with a high risk of marginal zone lymphoma (Chapter 13), which typically arises within the organ or tissue that is the target of the autoimmune inflammation.

KEY CONCEPTS

Sjögren Syndrome

- Sjögren syndrome is an inflammatory disease that affects primarily the salivary and lacrimal glands, causing dryness of the mouth and eyes.
- The disease is believed to be caused by an autoimmune T-cell reaction against an unknown self antigen expressed in these glands, or immune reactions against the antigens of a virus that infects the tissues.

Systemic Sclerosis (Scleroderma)

Systemic sclerosis is characterized by: (1) chronic inflammation thought to be the result of autoimmunity, (2) widespread damage to small blood vessels, and (3) progressive interstitial and perivascular fibrosis in the skin and multiple organs. Although the term *scleroderma* is ingrained in clinical medicine, this disease is better named *systemic sclerosis* because it is characterized by excessive fibrosis throughout the body. The skin is most commonly affected, but the gastrointestinal tract, kidneys, heart, muscles, and lungs also are frequently involved. In some patients the disease seems to remain confined to the skin for many years, but in the majority it progresses to visceral involvement with death from renal failure, cardiac failure, pulmonary insufficiency, or intestinal malabsorption. The clinical heterogeneity of systemic sclerosis has been recognized by classifying the disease into two major categories: *diffuse scleroderma*, characterized by widespread skin involvement at onset, with rapid progression and early visceral involvement; and *limited scleroderma*, in which the skin involvement is often confined to fingers, forearms, and face. Visceral involvement occurs late; hence, the clinical course is relatively benign. Some patents with the limited disease also develop a combination of calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia, called the *CREST syndrome*. Several other variants and related conditions, such as eosinophilic fasciitis, occur far less frequently and are not described here.

Etiology and Pathogenesis

The cause of systemic sclerosis is not known, but the **disease likely results from three interrelated processes—autoimmune responses, vascular damage, and collagen deposition** (Fig. 6-30).

- **Autoimmunity.** It is proposed that CD4+ T cells responding to an as yet unidentified antigen accumulate in the skin and release cytokines that activate inflammatory cells and fibroblasts. Although inflammatory infiltrates are typically sparse in the skin of patients with systemic sclerosis, activated CD4+ T cells can be found in many patients, and T_H2 cells have been isolated from the skin. Several cytokines produced by these T cells, including TGF-β and IL-13, can stimulate transcription of genes that encode collagen and other extracellular matrix proteins (e.g., fibronectin) in fibroblasts. Other cytokines recruit leukocytes and propagate the chronic inflammation.

  There is also evidence for inappropriate activation of humoral immunity, and the presence of various autoantibodies, notably ANAs, provides diagnostic and prognostic information. The role of these ANAs in the pathogenesis of the disease is unclear; it has been postulated that some of these antibodies may stimulate fibrosis, but the evidence in support of this idea is not convincing.
- **Vascular damage. Microvascular disease is consistently present early in the course of systemic sclerosis and may be the initial lesion.** Intimal proliferation is evident in the digital arteries of patients with systemic sclerosis. Capillary dilation with leaking, as well as destruction, is also common. Nailfold capillary loops are distorted early in the course of disease, and later they disappear. Telltale signs of endothelial activation and

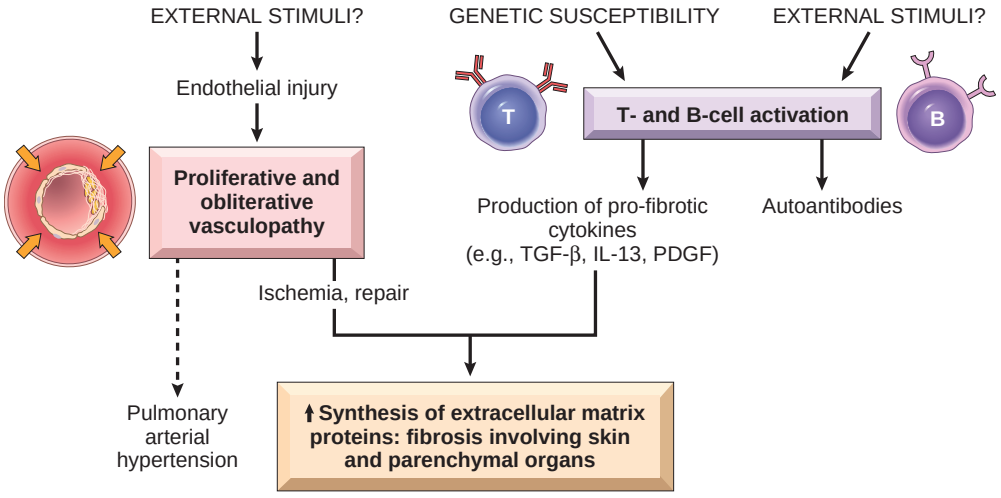

Figure 6-30 A model for the pathogenesis of systemic sclerosis. Unknown external stimuli cause vascular abnormalities and immune activation in genetically susceptible individuals, and both contribute to the excessive fibrosis.