- Fibrosis may be the result of activation of fibroblasts by cytokines produced by T cells, but what triggers T-cell responses is unknown.
- Endothelial injury and microvascular disease are commonly present in the lesions of systemic sclerosis, perhaps causing chronic ischemia, but the pathogenesis of vascular injury is not known.

Inflammatory Myopathies

Inflammatory myopathies comprise an uncommon, heterogeneous group of disorders characterized by injury and inflammation of mainly the skeletal muscles, which are probably immunologically mediated. Three distinct disorders, *dermatomyositis*, *polymyositis*, and *inclusion-body myositis*, are included in this category. These may occur alone or with other immune-mediated diseases, particularly systemic sclerosis. These diseases are described in Chapter 27.

Mixed Connective Tissue Disease

The term *mixed connective tissue disease* is used to describe a disease with clinical features that are a mixture of the features of SLE, systemic sclerosis, and polymyositis. The disease is characterized serologically by high titers of antibodies to ribonucleoprotein particle-containing U1 ribonucleoprotein. Typically, mixed connective tissue disease presents with synovitis of the fingers, Raynaud phenomenon and mild myositis, but renal involvement is modest and there is a good response to corticosteroids, at least in the short term. Because the clinical features overlap with other diseases, it has been suggested that mixed connective tissue disease is not a distinct entity but that different patients represent subsets of SLE, systemic sclerosis, and polymyositis. The disease can, over time, evolve into classic SLE or systemic sclerosis. However, a subset of patients do not evolve into other diseases and the salutary response to steroids is not universal, suggesting that there may be an entity of mixed connective tissue disease distinct from other autoimmune diseases. Serious complications of mixed connective tissue disease include pulmonary hypertension, interstitial lung disease, and renal disease.

Polyarteritis Nodosa and Other Vasculitides

Polyarteritis nodosa belongs to a group of diseases characterized by necrotizing inflammation of the walls of blood vessels and showing strong evidence of an immunologic pathogenetic mechanism. The general term *noninfectious vasculitis* differentiates these conditions from those due to direct infection of the blood vessel wall (such as occurs in the wall of an abscess) and serves to emphasize that any type of vessel may be involved—arteries, arterioles, veins, or capillaries.

Noninfectious vasculitis is encountered in many clinical settings. A detailed classification and description of vasculitides is presented in Chapter 11, where the immunologic mechanisms are also discussed.

IgG4-Related Disease

IgG4-related disease (IgG4-RD) is a newly recognized constellation of disorders characterized by tissue infiltrates dominated by IgG4 antibody-producing plasma cells and lymphocytes, particularly T cells, storiform fibrosis, obliterative phlebitis, and usually increased serum IgG4. Although recognized only recently when extra-pancreatic manifestations were identified in patients with autoimmune pancreatitis, IgG4-related disease has now been described in virtually every organ system: the biliary tree, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid, pericardium, and skin. Many medical conditions long viewed as confined to single organs are part of the IgG4-RD spectrum. These include Mikulicz syndrome (enlargement and fibrosis of salivary and lacrimal glands), Riedel thyroiditis, idiopathic retroperitoneal fibrosis, autoimmune pancreatitis, and inflammatory pseudotumors of the orbit, lungs, and kidneys, to name a few. The disease most often affects middle-aged and older men.

The pathogenesis of this condition is not understood, and although IgG4 production in lesions is a hallmark of the disease it is not known if this antibody type contributes to the pathology. The key role of B cells is supported by initial clinical trials in which depletion of B cells by anti–B cell reagents such as rituximab provided clinical benefit. It is unclear if the disease is truly autoimmune in nature, and no target autoantigens have been identified.

Rejection of Tissue Transplants

Transplant rejection is discussed here because it involves several of the immunologic reactions that underlie immune-mediated inflammatory diseases. A major barrier to transplantation is the process of *rejection*, in which the recipient's immune system recognizes the graft as being foreign and attacks it.

Mechanisms of Recognition and Rejection of Allografts

Rejection is a process in which T lymphocytes and antibodies produced against graft antigens react against and destroy tissue grafts. We next discuss how donor antigens from the graft are recognized by lymphocytes in the recipient and how the lymphocytes and their products destroy the graft.

Recognition of Graft Alloantigens by T and B Lymphocytes

The major antigenic differences between a donor and recipient that result in rejection of transplants are differences in HLA alleles. Grafts exchanged between individuals of the same species (the usual clinical situation) are called *allografts*, and grafts from one species to another (still an experimental procedure) are called *xenografts*. Because HLA genes are highly polymorphic, there are always some differences between individuals (except, of course, identical twins). Following transplantation, the recipient's T cells recognize donor antigens from the graft (the allogeneic