Although unilateral parotid swellings are most frequently seen in Columbia University’s Salivary Gland Center (SGC), patients with bilateral parotid swellings are not an unusual occurrence. Because these swellings are not localized to 1 gland, it must be assumed that systemic factors are usually in play. Numerous causes for bilateral parotid swellings have been identified (Table I). Consequently, the attainment of a definitive diagnosis requires a familiarity with the full range of possible etiologies for these swellings. Differential diagnostic skills must be implemented to achieve a precise diagnosis. Therefore, it is our purpose to review the various causes of bilateral parotid swelling. The list of bilateral parotid swellings that we have developed has evolved from the SGC’s experience with more than 6000 patients.

Emphasis will be placed on the symptomatology and therapy of the various entities with a highlighting of their salient features. Attainment of an accurate diagnosis for the patient with bilateral parotid swelling represents the desired objective.

MASSETERIC HYPERTROPHY (THE RED HERRING)

Surprisingly, the patient frequently referred to the SGC with a tentative diagnosis of bilateral parotid swelling does not have a parotid problem. On examination, the entity mistaken for bilateral parotid enlargement is seen to be masseteric hypertrophy (MH; Fig 1). The misdiagnosis is caused by the fact that the bulk of the large superficial parotid lobe rests anatomically in close proximity to the posterior lateral aspect of the masseter muscle.

MH is an asymptomatic persistent enlargement usually of both masseter muscles that results from a work hypertrophy. Occasionally, a congenital variety is observed. Classically, MH is initiated by constant clenching, bruxism, or gum chewing. This occurs primarily in younger adults. In older patients it is rarely seen because dental deterioration leads to pain during heavy occlusion and full activation of the masseters is subjectively impeded.

The masseter is a thick, quadrate, masticatory muscle consisting of 3 layers. It arises from the zygomatic arch and inserts into the lateral aspect and angle area of the mandibular ramus. Anatomically, most of the masseteric thickness is along the inferior portion of the mandibular ramus where the facial contour normally tapers. On stimulation, the previously flaccid muscle becomes firm and displays its discrete and prominent anatomic outline. With MH, the patient’s face takes on a characteristic rectangular configuration. Radio-graphically, in the area of the muscle’s mandibular insertion, bony hyperplasia may be observed due to the stimulatory effect on bone from increased muscle bulk and tension. Orally, tooth attrition from bruxism or clenching may be present.

Other than increased masseter muscle fiber length and diameter, histologic findings reveal no abnormalities. Therefore, therapy is conservative and involves reassurance, muscle relaxants, psychiatric care, behavioral modification, and dental bite plate construction. Surgery to reduce muscle mass is only indicated if cosmetic concerns become paramount. Botulinum toxin injections have been used to block motor end plates and prevent neurologic stimulation of the muscle. The resulting inactivation of the muscle leads...
to atrophy. Because nerve regeneration occurs within 4 to 6 months, the procedure is only successful if the clenching, bruxism, or gum chewing ceases within this effective time frame. Injections may be repeated until such time as the patient stops the causative habit.

In contradistinction to MH, parotid swellings tend to accentuate facial ovality because the major portion of the gland is situated at a higher level, adjacent to the ear. The parotid glands in MH are neither swollen nor tender. The salivary ducts are patent with a normal salivary flow, both quantitatively and qualitatively. Noninvolvement of the parotids is further evidenced by their normal imaging studies.

SIALADENOSIS

Sialadenosis is defined as a bilateral persistent, painless, soft, non-neoplastic, noninflammatory swelling usually involving both parotid glands (Fig 2, A) and at times the submandibular salivary glands. There is no sex predilection, and it usually develops after the patient has reached 30 years of age. Sialadenosis is associated with a variety of conditions that include alcoholism, endocrine disorders—particularly diabetes mellitus—and malnutrition, which in our society usually results from anorexia nervosa. It is also seen in a group of patients who have no known relationship to these systemic problems and whose etiologic background remains an enigma. The most commonly seen cause for sialadenosis is alcoholism, with 30% to 80% of patients with cirrhotic livers exhibiting enlarged parotids. Diagnosis of sialadenosis is facilitated by its clinical manifestations. The bilateral painless parotid swellings have been present for a prolonged time, they do not fluctuate in size in association with meals, and patent parotid ducts with a free and clear salivary flow can be observed. Blood chemistry studies are a significant aid in determining the existence of liver dysfunction, diabetes, or abnormalities associated with malnutrition.

Etiologically the common denominator possessed by patients with these various medical conditions seems to be an autonomic neuropathy associated with a widespread demyelinating polyneuropathy. The acinar cells of the parotid gland receive both parasympathetic and sympathetic innervation. The parasympathetic innervation is concerned with fluid and electrolyte secretion. The sympathetic stimulus is involved with intracellular protein synthesis and secretion. With dysregulation of the parotid’s autonomic innervation, particularly the sympathetic supply, excessive stimulation of acinar protein synthesis and/or inhibition of protein secretion occurs. Cytoplasmic engorgement by zymogen granules, the precursor of amylase, develops with acini increasing in size from a normal 40 µm to as much as 100 µm. The increase in acinar size translates into the clinically observed parotid hypertrophy of sialadenosis.

Sialography shows a normal duct pattern and caliber. However, because of the glandular hypertrophy, individual ducts are widely dispersed from each other and may even be thinned. A computed tomography (CT) scan will reveal bilaterally enlarged parotids with an increased density (Fig 2, B). This results from the replacement of the gland’s normal complement of lucent fat by the parenchymal hypertrophy. To substantiate further the existence of sialadenosis, fine-needle aspiration biopsy can be performed to show the enlarged acini.

The importance of diagnosing sialadenosis rests in the fact that a significant underlying systemic disease is usually present. Recognition mandates a medical referral and the initiation of the requisite care. Medical therapy for the systemic problem leads to some decrease in parotid gland size, but the results are variable. A variety of treatments aimed at reducing gland size have not met with significant success.

