limited potential for metastasis; others are slowly progressive yet metastasize and recur locally after durations of 10 or more years, and yet others are rapidly progressive, with both regional lymph node and distant metastases. The diagnosis is based on microscopic patterns of growth and cell differentiation. The parotid is the most common site for adenocarcinomas, followed by the intraoral minor glands. In the parotid, the lesions are firm to indurated tumefactions, and when the facial nerve is invaded, seventh nerve palsy is commonly observed (Figure 26–16). In the oral cavity, the palate is the most commonly involved site, followed by the buccal mucosa, lips, and tongue base. The tumor mass is often ulcerated or exhibits surface telangiectasia.

Adenoid cystic carcinoma (ACC) is comprised of small dark-staining cells that are arranged in solid nests, cribriform “Swiss cheese” patterns, and trabecular cords (Figure 26–17, A). These tumor cells are differentiated along the lines of intercalated ducts with surrounding myoepithelial cells. Clinically, these tumors are solid and usually indurated. In the parotid, they induce seventh nerve weakness when they invade the facial nerve that passes through the substance of the gland. In the oral cavity, ACC is usually located in the palate and may show a normal, telangiectatic, or ulcerated surface. These tumors can invade perineural lymphatics and spread for great distances along nerve trunks. This feature explains the tendency for local recurrences, even when the surgeon is certain that the entire tumor has been excised. The 5-year survival is generally good; however, because of the slow indolent course and tendency for recurrence, the survival rate drops significantly at 10 and 15 years post-treatment. Adenoid cystic carcinoma metastasizes both locally and distantly.

Mucoepidermoid carcinomas (MEC) are a varied group of malignancies with regard to natural history and metastatic potential. They are most commonly located in the parotid and intraoral minor glands. In the mouth, they are found in the palate, buccal mucosa, and tongue base. As the term implies, the tumor is repre-
sent by cells that differentiate along stratified squa-
mous lines and acinar (mucous cell) lines (Figure 26–17, 
B). Those that are cystic, with a high proportion of 
mucous cells, are low-grade tumors. They have a limited 
potential to metastasize; indeed, when located in the 
mouth, they rarely spread to regional lymph nodes 
when totally excised. Clinically, a low-grade MEC is 
soft and often feels encapsulated. Conversely, high-
grade MECs are characterized microscopically by a pre-
ponderance of epidermoid or squamous cells with small 
numbers of mucous cells. They tend to be solid rather 
than cystic. Such tumors have behavior not unlike squa-
mous cell carcinoma with both local and distant metas-
tases. High-grade MECs are indurated and fixed when 
in the parotid; in the oral cavity they may show surface 
telangiectasia or ulceration. Tumors with histologic fea-
tures midway between high and low grade are referred 
to as intermediate grade MEC, and their prognosis is 
likewise somewhere between the two extremes.

Acinic cell carcinoma is a tumor that is found 
almost exclusively in the parotid gland, only rare 
instances having been reported to arise from intraoral 
minor glands. This tumor is firm to palpation, yet may 
sometimes have cystic components. The tumor cells

Figure 26–15  A, Oncocytoma. Monomorphic cells with copious 
eosinophilic cytoplasm. B, Papillary cystadenoma lymphomatosum is 
represented by columnar ductal cells, cystic spaces, and a lymphoid com-
ponent. C, Basal cell adenoma is a monomorphic proliferation of basilar 
darkly stained cells. D, Canalicular adenoma of the upper lip shows a 
maze of anastomosing ductal channels. E, Pleomorphic adenoma is 
characterized by ductal structures, spindled myoepithelial cells, and a 
diverse myxoid stroma.
may differentiate as serous or mucous cells, and some are comprised of clear cells (Figure 26–17, C). The tumor cells are arranged in solid sheets, microcystic arrays, or cystic with papillary projections. The 5-year survival after parotidectomy is good, yet declines with ensuing years when local recurrence and metastasis may be encountered.

Polymorphous low-grade adenocarcinoma is a low-grade salivary tumor that is confined to minor glands. For all practical purposes, it does not arise in the major glands. As the term implies, the tumor cells assume a variety of growth patterns (Figure 26–17, D). The cells are arranged in solid sheets, cribriform patterns, ductal structures, and linear cords that bear a resemblance to ACC. These tumors are located in the palate and buccal mucosa as firm, relatively well-delineated submucosal masses. They recur when removed by excision, and their metastatic potential is low.

There are many other histopathologic types of salivary tumors that are rare. Included in this group are primary squamous cell carcinomas of salivary origin, adenocarcinoma arising in a benign mixed tumor (car-
parotid mixed tumors are treated by partial or total parotidectomy. Facial nerve palsy is a potential complication, yet the neurologic deficit can usually be mitigated in benign tumors. Intraoral benign adenomas are treated by local excision, and recurrence, even with pleomorphic adenoma, is unlikely.

Malignant salivary neoplasms of the major glands are treated by total sialectomy, and lymph node dissection is undertaken if there is clinical or imaging evidence of metastasis. Malignant intraoral salivary tumors are treated by wide local excision, with histologic examination of margins for completeness of the surgery. Palatal malignancies require partial or subtotal maxillectomy, since bony invasion is usually present. More radical surgery is performed for adenoid cystic carcinomas, because of their tendency for perineural extension. Lymph node dissection is performed when evidence of metastasis is encountered. Radiation therapy may be used as an adjunct, although most salivary tumors, with rare exceptions, are not radiosensitive.

Suggested reading