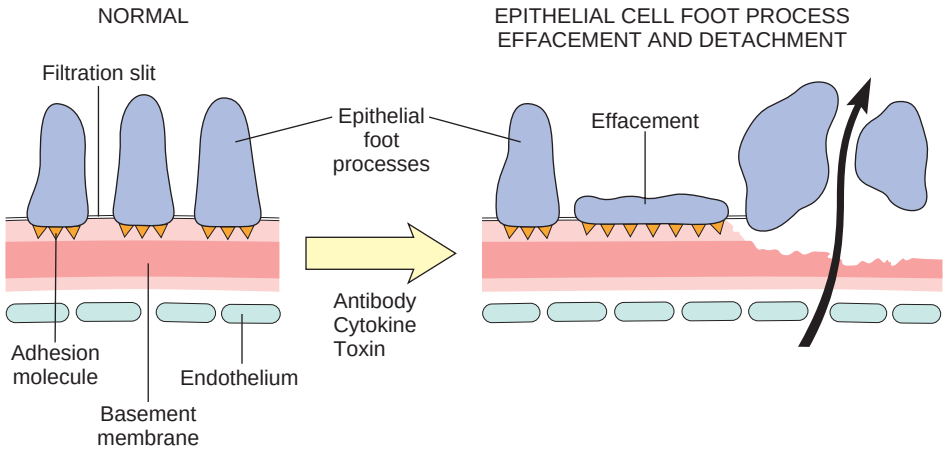

Figure 20-7 Epithelial cell injury. The postulated sequence is a consequence of antibodies specific to epithelial cell antigens, toxins, cytokines, or other factors causing injury; this results in foot process effacement and sometimes detachment of epithelial cells and protein leakage through defective GBM and filtration slits.

coagulation factors, particularly thrombin, may be a stimulus for crescent formation.

Epithelial Cell Injury

Podocyte injury is common to many forms of both primary and secondary glomerular diseases, of both immune and non-immune etiologies. The term *podocytopathy* has been applied to diseases with disparate etiologies whose principal manifestation is injury to podocytes. This can be induced by antibodies to podocyte antigens; by toxins, as in an experimental model of proteinuria induced by puromycin aminonucleoside; conceivably by certain cytokines; by certain viral infections such as human immunodeficiency virus (HIV) or by still inadequately characterized circulating factors, as in some cases of focal segmental glomerulosclerosis. Such injury is reflected by stereotypic morphologic changes in the podocytes, which include effacement of foot processes, vacuolization, and retraction and detachment of cells from the GBM, and functionally by proteinuria (Fig. 20-7).

Loss of podocytes, which have only a very limited capacity for replication and repair, may be a feature of multiple types of glomerular injury including focal and segmental glomerulosclerosis and diabetic nephropathy. Such loss typically cannot be recognized in pathologic specimens unless specialized morphologic techniques are applied. In most forms of glomerular injury, loss of normal slit diaphragms is a key event in the development of proteinuria (Fig. 20-6). Functional abnormalities of the slit diaphragm may also result from mutations in its components, such as nephrin and podocin, without actual inflammatory damage to the glomerulus. Such mutations are the cause of rare hereditary forms of the nephrotic syndrome.

Mechanisms of Progression in Glomerular Diseases

Thus far, the immunologic mechanisms and mediators that *initiate* glomerular injury have been discussed. The outcome of such injury depends on several factors, including the severity of renal damage, the nature and persistence of the antigens, and the immune status, age, and genetic predisposition of the host.

It has long been known that **once any renal disease, glomerular or otherwise, destroys functioning nephrons and reduces the GFR to about 30% to 50% of normal, progression to end-stage renal failure proceeds at a steady rate, independent of the original stimulus or activity of the underlying disease.** The secondary factors that lead to progression are of great clinical interest, since they can be targets of therapy that delays or even prevents the inexorable journey to dialysis or transplantation.

The two major histologic characteristics of such progressive renal damage are *focal segmental glomerulosclerosis* (FSGS) and *tubulointerstitial fibrosis*.

Focal Segmental Glomerulosclerosis (FSGS). **Progressive fibrosis involving portions of some glomeruli develops after many types of renal injury and leads to proteinuria and increasing functional impairment.** FSGS may be seen even in cases in which the primary disease was nonglomerular. The glomerulosclerosis seems to be initiated by the *adaptive change* that occurs in the relatively unaffected glomeruli of diseased kidneys. Such a mechanism is suggested by experiments in rats subjected to subtotal nephrectomy. *Compensatory hypertrophy* of the remaining glomeruli initially maintains renal function in these animals, but proteinuria and segmental glomerulosclerosis soon develop, leading eventually to total glomerular sclerosis and uremia. The glomerular hypertrophy is associated with *hemodynamic changes*, including increases in glomerular blood flow, filtration, and transcapillary pressure (glomerular hypertension), and often with systemic hypertension.

The sequence of events (Fig. 20-8) that is thought to lead to sclerosis in this setting entails endothelial and visceral epithelial cell injury, visceral epithelial cell loss leading to segments of GBM denuded of overlying foot processes and consequently increased glomerular permeability to proteins, and accumulation of proteins in the mesangial matrix. This is followed by proliferation of mesangial cells, infiltration by macrophages, increased accumulation of extracellular matrix (ECM), and segmental and eventually global sclerosis of glomeruli. With increasing reductions in nephron mass and ongoing compensatory changes, a vicious cycle of continuing glomerulosclerosis sets in. Most of the mediators of chronic inflammation and fibrosis, particularly TGF-β, play a role in the induction of

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