BULIMIA

The spectrum of eating disorders is most frequently seen in young women pursuing thinness. It includes anorexia nervosa (AN) and bulimia nervosa (BN), with a high incidence of crossover between AN and BN occurring in individual patients. Patients with BN are
not underweight. They indulge in uncontrolled recurrent episodes of high caloric binge eating, but their concerns about gaining weight lead to self-induced vomiting after the binges. Once the individual realizes that the weight gain caused by the binge can be nullified by emesis, less restraint is exerted on the binges. A natural progression is to resort to binges with emesis not only when hungry, but also when tense or anxious.15

The frequency of vomiting varies, but it can be as high as 140 episodes each week.15 Diffuse, persistent, asymptomatic, painless, noninflammatory salivary gland swellings, usually seen as bilateral parotid swellings with occasional involvement of the submandibular glands, are observed in 10% to 66% of the BN patients.16 The incidence and size of the swellings are directly proportional to the frequency of vomiting.17 After an early period of intermittent swellings, there is a tendency for the bilateral parotid sialadenopathy to become persistent.

Intraorally, the repeated exposures to the regurgitated gastric acids cause dental erosions with loss of enamel and a resulting thermal sensitivity (Fig 3). The enamel loss, combined with the BN patient’s high carbohydrate intake, produces increased cariogenic activity. Fluorides, bicarbonate mouthwashes, and good oral hygiene can play key roles in preventing this dental deterioration.

Fluorides, bicarbonate mouthwashes, and good oral hygiene can play key roles in preventing this dental deterioration.

It has been suggested that the cholinergic stimulus associated with the frequent vomiting activates the salivary glands as evidenced by the increased salivary flow during an emetic episode.18 This chronic work hypertrophy19 leads to the clinical bilateral parotid swelling. Substantiation for this hypothesis is derived from the observation that individuals who purge themselves with laxatives and do not vomit do not develop parotid swellings.20

It is also possible that patients with bulimia, like patients with sialadenosis, develop an autonomic neuropathy that leads to enlarged acinar cells from zymogen granule engorgement.8-13 The granule congestion results from a dysregulation in granule production and/or a lengthening of zymogen granule storage time. The malnourished AN patient would seem to fall into this category.19

Repetitive vomiting is also associated with serious aberrations in serum electrolyte levels, often requiring hospitalization. Hypokalemia, hyponatremia, and hypochloremia result from the loss of electrolytes in the gastric juices contained within the vomitus. Hyperamylasemia has also been reported, and its existence also can be used as a diagnostic tool.21

Treatment is multifactorial with attention primarily directed toward the existence of electrolyte depletion
and the need for hospitalization. Cardiac arrhythmias, hypotension, hypothermia, and dependent edema can be anticipated with the loss of electrolytes. Most patients have psychiatric disorders, with depression being a frequent finding. Psychiatric care with diet correction and discontinuance of the vomiting usually lead to regression of the glandular swellings.

**ACUTE SUPPURATIVE PAROTITIS**

Acute suppurative parotitis (ASP) probably develops from an ascending ductal infection, facilitated by dehydration, that originates from oral bacteria localizing in the parotid gland. The resulting parotid swelling is usually unilateral, although the incidence of bilateral parotid involvement has been reported to vary from 15% to 25%. The disease is seen in the newborn infant, the debilitated patient, the systemically ill patient who may usually be recovering from an abdominal surgical procedure and have had inadequate fluid replacement, and the immunocompromised patient. Those cases that occur in infancy are thought to originate from a blood borne bacteremia. The onset of ASP can prognosticate a fatal consequence. Undoubtedly, this grim outcome results from the fact that the parotitis acts as an oppressive complication in a feeble and already weakened patient.

The primary cause of ASP is dehydration and is encouraged by diminished patient resistance and poor oral hygiene. Severe dehydration, brought about by factors such as sweating, diarrhea, and inadequate fluid replacement, leads to a decreased salivary flow. The reduction in salivary flow may be further accentuated by a variety of medications that have xerostomic side effects and have been prescribed for the patient’s primary medical problem. In addition, many patients are unable, unwilling, or forbidden to take oral nourishment and will lose the stimulatory effects of mastication on their salivary glands. These factors all lead to a significant xerostomia with a loss of the lavaging and inhibitory action of saliva on oral bacteria.

The most frequent culpable organism in ASP is the penicillin-resistant *Staphylococcus aureus*, but *Streptococcus viridans*, *Streptococcus hemolyticus*, *Streptococcus pneumoniae*, and a variety of anaerobic bacteria have been detected. Their presence can readily be identified by culturing the pus from the Stensen orifice.

Although unilateral or bilateral parotid swellings are present, the submandibular salivary gland is rarely involved. Parotid susceptibility may be due to the absence of the bacteriostatic mucin in its serous secretion.

The onset of the parotid swelling is rapid. Palpation reveals a firm and tender swelling. Pain can be severe because the suppurative process is confined under pressure by the dense fibrous parotid capsule. The resistant capsule also serves to mask any fluctuation that may be present. Pus usually can be observed intraorally exiting from the duct orifice (Fig 4). Trismus, toxicity, leukocytosis, fever, malaise, and loss of appetite develop.

The incidence of ASP has dropped markedly over the years. Improved control of fluid and electrolyte balance and the advent of more effective antibiotics deserve the credit. If the condition does develop, it will usually respond to supportive therapy, which includes hydration, electrolyte replacement, good oral hygiene, sialagogues, rebuilding of the patient’s resistance, treatment of any underlying systemic disease, and appropriate antibiotic therapy. Surgical incision is usually not warranted because histologically the microabscesses that are present fail to coalesce to form the macroabscess that would respond to such an
EPIDEMIC PAROTITIS (MUMPS)

Epidemic parotitis (mumps), a viral parotitis, is an acute contagious disease that primarily affects children younger than the age of 15 years, has a predilection for nervous and glandular tissues, and confers a lifelong immunity. Mumps is caused by a specific virus, a Paramyxovirus. After contact with airborne saliva droplets of an infected individual, the virus enters the nose or mouth and proliferates in salivary gland tissue or in the superficial epithelium of the respiratory tract. A generalized infection results with viral particles detectable during the acute phase in human saliva, blood, urine, and cerebrospinal fluid. Other viral agents including the parainfluenza and coxsackie viruses can also cause an infectious process similar to mumps.

