injury (e.g., increased levels of von Willebrand factor) and increased platelet activation (increased percentage of circulating platelet aggregates) have also been noted. However, what causes the vascular injury is not known; it could be the initiating event or the result of chronic inflammation, with mediators released by inflammatory cells inflicting damage on microvascular endothelium. Repeated cycles of endothelial injury followed by platelet aggregation lead to release of platelet and endothelial factors (e.g., PDGF, TGF-β) that trigger perivascular fibrosis. Vascular smooth muscle cells also show abnormalities, such as increased expression of adrenergic receptors. Eventually, widespread narrowing of the microvasculature leads to ischemic injury and scarring.

- **Fibrosis.** The progressive fibrosis characteristic of the disease may be the culmination of multiple abnormalities, including the accumulation of alternatively activated macrophages, actions of fibrogenic cytokines produced by infiltrating leukocytes, hyperresponsiveness of fibroblasts to these cytokines, and scarring following upon ischemic damage caused by the vascular lesions. There is some evidence that fibroblasts from patients with systemic sclerosis have an intrinsic abnormality that causes them to produce excessive amounts of collagen, which is structurally normal. This idea is based on studies with cultured fibroblasts, and whether or how this abnormality relates to pathogenesis in vivo is unknown.

MORPHOLOGY

Virtually all organs can be involved in systemic sclerosis. Prominent changes occur in the skin, alimentary tract, musculoskeletal system, and kidney, but lesions also are often present in the blood vessels, heart, lungs, and peripheral nerves.

Skin. A great majority of patients have diffuse, sclerotic atrophy of the skin, which usually begins in the fingers and distal regions of the upper extremities and extends proximally to involve the upper arms, shoulders, neck, and face. Histologically, there are edema and perivascular infiltrates containing CD4+ T cells, together with swelling and degeneration of collagen fibers, which become eosinophilic. Capillaries and small arteries (150 to 500 μm in diameter) may show thickening of the basal lamina, endothelial cell damage, and partial occlusion. With progression of the disease, there is increasing fibrosis of the dermis, which becomes tightly bound to the subcutaneous structures. There is marked increase of compact collagen in the dermis, usually with thinning of the epidermis, loss of rete pegs, atrophy of the dermal appendages, and hyaline thickening of the walls of dermal arterioles and capillaries (Fig. 6-31*B*). Focal and sometimes diffuse subcutaneous calcifications may develop, especially in patients with the CREST syndrome. In advanced stages the fingers take on a tapered, clawlike appearance with limitation of motion in the joints, and the face becomes a drawn mask. Loss of blood supply may lead to cutaneous ulcerations and to atrophic changes in the terminal phalanges (Fig. 6-31*C*). Sometimes the tips of the fingers undergo autoamputation.

Alimentary Tract. The alimentary tract is affected in approximately 90% of patients. Progressive atrophy and collagenous fibrous replacement of the muscularis may develop at any level of the gut but are most severe in the esophagus. The lower two thirds of the esophagus often develops a rubber-hose–like inflexibility. The associated dysfunction of the lower esophageal sphincter gives rise to gastroesophageal reflux and its complications, including Barrett metaplasia (Chapter 17) and strictures. The mucosa is thinned and may be ulcerated, and there is excessive collagenization of the lamina propria and submucosa. Loss of villi and microvilli in the small bowel is the anatomic basis for the malabsorption syndrome sometimes encountered.

Musculoskeletal System. Inflammation of the synovium, associated with hypertrophy and hyperplasia of the synovial soft tissues, is common in the early stages; fibrosis later ensues. These changes are reminiscent of rheumatoid arthritis, but joint destruction is not common in systemic sclerosis. In a small subset of patients (approximately 10%), inflammatory myositis indistinguishable from polymyositis may develop.

Kidneys. Renal abnormalities occur in two-thirds of patients with systemic sclerosis. The most prominent are the vascular lesions. Interlobular arteries show intimal thickening as a result of deposition of mucinous or finely collagenous material, which stains histochemically for glycoprotein and acid mucopolysaccharides. There is also concentric proliferation of intimal cells. These changes may resemble those seen in malignant hypertension, but in scleroderma the alterations are restricted to vessels 150 to 500 μm in diameter and are not always associated with hypertension. Hypertension, however, does occur in 30% of patients with scleroderma, and in 20% it takes an ominously rapid, downhill course (malignant hypertension). In hypertensive patients, vascular alterations are more pronounced and are often associated with fibrinoid necrosis involving the arterioles together with thrombosis and infarction. Such patients often die of renal failure, which accounts for about 50% of deaths in persons with this disease. There are no specific glomerular changes.

Lungs. The lungs are involved in more than 50% of individuals with systemic sclerosis. This involvement may manifest as pulmonary hypertension and interstitial fibrosis. Pulmonary vasospasm, secondary to pulmonary vascular endothelial dysfunction, is considered important in the pathogenesis of pulmonary hypertension. Pulmonary fibrosis, when present, is indistinguishable from that seen in idiopathic pulmonary fibrosis (Chapter 15).

Heart. Pericarditis with effusion, myocardial fibrosis, and thickening of intramyocardial arterioles occur in one third of the patients. Clinical impairment by myocardial involvement, however, is less common.

Clinical Features. Systemic sclerosis has a female-to-male ratio of 3:1, with a peak incidence in the 50- to 60-year age group. Although systemic sclerosis shares many features with SLE, rheumatoid arthritis (Chapter 26), and polymyositis (Chapter 27), its distinctive features are the striking cutaneous changes, notably skin thickening. *Raynaud phenomenon*, manifested as episodic vasoconstriction of the arteries and arterioles of the extremities, is seen in virtually all patients and precedes other symptoms in 70% of cases. *Dysphagia* attributable to esophageal fibrosis and its resultant hypomotility are present in more than 50% of patients. Eventually, destruction of the esophageal wall leads to