to double-stranded DNA are rarely present. Immunofluorescence studies of skin biopsy specimens show deposition of immunoglobulin and C3 at the dermoepidermal junction similar to that in SLE.

Subacute Cutaneous Lupus Erythematosus. This condition also presents with predominant skin involvement and can be distinguished from chronic discoid lupus erythematosus by several criteria. The skin rash in this disease tends to be widespread, superficial, and nonscarring, although scarring lesions may occur in some patients. Most patients have mild systemic symptoms consistent with SLE. Furthermore, there is a strong association with antibodies to the SS-A antigen and with the *HLA-DR3* genotype. Thus, the term *subacute cutaneous lupus erythematosus* seems to define a group intermediate between SLE and lupus erythematosus localized only to skin.

Drug-Induced Lupus Erythematosus

A lupus erythematosus-like syndrome may develop in patients receiving a variety of drugs, including hydralazine, procainamide, isoniazid, and D-penicillamine, to name only a few. Somewhat surprisingly, anti-TNF therapy, which is effective in rheumatoid arthritis and other autoimmune diseases, can also cause drug-induced lupus. Many of these drugs are associated with the development of ANAs, but most patients do not have symptoms of lupus erythematosus. For example, 80% of patients receiving procainamide test positive for ANAs, but only one third of these manifest clinical symptoms, such as arthralgias, fever, and serositis. Although multiple organs are affected, renal and central nervous system involvement is distinctly uncommon. There are serologic and genetic differences from classic SLE, as well. Antibodies specific for double-stranded DNA are rare, but there is an extremely high frequency of antibodies specific for histones. Persons with the *HLA-DR4* allele are at a greater risk of developing a lupus erythematosus-like syndrome after administration of hydralazine, whereas those with *HLA-DR6* (but not *DR4*) are at high risk with procainamide. The disease remits after withdrawal of the offending drug.

KEY CONCEPTS

Systemic Lupus Erythematosus

- SLE is a systemic autoimmune disease caused by autoantibodies produced against numerous self antigens and the formation of immune complexes.
- The major autoantibodies, and the ones responsible for the formation of circulating immune complexes, are directed against nuclear antigens. Other autoantibodies react with erythrocytes, platelets, and various complexes of phospholipids with proteins.
- Disease manifestations include nephritis, skin lesions and arthritis (caused by the deposition of immune complexes), and hematologic and neurologic abnormalities.
- The underlying cause of the breakdown in self-tolerance in SLE is unknown; it may include excess or persistence of nuclear antigens, multiple inherited susceptibility genes, and environmental triggers (e.g., UV irradiation, which results in cellular apoptosis and release of nuclear proteins).

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic inflammatory disease that affects primarily the joints but may involve extraarticular tissues such as the skin, blood vessels, lungs, and heart. Abundant evidence supports the autoimmune nature of the disease. Because the principal manifestations of the disease are in the joints, it is discussed in Chapter 26.

Sjögren Syndrome

Sjögren syndrome is a chronic disease characterized by dry eyes (*keratoconjunctivitis sicca*) and dry mouth (*xerostomia*) resulting from immunologically mediated destruction of the lacrimal and salivary glands. It occurs as an isolated disorder (primary form), also known as the sicca syndrome, or more often in association with another autoimmune disease (secondary form). Among the associated disorders, rheumatoid arthritis is the most common, but some patients have SLE, polymyositis, scleroderma, vasculitis, mixed connective tissue disease, or thyroiditis.

Etiology and Pathogenesis

The characteristic decrease in tears and saliva (*sicca syndrome*) is the result of lymphocytic infiltration and fibrosis of the lacrimal and salivary glands. The infiltrate contains predominantly activated CD4+ helper T cells and some B cells, including plasma cells. About 75% of patients have rheumatoid factor (an antibody reactive with self IgG) whether or not coexisting rheumatoid arthritis is present. ANAs are detected in 50% to 80% of patients by immunofluorescence assay. A host of other organ-specific and non–organ-specific antibodies have also been identified. Most important, however, are antibodies directed against two ribonucleoprotein antigens, SS-A (Ro) and SS-B (La) (Table 6-10), which can be detected in as many as 90% of patients by sensitive techniques. These antibodies are thus considered serologic markers of the disease. Patients with high titers of antibodies to SS-A are more likely to have early disease onset, longer disease duration, and extraglandular manifestations, such as cutaneous vasculitis and nephritis. These autoantibodies are also present in a smaller percentage of patients with SLE and hence are not diagnostic of Sjögren syndrome.

As with other autoimmune diseases, Sjögren syndrome shows some association, albeit weak, with certain HLA alleles. Studies of whites and blacks suggest linkage of the primary form with *HLA-B8*, *HLA-DR3*, and *DRW52* as well as *HLA-DQA1* and *HLA-DQB1* loci; in patients with anti-SS-A or anti-SS-B antibodies, specific alleles of *HLA-DQA1* and *HLA-DQB1* are frequent. This suggests that, as in SLE, inheritance of certain class II molecules predisposes to the development of particular autoantibodies.

Although the pathogenesis of Sjögren syndrome remains obscure, aberrant T-cell and B-cell activation are both implicated. The initiating trigger may be a viral infection of the salivary glands, which causes local cell death and release of tissue self antigens. In genetically susceptible individuals, CD4+ T cells and B cells specific for these self antigens may have escaped tolerance and are able to react. The result is inflammation, tissue damage, and, eventually, fibrosis. However, the role of particular cytokines or T cell