Clinically, a mumps infection becomes evident after an incubation period of 16 to 18 days. However, 30% to 40% of patients who are infected have no clinically apparent symptoms. Patients with clinical symptoms exhibit a broad range of severity that is dependent on the site of infection. In the classic case of mumps, parotid involvement alone, either bilaterally (75%) or unilaterally, is observed. Before the enlargement of the parotid glands, the patient will experience a prodrome of symptoms including fever, headache, myalgia, and malaise. Involvement of the parotid gland is signaled by the onset of pain localized to the gland, some trismus, and dysphagia.

After the incubation period, parotid swelling develops and peaks in 1 to 5 days. Initially, 1 gland becomes swollen with the contralateral side following suit within 5 days. In some cases, bilateral swellings will commence simultaneously. Subsequently, the enlarged parotids will gradually decrease in size during a period of 3 to 7 days. Inflammation of the orifice of the Stensen duct is present, but a clear salivary return after stimulation can be observed.

Submandibular or sublingual salivary gland enlargement, with or without the usual bilateral parotid involvement, can also be seen. Additional clinical features of mumps include orchitis, meningoencephalitis, and in rare cases pancreatitis, oophoritis, thyroiditis, and mastitis. Although serious complications may develop, particularly in the adult, patients generally have a favorable prognosis.

With parotid swelling, laboratory substantiation is often unnecessary. Support for a firm diagnosis of mumps is derived from a history of never having had mumps, an exposure to the mumps virus 2 to 3 weeks before the onset of symptoms, and a compatible clinical picture of parotitis. In the absence of parotitis, laboratory testing can confirm the presence of viral particles in saliva, urine, blood, and cerebrospinal fluid.

Mumps is a self-limiting disease, and treatment is primarily symptomatic and supportive. Because of the immunity that develops, reports of recurrence are considered errors of diagnosis.

Vaccination with a live attenuated virus usually affords protection. This method of active immunization produces a subclinical noncommunicable infection with very few side effects. Before vaccination, consideration must be given to the patient’s immune status because the attenuated virus in the vaccine may be potentiated in the immunodeficient patient or in those who have a suppressed immune response.

HUMAN IMMUNODEFICIENCY VIRUS DISEASE

Patients with human immunodeficiency virus–1 (HIV) are often seen with head- and neck-related symptoms, some of which involve the parotid gland. Persistent, painless parotid enlargements, usually bilateral, occur in 5% of the HIV-positive patients. During embryologic development, many lymph nodes are trapped within the parotid gland. These nodes have been shown to contain salivary gland acini and ducts. With the viral replication that occurs in HIV disease, lymphoproliferative activity of the parotid lymph nodes or proliferation of lymphocytes that are normally present within the gland or have infiltrated into the gland will result in an enlarged parotid gland. Bilateral benign parotid lymphoepithelial cysts can also develop and cause glandular swellings. These cysts are thought to originate from the included epithelium in the intraparotid lymph nodes.

Patients who develop HIV-related parotid swellings belong to a subset of HIV patients. They are defined as having diffuse infiltrative CD8 lymphocytosis syndrome (DILS). Diagnosis of the DILS subset is based on the presence of a persistent circulating CD8 lymphocytosis, a diffuse CD8 lymphocytic tissue infiltration, clinically apparent painless parotid swellings, and cervical lymphadenopathy in a patient with a positive HIV serology. The syndrome seems to be the result of a genetically determined immune response to HIV.

DILS most commonly involves the parotid gland bilaterally and the lungs. The increased parotid lymphocytic presence is probably a response to HIV-related antigens within salivary gland macrophages. The development of the parotid lymphoepithelial cyst seems to occur after the inflammatory state has exerted
its effect on the glandular epithelium trapped within the intraparotid lymph nodes.40,42

The CT scan typically reveals single or multiple bilateral parotid cystic lesions (Fig 5) or densely enlarged parotid glands that reflect a massive CD8 infiltration. Chest films show lung infiltrations.

Successful treatment of the parotid swellings in DILS has been accomplished with cocktails of the newer protease inhibitors.43,44 A positive response requires at least a 6-week course of the medications.

Because these patients are susceptible to the development of a B-cell lymphoma,45,46 continued observation is mandatory. If no clinical manifestations of malignancy are evident, such as changes in growth patterns, parotid monitoring with an annual needle aspiration biopsy to detect early malignant transformation represents reasonable care.

RECURRENT PAROTITIS IN CHILDREN

Recurrent parotitis in children (RPC) is an unusual inflammatory disease that tends to involve both parotid glands. It occurs in youngsters before puberty, mostly boys between 3 and 6 years of age. With puberty, symptoms subside and may even resolve totally.47 However, clinical symptoms may persist into early adult life and can even extend throughout adult life.47-49

The parotid swellings develop suddenly with a tendency to occur on 1 side and subsequently on the other side. Often both parotids are swollen simultaneously, and sometimes fever and pain are present. The swellings last from several days to as long as 2 weeks. Remissions can occur spontaneously, but recurrences can be expected.49

Salivary production may be temporarily decreased, and an ascending duct infection as a result of RPC may develop. Extraoral manual milking of the swollen parotid will produce an intraoral salivary flow that contains mucous plugs. The plugs represent accumulations of cells, mucus, and pus resulting from infection and/or stagnation in the duct system. A clear salivary flow returns with subsidence of the acute swelling. Regardless, sialochemistry will reflect chemical changes, even during remission, characteristic of low-grade inflammation. Moderate increases in sodium and chloride levels with a decrease in phosphate levels are noted.

The etiology of RPC remains unknown. It may have an autoimmune etiology,50 or it may represent a congenital malformation of portions of the salivary ducts, which become secondarily infected from an ascending infection.47 Histologically, the ducts are surrounded by a chronic lymphoproliferation, autoimmune or infectious in origin.

Parotid sialography has proved to be a major aid in the diagnosis of RPC. Classically, a sialectic pattern (Fig 6) is seen bilaterally even if the presenting symptoms are only unilateral.48,49 Sialectasis reflects the presence of interlobular duct dilatations that are imaged sialographically as an abnormal droplet, or stippled, pattern within the gland. Occasionally, sialectasis will be absent or it will only be visualized unilaterally.49,50 The sialectasis can diminish or even disappear with progression into adult life,49,51 but persistence has been reported.49 Abnormalities also include irregularities in the outline of the major ducts with dilatation of the Stensen duct.49

Ultrasonography is another imaging modality that can substantiate a clinical diagnosis of RPC.
Hypoechoic areas are observed, reflecting both the presence of duct dilatations and the sonolucent periductal lymphocytic infiltration. Imaging with ultrasound is well-suited for children because it is noninvasive, painless, rapid, and has proved to be an effective diagnostic adjunct.

