steroid-dependent or resistant. Nevertheless, the long-term prognosis for patients is excellent, and even steroid-dependent disease usually resolves when children reach puberty. Although adults are slower to respond, their long-term prognosis is also excellent.

As has been noted, minimal-change disease in adults can be associated with Hodgkin lymphoma and, less frequently, other lymphomas and leukemias. In addition, secondary minimal-change disease may follow NSAID therapy, usually in association with acute interstitial nephritis, to be described later in this chapter.

Focal Segmental Glomerulosclerosis (FSGS)

Primary focal segmental glomerulosclerosis is the most common cause of nephrotic syndrome in adults in the United States. It is sometimes considered to be a primary disorder of podocytes, like minimal change disease. As the name implies, this lesion is characterized by sclerosis of some, but not all, glomeruli (thus, it is focal); and in the affected glomeruli, only a portion of the capillary tuft is involved (thus, it is segmental). Focal segmental glomerulosclerosis is frequently manifest clinically by the acute or subacute onset of nephrotic syndrome or nonnephrotic proteinuria. Hypertension, microscopic hematuria, and some degree of azotemia are commonly present when the disease is first clinically recognized.

Classification and Types. Focal segmental glomerulosclerosis occurs in the following settings:

- As a primary disease (idiopathic focal segmental glomerulosclerosis)
- In association with other known conditions, such as HIV infection (HIV-associated nephropathy), heroin addiction (heroin nephropathy), sickle-cell disease, and massive obesity
- As a secondary event, reflecting scarring of previously active necrotizing lesions, in cases of focal glomerulonephritis (e.g., IgA nephropathy)
- As a component of the adaptive response to loss of renal tissue (renal ablation, described earlier), whether from congenital anomalies (e.g., unilateral renal agenesis or renal dysplasia) or acquired causes (e.g., reflux nephropathy), or in advanced stages of other renal disorders, such as hypertensive nephropathy.
- In uncommon inherited forms of nephrotic syndrome where the disease may be caused by mutations in genes that encode proteins localized to the slit diaphragm, e.g., podocin, α-actinin 4, and TRPC6 (transient receptor potential calcium channel-6)

Idiopathic focal segmental glomerulosclerosis accounts for 10% and 35% of cases of nephrotic syndrome in children and adults, respectively. FSGS (both primary and secondary forms) has increased in incidence and is now the most common cause of nephrotic syndrome in adults in the United States, particularly in Hispanic and African-American patients. The clinical signs differ from those of minimal-change disease in the following respects: (1) there is a higher incidence of hematuria, reduced GFR, and hypertension; (2) proteinuria is more often nonselective; (3) there is poor response to corticosteroid therapy; and (4) there is progression to chronic kidney disease, with at least 50% developing ESRD within 10 years.

Pathogenesis. The characteristic degeneration and focal disruption of visceral epithelial cells with effacement of foot processes resemble the diffuse epithelial cell change typical of minimal-change disease and other podocytopathies. *It is this epithelial damage that is the hallmark of FSGS.* Multiple different mechanisms can cause such epithelial damage, including circulating factors and genetically determined defects affecting components of the slit diaphragm complex. The hyalinosis and sclerosis stem from entrapment of plasma proteins in extremely hyperpermeable foci and increased ECM deposition. The recurrence of proteinuria after transplantation, sometimes within 24 hours, with subsequent progression to overt lesions of FSGS, suggests that an unknown circulating factor is the cause of the epithelial damage in some patients.

The discovery of a genetic basis for some cases of FSGS and other causes of the nephrotic syndrome has improved the understanding of the pathogenesis of proteinuria in the nephrotic syndrome and has provided new methods for diagnosis and prognosis of affected patients. Leading examples of this include:

- The first relevant gene to be identified, *NPHS1*, maps to chromosome 19q13 and encodes the protein *nephrin*. Nephrin is a key component of the slit diaphragm (Fig. 20-3), the structure that controls glomerular permeability. Several mutations of the *NPHS* gene have been identified that give rise to *congenital nephrotic syndrome* of the Finnish type, producing a minimal-change disease like glomerulopathy with extensive foot process effacement.
- A distinctive pattern of autosomal recessive FSGS results from mutations in the *NPHS2* gene, which maps to chromosome 1q25-q31 and encodes the protein product *podocin*. Podocin has also been localized to the slit diaphragm. Mutations in *NPHS2* result in a syndrome of steroid-resistant nephrotic syndrome of childhood onset.
- A third set of mutations in the gene encoding the podocyte actin-binding protein α-actinin 4 underlies some cases of autosomal dominant FSGS, which can be insidious in onset but has a high rate of progression to renal insufficiency.
- A fourth type of mutation was found in some kindreds with adult-onset FSGS, in the gene encoding TRPC6. This protein is widely expressed, including in podocytes, and the pathogenic mutations may perturb podocyte function by increasing calcium flux in these cells.

What these proteins have in common is their localization to the slit diaphragm and to adjacent podocyte cytoskeletal structures. Their specific functions and interactions are incompletely understood, but it is clear that the integrity of each is necessary to maintain the normal glomerular filtration barrier. Recently two sequence variants in the apolipoprotein L1 gene (APOL1) on chromosome 22 have been strongly associated with an increased risk of FSGS and renal failure in individuals of African descent, although the mechanisms underlying this association are not yet known. These sequence variants are particularly remarkable because the selective pressures for their conservation in people of African descent is a result of resistance to trypanosome infection conferred by these polymorphisms.