subsets in the development of the lesions is not established. The nature of the autoantigens recognized by these lymphocytes is still mysterious. A cytoskeletal protein called α-fodrin is a candidate autoantigen, but its role in disease development has not been established yet. Sjögren syndrome-like disease is seen in some patients with human T-lymphotropic virus (HTLV), human immunodeficiency virus (HIV) or hepatitis C virus infections, but the link between these viruses and the autoimmune disorder is obscure.

MORPHOLOGY

As mentioned earlier, **lacrimal and salivary glands are the major targets of the disease,** although other exocrine glands, including those lining the respiratory and gastrointestinal tracts and the vagina, may also be involved. The earliest histologic finding in both the major and the minor salivary glands is periductal and perivascular lymphocytic infiltration. Eventually the lymphocytic infiltrate becomes extensive (Fig. 6-29), and in the larger salivary glands lymphoid follicles with germinal centers may be seen. The ductal lining epithelial cells may show hyperplasia, thus obstructing the ducts. Later there is atrophy of the acini, fibrosis, and hyalinization; still later in the course atrophy and replacement of parenchyma with fat are seen. In some cases the lymphoid infiltrate may be so intense as to give the appearance of a lymphoma. Indeed, these patients are at high risk for development of B-cell lymphomas, and molecular assessments of clonality may be necessary to distinguish intense reactive chronic inflammation from early involvement by lymphoma.

The lack of tears leads to drying of the corneal epithelium, which becomes inflamed, eroded, and ulcerated; the oral mucosa may atrophy, with inflammatory fissuring and ulceration; and dryness and crusting of the nose may lead to ulcerations and even perforation of the nasal septum.

Clinical Features. Sjögren syndrome occurs most commonly in women between the ages of 50 and 60. As might be expected, symptoms result from inflammatory destruction of the exocrine glands. The *keratoconjunctivitis* produces blurring of vision, burning, and itching, and thick secretions accumulate in the conjunctival sac. The *xerostomia* results in difficulty in swallowing solid foods, a decrease in the ability to taste, cracks and fissures in the mouth, and dryness of the buccal mucosa. Parotid gland enlargement is present in half the patients; dryness of the nasal mucosa, epistaxis, recurrent bronchitis, and pneumonitis are other symptoms. Manifestations of *extraglandular disease* are seen in one third of patients and include synovitis, diffuse pulmonary fibrosis, and peripheral neuropathy. These are more common in patients with high titers of antibodies specific for SS-A. In contrast to SLE, glomerular lesions are extremely rare in Sjögren syndrome. Defects of tubular function, however, including renal tubular acidosis, uricosuria, and phosphaturia, are often seen and are associated histologically with tubulointerstitial nephritis (Chapter 20). About 60% of patients have another accompanying autoimmune disorder, such as rheumatoid arthritis, and these patients also have the symptoms and signs of that disorder.

The combination of lacrimal and salivary gland inflammatory involvement was once called *Mikulicz disease.* The name has now been replaced by *Mikulicz syndrome*, broadened to include lacrimal and salivary gland enlargement from any cause, including sarcoidosis, lymphoma, and other tumors. *Biopsy of the lip (to examine minor salivary glands) is essential for the diagnosis of Sjögren syndrome.*

The lymph nodes of patients with Sjögren syndrome are often hyperplastic, but the most intense lymphocytic response is seen in the tissues that are the focal point of the autoimmune response, particularly the salivary and lacrimal glands. In early stages of the disease, this immune infiltrate consists of a mixture of polyclonal T and B cells. However, if the reaction continues unabated there is a strong tendency over time for individual clones within the population of B cells to gain a growth advantage, presumably because of the acquisition of somatic mutations. Emergence of a dominant B-cell clone is usually indicative of the development of a marginal zone lymphoma, a specific type of B-cell malignancy that often arises in the setting of chronic lymphocytic inflammation. About 5% of Sjögren patients develop lymphoma, an incidence that is 40-fold greater than normal. Certain other autoimmune disorders (e.g., Hashimoto thyroiditis) are also associated

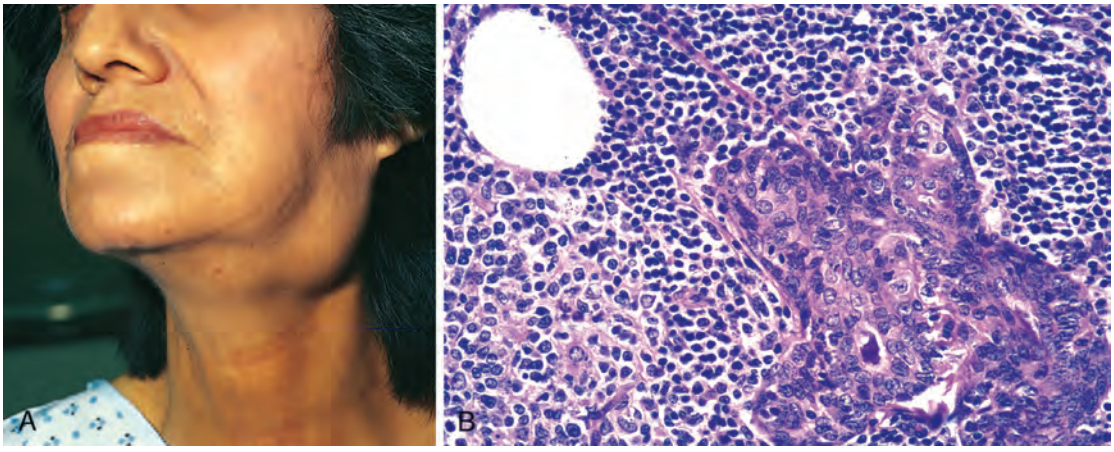

Figure 6-29 Sjögren syndrome. **A,** Enlargement of the salivary gland. **B,** Intense lymphocytic and plasma cell infiltration with ductal epithelial hyperplasia in a salivary gland. (**A,** Courtesy Dr. Richard Sontheimer, Department of Dermatology, University of Texas Southwestern Medical School, Dallas, Texas. **B,** Courtesy Dr. Dennis Burns, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)