No underlying systemic disease has been found in RPC. There are reports that some RPC patients with sialectasis are young individuals with Sjögren's syndrome (SS) or in whom SS will develop in adulthood. Differentiation of RPC from SS rests in the fact that the pathognomonic serum autoantibodies associated with SS are not present in RPC. Furthermore, the pattern of lymphocytic infiltration into the salivary glands seen in RPC differs microscopically from that seen in SS.

Because the natural history of RPC includes frequent spontaneous resolution, conservative treatment is indicated. Ductal dilatation with probes, salivary stimulation with sugarless sour candy followed by forceful gland massage to flush the duct system, and antibiotic therapy when indicated represent satisfactory therapeutic approaches. Parotidectomy is rarely needed and should be limited to those very severe cases whose acute symptoms do not resolve with conservative treatment.

**RECURRENT PAROTITIS IN ADULTS**

Recurrent parotitis in adults (RPA) does not differ much in its clinical manifestations from its counterpart in children (RPC), except that infection has become a significant feature. As in RPC, adult patients have a history of alternating parotid swellings, at times bilateral and at times unilateral. The swellings are sporadic in nature, may be initiated during eating, and have a long-standing history.

RPA may arise spontaneously in adult life, or it may represent a progression of the disease from childhood. Usually, the childhood form of recurrent parotitis disappears with puberty, but reports exist regarding the advance of the disease into adult life. Some of these adult patients, who initially had only parotid swellings, subsequently develop the systemic signs of SS. Recurrent parotid swellings can precede the ocular and systemic signs of SS by 2 to 24 years, with a mean of 9 years. Therefore, it is possible that some patients with RPA had early signs of SS, even as children, and with time will develop classic SS.

Infection can occur as a secondary manifestation in RPA patients. In those patients with a history of RPC, the parotid glands may have been compromised by the pathologic condition associated with sialectasis, and a secondary infection is made easier. Regardless of the background, the ascending infectious process causes further gland degeneration with the occasional acute exacerbations associated with RPA.

With infection, pus is usually noted exiting from the Stensen orifice when the involved gland is massaged. Often, even during quiescent periods, the salivary return is abnormal. Flocculations in a clear saliva or a gelatinous type of saliva may be observed when the gland is milked.

Sialography, performed when the acute symptoms subside, will reveal a pathognomonic pattern. The sialectasis seen in children has become more gross and may have evolved into a parenchymal cavitary or destructive stage as a result of the duration of parotid involvement and the devastation caused by repeated bacterial incursions (Fig 7). In addition, the ducts, particularly Stensen, will show the effects of the ascending infection. A sialographic pattern referred to as “sausaging” will be seen. It reflects the presence of duct strictures from healing with scar formation and

**Fig 7.** A, Recurrent parotitis in adults. Sialogram of left parotid gland in 29-year-old man. Sialectasis and moderate sausaging of Stensen duct are present. Patient stated that he has had bilateral parotid gland swellings since the age of 10 years. B, Same patient as seen in A. Sialogram of right parotid gland. Gross sausaging of ducts and evidence of a preexisting sialectasis are visible.
duct wall weakening from infection combined with duct dilatation from salivary retention as a result of the strictures.

A CT scan also can be helpful in diagnosis. Increased density of both parotids is observed. This density represents the inflammatory infiltrate that has displaced the lucent fat content of the parotid.

Treatment modalities include duct probing to unclog a duct obstructed by mucus plugs, massage to increase salivary flushing of the duct, steroids, and antibiotics. Such approaches are symptomatic and best reserved for those patients who have milder complaints. However, recurrences can be expected, and a downhill spiral of events can be predicted. More aggressive management has been advocated. Ligation of the main duct has met with some success, but the failure rate is high. Superficial parotidectomy represents a relatively aggressive approach fraught with danger to the facial and auriculotemporal nerves. Recently, retrograde ductal injection of methyl violet has been advocated. The methyl violet incites an inflammatory response in the major and minor duct radicles. Duct fibrosis with glandular atrophy is the hoped-for end result.

**SJÖGREN’S SYNDROME (AUTOIMMUNE DISEASE)**

Sjögren’s syndrome (SS) is a chronic autoimmune disease characterized by mononuclear infiltrations that create destructive lesions in exocrine glands, primarily the lacrimal and salivary glands. Bilateral parotid swellings often develop, and because the disease is not limited to exocrine glands, multiple systemic organs can be involved. Primary SS involves the lacrimal and salivary glands with the absence of an associated systemic autoimmune disease. Secondary SS is associated with the presence of other systemic autoimmune disorders such as rheumatoid arthritis, lupus erythematosus, scleroderma, and polymyositis.

Clinically, women in the fourth and fifth decades of life are most susceptible to the disease, but men, the elderly, and children are not exempt. The criteria for an objective diagnosis of SS have been established by a European study group. Ocular symptoms may include an awareness of a dry eye that may cause a sensation of the presence in the eye of sand or gravel. Evidence for ocular involvement can also be derived from a positive result on a Schirmer test, a tear volume study, or a rose Bengal test that reveals the corneal ulcerations that result from xerophthalmia. Oral symptoms include a dry mouth, which can necessitate frequent drinking to aid in the swallowing of food. Salivary gland swellings may also be present. Salivary scintigraphy, parotid sialography, and volume studies of unstimulated salivary flow also may testify to the existence of SS. A diagnosis of SS can be determined when a labial gland biopsy specimen histologically shows a diagnostic focus score of mononuclear cells. An accumulation of 50 mononuclear cells in 4 mm$^2$ is considered 1 focus. The presence of autoantibodies, such as the antinuclear antibody, the rheumatoid factor, or antibodies to SS-A or SS-B antigens, has also been observed.

As can be expected, patients with 1 autoimmune disease are susceptible to the development of other autoimmune diseases. Signs of SS have been found in autoimmune entities such as primary biliary cirrhosis, primary sclerosing cholangitis, and graft versus host disease. These patients may develop the bilateral parotid swellings often associated with SS.

