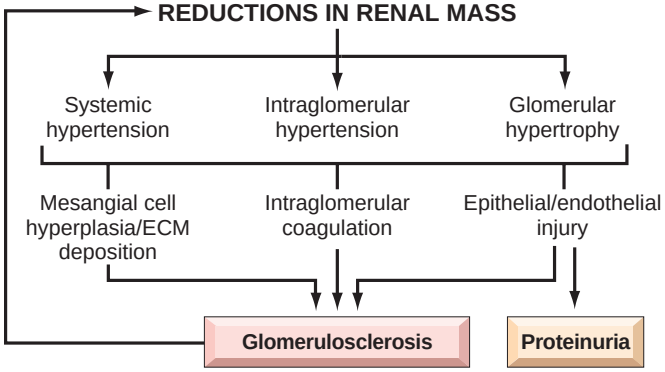

Figure 20-8 Focal segmental glomerulosclerosis associated with loss of renal mass. The adaptive changes in glomeruli (hypertrophy and glomerular capillary hypertension), as well as systemic hypertension, cause epithelial and endothelial injury and resultant proteinuria. The mesangial response, involving mesangial cell proliferation and ECM production, together with intraglomerular coagulation, causes the glomerulosclerosis. This results in further loss of functioning nephrons and a vicious circle of progressive glomerulosclerosis.

sclerosis. Currently, the most successful interventions to interrupt these mechanisms of progressive glomerulosclerosis involve treatment with inhibitors of the renin-angiotensin system, which not only reduce intraglomerular hypertension, but also have direct effects on each of the mechanisms identified above. Importantly, these agents have been shown to ameliorate progression of sclerosis in both animal and human studies.

Tubulointerstitial Fibrosis. **Tubulointerstitial injury, manifested by tubular damage and interstitial inflammation, is a component of many acute and chronic glomerulonephritides.** Tubulointerstitial fibrosis contributes to progression in both immune and nonimmune glomerular diseases, for example, diabetic nephropathy. Indeed, **there is often a much better correlation of decline in renal function with the extent of tubulointerstitial damage than with the severity of glomerular injury.** Many factors may lead to such tubulointerstitial injury, including ischemia of tubule segments downstream from sclerotic glomeruli, acute and chronic inflammation in the adjacent interstitium, and damage or loss of the peritubular capillary blood supply. Current work also points to the effects of *proteinuria* on tubular cell structure and function. It appears that proteinuria can cause *direct injury to and activation of tubular cells*. Activated tubular cells in turn express adhesion molecules and elaborate pro-inflammatory cytokines, chemokines, and growth factors that contribute to interstitial fibrosis. Filtered proteins that may produce these tubular effects include cytokines, complement products, the iron in hemoglobin, immunoglobulins, lipid moieties, and oxidatively modified plasma proteins.

KEY CONCEPTS

Progression of Glomerular Disease

- Progressive glomerular injury can be the result of either primary or secondary glomerular injuries, of diseases that are either renal limited or systemic, and of diseases that initially involve renal structures other than glomeruli.
- The principal glomerular manifestation of progressive injury is focal segmental glomerulosclerosis, eventually leading to global glomerular involvement and glomerular obsolescence.
- Progressive injury ensues from a cycle of glomerular and nephron loss, compensatory changes that lead to further glomerular injury and glomerulosclerosis, and eventually end-stage renal disease.
- Progressive glomerular injury is accompanied by chronic injuries to other renal structures, typically manifest as tubulointerstitial fibrosis.

Having discussed the factors involved in the initiation and progression of glomerular injury, we now turn to a discussion of individual glomerular diseases. Table 20-5 summarizes the main clinical and pathologic features of the major forms of primary glomerulopathies.

Nephritic Syndrome

Glomerular diseases presenting with a nephritic syndrome are often characterized by inflammation in the glomeruli. The nephritic patient usually presents with hematuria, red cell casts in the urine, azotemia, oliguria, and mild to moderate hypertension. Proteinuria and edema are common, but these are not as severe as those encountered in the nephrotic syndrome, discussed later. The acute nephritic syndrome may occur in such multisystem diseases as SLE and microscopic polyangiitis. Typically, however, it is characteristic of acute proliferative and exudative glomerulonephritis and is an important component of crescentic glomerulonephritis, which is described later.

Acute Proliferative (Poststreptococcal, Postinfectious) Glomerulonephritis

As the name implies, **this cluster of diseases is characterized histologically by diffuse proliferation of glomerular cells associated with influx (exudation) of leukocytes. These lesions are typically caused by immune complexes.** The inciting antigen may be exogenous or endogenous. The prototypic exogenous antigen-induced disease pattern is postinfectious glomerulonephritis, whereas an example of an endogenous antigen-induced disease is the nephritis of SLE, described in Chapter 6. The most common underlying infections are streptococcal, but the disorder may also be associated with other infections.

Poststreptococcal Glomerulonephritis

This is a prototypical glomerular disease of immune complex etiology, which is decreasing in frequency in the United States but continues to be a fairly common disorder worldwide. It usually appears 1 to 4 weeks after a streptococcal infection of the pharynx or skin (impetigo). Skin infections are commonly associated with overcrowding and poor hygiene. Poststreptococcal glomerulonephritis occurs most frequently in children 6 to 10 years of age, but children and adults of any age can also be affected.