Orally, the major concern of patients with SS is xerostomia. The dryness results in painful burning sensation of the mucosa, difficulty with chewing food, rampant dental caries, and altered taste. What little saliva is produced is viscous in nature. The tongue is smooth, reflecting the absence of filiform papilla, and it may develop a cobblestone appearance. Fungal infection of the mucosa is facilitated by the decreased salivary production.

Both major and minor salivary glands are implicated in SS, but bilateral parotid involvement, often causing an enlargement, can be seen. The parotid swellings that occur are caused by inflammatory duct obstructions, which favor the development of secondary infections. It is also possible that the primary problem is the decreased salivation, which causes a failure of duct lavage and promotes the ascent of oral bacteria into the duct system. The ensuing swellings are intermittent, with durations that last from weeks to months and are followed by varying periods of remission. The swellings tend to be moderately painful and are exacerbated by eating. Because the Stensen duct acts as an adequate drainage mechanism, pus can be observed exiting intraorally from the duct orifice. Besides infectious damage to the gland, duct wall damage also occurs. The resulting wall irregularities allow for bacterial reproduction in areas safe from the lavaging effects of the little saliva that is produced.

Treatment of the infected gland consists of steroids and appropriate antibiotic therapy. Supportive care includes duct probing to free the duct lumen from the clogging effects of the inflammation-produced mucous plugs. The cholinergic agents, pilocarpine and cevimeline, are sialagogues that have been used to stimulate the residual parenchyma and to flush the duct to discourage further plug formation.

The recognition of a bilaterally infected parotid gland in a patient with SS is based on an ability to diagnose SS objectively and an understanding that SS is the primary problem. The infected parotid glands are a result of the decreased salivation.
Bilateral parotid swellings from an atypical benign tumorlike lymphoproliferation or from a true neoplastic disease also develop in patients with SS. These entities reflect the proliferation of mucosa-associated lymphoid tissue (MALT) and the development of a MALT lymphoma. Such parotid swellings tend to have a long-standing presence with no signs of fluctuation in size. There is no suppuration, the swellings tend to be painless, and they can become a cosmetic problem.

Sialography can be a valuable tool in the diagnosis of SS and in differentiating the swelling of a secondary infected parotid from that caused by a lymphoma. Sialodacryography, a droplet pattern, will usually be seen involving the parotid parenchyma of a patient with SS. With secondary infection, because the wall of the Stensen duct has been damaged, irregular stricturing and dilatation of the duct wall (sausaging) are usually seen. The combination of sialodacryography with duct sausaging suggests infection of the parotid as a result of SS. Those patients who have developed a bilateral lymphoma will also exhibit sialodacryography, but because infection is absent, a sausaged Stensen duct will not be observed (Fig 8).

**WEGENER GRANULOMATOSIS**

Wegener granulomatosis (WG) is defined as an aseptic, necrotizing, granulomatous inflammation and vasculitis affecting the upper and lower respiratory tracts and the kidneys. The etiology of WG has not yet been established, although it may be autoimmune in origin. Numerous systemic structures become involved, and limited forms of the disease also can occur. Various combinations of salivary gland involvement may be seen, with bilateral parotid swelling as a feature.

There is no sex predilection, and 97% of the patients are white and develop the disease in the fourth or fifth decades of life. The histopathologic hallmarks of WG consist of the triad of granulomatous inflammation, necrosis, and vasculitis of the small and medium-sized arteries and veins. The condition begins as a localized process that if left untreated can progress with unpredictable speed to affect multiple organs and eventually result in death from kidney failure.

Initially, patients are seen with respiratory symptoms and sinus pain. Ninety percent of the patients with WG have head and neck symptoms. Orofacial manifestations occur with a relatively low frequency (6% to 13%) and besides the salivary glands include ulcerative stomatitis and hyperplastic gingivitis.

Parotid involvement may be bilateral or unilateral, with pain and fever sometimes accompanying the gland swellings. The gland swellings persist for prolonged periods and do not fluctuate in size with meals. Respiratory difficulties, sinus pain, hearing loss, ocular pain, ocular drainage, or nasal discharge are often seen in conjunction with the parotid swellings. A diagnosis of WG in a patient who has parotid swelling is made possible by obtaining a blood sample and performing indirect immunofluorescence for the detection of the antineutrophil cytoplasm antibody (ANCA). ANCA is positive in 67% of the patients who have the limited form of WG, which is often the case in patients with salivary gland symptoms. For those patients with active generalized WG, ANCA’s presence increases to 95%. Because sensitivity of this serologic test is decreased in those with limited WG, multiple longitudinal studies to monitor the status of ANCA are indicated. Diagnostic confirmation can only be attained from a biopsy specimen that exhibits the classic histopathologic findings.

A biopsy specimen of salivary glands in WG patients reveals a parenchymal and vascular pathologic condition. Salivary parenchymal changes include the previously described histologic triad, but this triad is seen in only 16% of the specimens, whereas 2 of these features...
are evident in 22% of the biopsy specimens. The pathologic changes focus on the salivary ducts and acini and are partly vasculocentric.

Once a diagnosis of WG has been confirmed, the treatment protocol consists of a regimen of prednisone and/or cyclophosphamide. Regression of inflammation and decreased swelling of the parotid glands result. Clinical relapse has been reported and tends to occur during the course of the tapering down of the patient’s medication. Increasing the medication dosages will again lead to remission.

The significance of recognizing bilateral or unilateral parotid swellings as an initial manifestation of WG is 2-fold. A biopsy of the salivary gland can be performed. It avoids the increased morbidity associated with an open lung biopsy. In addition, the visible salivary gland swelling serves as a marker for early investigation, which in turn will lead to early treatment and decreased likelihood of disease progression.

SARCOID

Sarcoidosis is a chronic multisystem granulomatous disease of unknown origin with a special predilection for the lungs and hilar lymph nodes. It commonly affects young adults and particularly black women in the 30- to 40-year-old age range (Fig 9). Most patients have respiratory symptoms such as coughing, dyspnea, or chest pains.

Salivary glands are quite susceptible to sarcoideal disease. Major salivary gland swelling, involving both parotid glands and at times the submandibular glands, is often present. Bilateral parotid sialadenopathy is seen in 4% to 30% of patients with this disease. The glands tend to be firm, only slightly painful, and they do not fluctuate in size when eating. Because the sarcoideal granulomas replace the glandular parenchyma, a moderate decrease in salivary production results. The parotid sialogram reveals a normal duct distribution, but the ducts are diminished in number.

Not only are the major salivary glands frequently compromised, but minor glands also are implicated. Consequently, a labial gland biopsy has been suggested as a diagnostic index. Granulomas are seen in 58% of these biopsy specimens. Furthermore, positive biopsy specimens are obtained whether or not sialadenopathy exists simultaneously with the symptoms of systemic sarcoid disease.

Diagnosis is based on the radiologic identification of both a distinctive lung infiltrate and a hilar lymphadenopathy. Final diagnosis awaits the histologic demonstration of the granulomas in an organ structure. Noncaseating granulomas, with a core of epithelioid and giant cells and a periphery of lymphocytes and fibroblasts, are seen. Blood studies often show elevated calcium and alkaline phosphatase levels, increased serum angiotensin converting enzyme levels, and hypergammaglobulinemia. The Kveim test, an intradermal injection of a sarcoidal suspension, is positive 80% of the time.

An infrequent symptom complex of sarcoidosis is uveoparotid fever, also known as Heerfordt syndrome. It is typified by a triad of symptoms: inflammation of the eye’s uveal tract, bilateral parotid gland swelling, and cranial nerve involvement usually seen as a transient seventh nerve paralysis.

Treatment of the disease is generally symptomatic. Spontaneous resolution can be expected. In severe cases, corticosteroids are used and are particularly helpful if an aggressive therapeutic approach is required to abort the advance of an ocular lesion to blindness. Ocular symptoms mandate referral to an ophthalmologist.

KIMURA DISEASE

Kimura disease, first described in 1937, is a reactive, self-limiting, painless, persistent, indolent lesion, mimicking a neoplasm, whose etiology is unknown. It occurs most frequently in the head and neck region of young Asian men whose mean age is 28.6 years. A lymphocytic hyperplasia of the intraparotid or paraparotid lymph nodes, with secondary involvement of the salivary parenchyma, causes parotid swellings. Clinically, cervicofacial lesions are most common, with bilateral painless parotid gland swellings often being observed. The salivary glands may be involved alone, or they may be associated with lesions elsewhere. Lymph nodes in other areas of the head and neck, as well as subcutaneous nodules in distant anatomic sites, can be seen and may manifest themselves as solitary and at times multiple lesions.

Histologically, the lesions show a lymphoproliferation and the presence of multiple prominent lymphoid follicles with florid germinal centers. Interspersed...
within the lymphocytic hyperplasia, a marked eosinophil infiltration and multiple thin-walled capillaries are evident. The blood picture is hallmarked by an eosinophilia and an immunoglobulin A elevation.84,87

A clinical diagnosis is difficult to attain without a biopsy, but a CT scan can be helpful. Lesion enhancement is evident because the pathologically increased vascular component “lights up” with the contrast dye.87

Although Kimura disease may be immunologically mediated,86,88 steroid therapy has only been partly successful.85 Surgical excision is recommended, but recurrences are not uncommon.89 Radiation is best saved for the refractory lesion.85,87

POLYCYSTIC PAROTID DISEASE

Polycystic parotid disease is a rare congenital lesion of the parotid gland, which may have a hereditary background.90 The first 2 cases were reported by Seifert et al,91 who believed the entity resulted from a developmental disorder of the distal ductal system. Clinically, a nontender, slowly progressive, almost always bilateral parotid gland swelling of many years’ duration is observed in female patients during childhood or early adult life.90,92,93

Histologically, numerous various-sized cysts, lined by a thinned cuboidal or squamous epithelium, can be distinguished. The cystic spaces contain clear fluid or amorphous matter, which may show areas of dystrophic calcification called spheroliths. In between the cystic lesions, normal serous acini are present. Inflammatory changes are usually not found.92,93

Visually, the parotid salivary flow is clear and normal in volume. CT, magnetic resonance imaging, and ultrasound clearly depict the presence of the multiple cysts. Ficarra et al93 demonstrated the cysts sialographically, whereas Brown et al92 reported that the ducts were intact and are seen on the sialogram to stretch around the cystic lesions.

Surgical intervention, superficial parotid lobectomy, can be performed for definitive diagnosis or for cosmetic purposes. However, recurrences may originate from the surgically retained deep lobe.90 Observation represents a therapeutic option because spontaneous resolution has been reported.92

PNEUMOPAROTID

Pneumoparotid, the reflux forcing of air through the parotid orifice and into the ducts, has been observed to cause unilateral or bilateral parotid swellings. It can occur in wind instrument players, glass blowers, or any individual who increases intraoral pressure by forcefully blowing up the cheeks consciously or as a neurotic habit or tic.94-97 Such habits may have emotional overtones. The anatomic design of the slit-like parotid duct orifice, as it exits on its redundant papillary fold of buccal tissue, discourages such air reflux. Nevertheless, significant increases in the intraoral pressure distort the musculature surrounding the orifice and favor the entrance of air into the duct.

Although parotid swellings are usually unilateral, 11 of 38 cases of pneumoparotid reviewed by Alcade et al98 were bilateral in occurrence. Subsequently, 3 more bilateral cases have been reported.99-101 The extraoral swelling is accompanied by a sense of fullness and follows the anatomic outline of the parotid gland. Palpation of the usually painless swelling shows the classic crackling sensation associated with tissue emphysema. The tell-tale sign of a frothy bubbly saliva, exiting from the intraoral parotid orifice when the gland is manually pressured, clinches the diagnosis (Fig 10). This unique feature represents the mixture of air and saliva within the limited confines of the ductal system.102

A markedly dilated Stensen duct is usually seen sialographically. This dye pattern results from the long-term forced influx of air into the parotid system. Radiolucencies within the dye may be seen and result from pockets of air previously forced into the duct and trapped by the dye injection.102

Infection is an inevitable sequela of continued forced reflux. Consequently, chronic parotitis can be superimposed on the pneumoparotid. Painful glandular enlargements with suppuration may be observed. Sialography will then show the ductal dilatations and strictures (sausageing) associated with chronic infection.

Spontaneous regression of the pneumoparotid swelling represents the normal course of events. Because infection is a possibility, therapy requires cessation of the autoinsufflation. However, an uninten-
tional habit often is involved, and a conscious effort to stop may be difficult. Psychobehavioral or psychiatric care is indicated for those patients whose condition emanates from an emotional disturbance. The surgical rerouting of the parotid duct into the tonsillar fossa has been advocated. Surgical removal of the gland is only indicated in those situations in which infection has become a nonretractable problem.

ANESTHESIA “MUMPS”

Bilateral and at times unilateral parotid sialadenopathy can be seen in association with general anesthesia during the intra-anesthetic or postanesthetic periods. The exact mechanism for development of this anesthesia “mumps” is not fully understood, but it may represent a form of pneumoparotid. The straining, coughing, and sneezing of a patient during a difficult anesthesia or postanesthesia period serve to increase the positive pressure in the oral cavity. Simultaneously, agents such as succinylcholine used as a muscle relaxant during the anesthetic procedure cause a loss of muscle tone around the Stensen orifice. The flaccid musculature facilitates the retrograde passage of air into the parotid gland when the positive pressure in the oral cavity is significantly increased. Crepitation ascertained by palpation, a sign of tissue emphysema, is usually present and confirms the existence of an air-distended parotid gland.

It is also possible that activation of a pharyngeal reflex causes a parasympathetic nerve stimulation that leads to vasodilation and hyperemia in the parotid glands. The violence of intracheal intubation, associated with coughing and straining against the endotracheal tube, serves as the stimulus for the pharyngeal reflex. Besides the endotracheal tube, endoscopy, bronchoscopy, and rigid esophagoscopy have all been implicated in the onset of bilateral parotid swelling. The parotid swellings linked to a general anesthetic procedure are usually noted in the recovery room, often during extubation. Because the problem is only cosmetic and transient in nature, no treatment other than reassurance is indicated. Rapid subsidence of the swellings can be expected during a 1- to 5-day period.

IODIDE “MUMPS”

Iodide “mumps” was first described in a kidney-impaired patient after intravenous pyelography. It can develop after any imaging procedure that uses iodine-based contrast medium. Patients usually exhibit painless bilateral parotid or submandibular gland swellings that are rapid in onset (5 minutes to several days) and gradually disappear during the next 6-day period. At times, all salivary glands are enlarged, whereas sometimes only 1 gland is swollen, but either bilateral parotid or submandibular salivary gland swellings are the norm. No long-term consequences, other than 1 case of facial palsy, have been reported.

The etiologic key for the glandular swellings seems to be the plasma iodide level. Increased levels result from an inadequately functioning kidney and/or the intravenous introduction of large amounts of iodine-containing compounds, the contrast dyes. More frequently, high osmolar and less frequently low osmolar contrast media cause the markedly elevated plasma iodide level. In addition, iodine-containing expectorants and agents increasing serum iodide levels, such as thioctic acid, have also been implicated. Deiodination of contrast media occurs in the plasma. Although the chief route of iodide excretion is the kidney, salivary glands also have the ability to concentrate iodide and clear it from the plasma.

The site of salivary iodide concentration seems to be the salivary ducts. Extremely high plasma iodide levels can cause a toxic effect on the salivary duct system. Duct wall inflammation will lead to obstruction with glandular swelling.

Many patients with iodide manifestations have immediate reactions that probably are allergic in origin. Urticaria with pruritus, bronchospasms, and angioneurotic edema often accompany their salivary gland swellings. Patients with delayed swellings are likely reflecting a toxic gland reaction. Preventive treatment is used in patients with allergic histories or histories of reaction to contrast media. Prednisone and antihistamines can be administered. In addition, the low osmolar nonionic dyes should be chosen. If a gland swelling develops, anti-inflammatory agents, antihistamines, steroids, and no treatment all represent accepted therapeutic modalities.

RADIOACTIVE IODINE

After the use of radioactive iodine ( ¹³¹I) treatment for thyroid cancer, radiation sialadenitis with bilateral parotid gland swelling has been observed. Along with the thyroid gland, salivary glands have the unique ability to selectively concentrate iodine. The epithelial lining of the interlobular ducts probably extracts the radioactive iodine from the periductal capillaries, and in the process the glands become exposed to the effects of the radiation.

All salivary glands can absorb the ¹³¹I radiation, but serous parenchymal cells seem to have a greater susceptibility to radioactivity than the mucous cells. Inevitably, the serous parotid gland will show a more significant deleterious effect from the radioactive iodine than the mixed mucous and serous submandibular and sublingual salivary glands.
Transient bilateral and unilateral swellings of the salivary glands, usually the parotid, are a known complication of therapy with \(^{131}\text{I}\). The effect on the parotid is rapid in onset and dose related. Tender bilateral parotid swellings are usually observed within 24 hours of \(^{131}\text{I}\) ingestion and can be expected to subside spontaneously within a week. Sour candies can be used during the immediate post-therapeutic period to increase salivation and thus shorten the transit time of \(^{131}\text{I}\) through the parotid. The sialogogue pilocarpine can also be prescribed before and after treatment. Because sour candy and pilocarpine significantly reduce the time of parotid gland radiation exposure, they offer an opportunity to decrease the incidence and severity of parotid damage.

Although most parotid swellings are transient after \(^{131}\text{I}\) therapy, permanent damage does develop and can manifest itself in time with the persistent complaints associated with chronic sialadenitis.\(^{126}\) Intermittent periods of swelling, pain, and infection can occur bilaterally or unilaterally. Xerostomia and alterations in taste have also been reported.\(^{130,131}\) The objective and subjective parotid gland symptoms tend to become more severe as the effects of the incorporated ionizing radiation in the cell’s genetic structure make themselves apparent in succeeding cell generations.

Treatment for the long-term effects of \(^{131}\text{I}\) irradiation is limited. Parenchymal damage is permanent, and therapy can only be aimed at symptoms. Sialogogic agents, artificial saliva, analgesics, and mouthwashes have all been used with little satisfaction on the patient’s part. The role of amifostine, a scavenger of free radicals, has not been clearly determined for patients receiving \(^{131}\text{I}\) or external beam radiation.\(^{132,133}\)

**PAPILLARY CYSTADENOMA LYMPHOMATOSUM**

Papillary cystadenoma lymphomatosum (PCL), also known as Warthin tumor, is a benign epithelial tumor believed to originate from salivary gland tissue.\(^{134}\) Approximately 10% of the cases can be multifocal within a single parotid gland,\(^{135}\) but the tumor can also occur bilaterally, causing bilateral parotid swelling in 4% to 14% of reported cases.\(^{136-138}\) PCL is the second most common benign parotid gland tumor, the most common being the pleomorphic adenoma, and it represents 6% to 13.5% of all parotid tumors.\(^{139}\) Although the tumor has a marked predilection for the parotid gland, particularly the lower pole of the superficial lobe behind the angle of the mandible, its appearance has been reported in several other sites, including the submandibular and sublingual salivary glands.\(^{140}\)

There are 2 theories regarding the pathogenesis of the tumor. The most widely accepted hypothesis proposes that the tumor represents a proliferation of salivary gland ducts that were included embryologically in the developing intraparotid lymph nodes.\(^{134}\) A second theory suggests that the tumor arises within the gland from ductal epithelium with secondary lymphocytic infiltration.\(^{140}\) The latter theory may provide an explanation for the appearance of Warthin tumor in locations in which lymph nodes are not commonly found.

PCL most often occurs in the white population with a male to female ratio ranging from 1.5:1 to 10:1.\(^{137}\) Individuals older than the age of 40 years, mean age 62 years, are the primary targets.\(^{135,137}\) Recent studies have shown a strong association between the development of the tumor and smoking.\(^{141}\) Clinically, PCL is a single nodular, well-defined, slow growing, firm to soft mass in the parotid region. It is painless, movable, and is usually completely encapsulated.

Imaging techniques reveal a well-circumscribed mass with areas of lucency and density representing the cystic and solid tumor elements, respectively. Definitive diagnosis of the tumor is established by histologic examination.

Microscopically, the tumor is composed of epithelial and lymphocytic elements. The epithelial element is represented by papillary, glandular, and cystic formations, whereas the lymphocytic aspect is characterized by the presence of lymphoreticular elements and numerous germinal centers. Mucus-containing cells can also be found interspersed within the epithelium. The cysts contain eosinophilic secretions, amorphous material, cholesterol clefts, and epithelial and inflammatory cells.

Treatment of the PCL requires a superficial parotidectomy. Recurrence rates of 9% to 15%\(^{142}\) have been reported and are likely due to incomplete removal of the tumor resulting from the inability to detect and excise existing multifocal lesions present throughout the parotid gland.\(^{143}\) Malignant transformation to squamous cell carcinoma, mucoepidermoid carcinoma, or lymphoma has been shown on rare occasions.\(^{144}\)

**MALT TUMOR**

Histologically, the parotid gland in SS is characterized by a periductal lymphocytic infiltration for the purpose of processing luminal antigens. The cells are reactive and polyclonal in nature, with T cells dominating over B cells. With a continued lymphoid infiltration, normal parenchyma is replaced. Simultaneously, ductal epithelial cells are invaded, and the epithelial cells proliferate to form lymphoepithelial islands. This salivary gland histologic pattern of parenchymal infiltration and duct proliferation is now referred to as
lymphoepithelial sialadenitis (LESA). Approximately 4% to 7% of patients with LESA will develop a lymphoma. Others may develop a benign but atypical lymphoproliferative disorder with a potential to become a malignant lymphoma. Most primary salivary gland lymphomas are B cell in type and originate from the proliferation of a monoclonal B-cell clone in LESA. These B-cell extranodal salivary lymphomas are derived from MALT normally present in the gastrointestinal tract. MALT cells have an affinity for extranodal glandular epithelium including the salivary glands, thyroid, and breast.

Salivary glands normally are devoid of MALT. The lymphoid cells are acquired by the gland as part of the antigenic stimulation that leads to LESA. With lymphoproliferation, parotid enlargement develops. In the absence of extraglandular involvement, this manifestation of glandular enlargement has been called pseudolymphoma. However, with the availability of the newer immunohistochemical techniques, monoclonality has been shown in most pseudolymphomas, and these lesions are now recognized as MALT lymphomas. If monoclonality is not shown, it is best to make a diagnosis of benign lymphoproliferative disease.

Most salivary gland lymphomas are extranodal and histologically are marginal zone B-cell lymphomas, MALT in type. However, some lymphomas such as the follicular lymphoma may arise from an intrasalivary gland lymph node. The diffuse large B-cell lymphoma represents a third type of salivary gland lymphoma. It may arise from a preexisting MALT lymphoma, transformation of a follicular lymphoma, or de novo from an intrasalivary gland lymph node.

Clinically, the salivary lymphoma can involve any salivary gland with bilateral parotid enlargement often seen. The most frequently observed parotid lymphoma, the MALT lymphoma, occurs in patients previously diagnosed with SS or HIV disease. It represents a site-specific type of low-grade lymphoma in susceptible patients as a direct result of their immunosuppression. The tumor is indolent in nature, remains localized for long periods, and can eventually spread to regional lymph nodes but not readily to distant areas.

Lymphomas of all types represent 2% to 5% of the salivary gland neoplasias, with 20% associated with SS. Patients with MALT lymphomas are usually seen with bilateral, persistent, firm, painless, long-standing parotid swellings, varying in size but often quite large and whose onset has been rapid. Fluctuation in size in association with eating does not occur. Saliva tends to be clear, reflecting the absence of pus from infection, and adequate in amount.

Sialography can be of some diagnostic aid. A sialectic pattern seen in a patient with a neoplastic clinical picture will testify to the preexistence of SS from which the MALT lymphoma has evolved (Fig 8).

With or without treatment, the behavior pattern of most MALT lymphomas results in little morbidity or mortality. The impetus to treat is based on histologic findings and the possible progression to a high-grade lymphoma. Treatment options for the localized salivary lesion include surgery and/or radiation, whereas disseminated disease requires chemotherapy. Of interest is the fact that in gastric MALT lymphomas, whose etiologic antigen is Helicobacter pylori, antibi-otic eradication of the organism has resulted in tumor remissions. Extrapolation of this therapeutic modality to the salivary MALT lymphoma will probably not meet with success because the parotid’s antigenic stimulus and its susceptibility have not been identified.

Follicular lymphomas and other more aggressive salivary gland lymphomas demand a more aggressive therapeutic management. Appropriate use of combinations of surgery, radiation, and chemotherapy are indicated.

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