

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is not a single disease but rather a diagnostic term for a clinicopathologic syndrome that has multiple causes, pathogenic mechanisms, and histologic patterns of injury. The ubiquitous clinical feature of the syndrome is proteinuria, which may be nephrotic or non-nephrotic, and the ubiquitous pathologic feature is focal segmental glomerular consolidation and scarring, which may have several distinctive patterns, including perihilar, collapsing, cellular, and tip lesion variants. As shown in [Table 28-10](#), FSGS may appear to be a primary renal disease, or may be associated with, and possibly caused by, a variety of other conditions.

Epidemiology

Over the past 2 decades, there has been an increased incidence of FSGS. Whether this is a true increase in incidence or whether the condition has been better defined and more readily diagnosed by nephropathologists is debatable. Nonetheless, for the past 20 years, the yearly incidence of primary FSGS has risen from less than 10% to approximately 25% of adult nephropathies.^{[196] [197] [198] [199] [200]} A substantial portion of this increase may be attributable to an increase in the collapsing variant of FSGS^{[200] [201]} and FSGS caused by obesity.^[202]

Moreover, there appears to be an emerging racial difference in the prevalence of FSGS in that there are progressively more black patients with FSGS than there are white patients.^{[199] [203] [204]} The data in these studies are similar to the cases seen in the UNC Nephropathology Laboratory, which demonstrates that the proportional prevalence of typical FSGS and collapsing FSGS in black patients is substantially higher than in whites, although the glomerular tip lesion variant of FSGS has a predilection for whites (see [Table 28-7](#)). Although the ratio of blacks to whites is equivalent in FSGS, the proportion of blacks in our biopsy population is approximately 30%. Thus, the relative incidence of FSGS is higher for blacks than for whites.

TABLE 28-10 -- Focal Segmental Glomerulosclerosis (FSGS)
Primary (idiopathic) FSGS
Typical (not otherwise specified) FSGS
Glomerular tip lesion variant of FSGS
Collapsing glomerulopathy variant of FSGS
Perihilar variant of FSGS
Familial FSGS
Secondary FSGS
With HIV disease (typically collapsing variant)
With IV drug abuse
With glomerulomegaly (usually perihilar variant)
Morbid obesity
Sickle cell disease
Cyanotic congenital heart disease
Hypoxic pulmonary disease
Reduced nephron numbers (usually perihilar variant)
Unilateral renal agenesis
Oligomeganephronia
Reflux-interstitial nephritis
Postfocal cortical necrosis
Post nephrectomy
Drug toxicity
Pamidronate (collapsing FSGS)
Lithium
Familial
α -Actinin 4 mutations (autosomal dominant)
Podocin mutations (autosomal recessive)
Nephrin mutations (autosomal recessive)

Pathology

LIGHT MICROSCOPY

FSGS is characterized by focal and segmental glomerular sclerosis. ^[205] ^[206] ^[207] This may begin as segmental consolidation caused by insudation of plasma proteins causing hyalinosis, by accumulation of foam cells, by swelling of epithelial cells, and by collapse of capillaries resulting in obliteration of capillary lumens. These events are accompanied by an increase in collagenous matrix material that ultimately produces a sclerotic component to the lesion.

Based on the character and glomerular distribution of these lesions, FSGS can be categorized into structural variants that have distinctive natural histories (prognoses) and may have different causes and pathogenic mechanisms. The pathologic categorization of FSGS remains controversial. The approach that we use was formulated in 2002 by Vivette D'Agati, J. Charles Jennette, Agnes Fogo, and Jan Bruijn at a consensus conference held at Columbia University College of Physicians and Surgeons, but has not yet been published. This approach divides FSGS into five morphologic variants: perihilar, tip lesion, collapsing, cellular, and not otherwise specified (NOS).

The NOS category of FSGS is the default category when the criteria for the four more specific variants of FSGS are not identified. NOS FSGS has randomly distributed focal and segmental consolidation of glomerular tufts by sclerosis that obliterates some glomerular capillary lumens and often forms adhesions to the Bowman capsule. Sclerotic lesions can affect any segments, including perihilar and peripheral segments. Podocyte hypertrophy or hyperplasia usually is minimal or absent, but, the presence of podocyte hypertrophy and hyperplasia in the absence of the other features of collapsing FSGS does not rule out NOS FSGS. Hyalinosis and a few foam cells are common. Mild mesangial hypercellularity and glomerulomegaly may be observed. This is the most common form of FSGS. All of the other variants of FSGS may evolve into this pattern as the sclerosis progresses and obscures their more specific features, but, this variant of FSGS probably can arise through other pathways as well.

The perihilar variant of FSGS has perihilar sclerosis and hyalinosis involving over half of the glomeruli that have

Figure 28-5 Light micrographs and diagrams depicting patterns of focal segmental glomerulosclerosis. One pattern (**A** and **D**) has a predilection for sclerosis in the perihilar regions of the glomeruli. The glomerular tip lesion variant has segmental consolidation confined to the segment adjacent to the origin of the proximal tubule (**B** and **E**). The collapsing glomerulopathy variant has segmental collapse of capillaries with hypertrophy and hyperplasia of overlying epithelial cells (**C** and **F**). (Jones methenamine silver, $\times 100$.)

sclerotic lesions ([Fig. 28-5A, B](#)). Other glomeruli may have randomly distributed lesions identical to those in NOS FSGS. Glomerulomegaly and adhesions are common. There often is arteriolar hyalinosis that may be contiguous to hyalinosis in the perihilar segment. This variant of FSGS may occur in idiopathic FSGS; however, it is the typical expression of FSGS secondary to obesity, cyanotic congenital heart disease, reflux nephropathy, renal agenesis, dysplasia, oligomeganephronia, or any advanced renal disease with a reduced number of functioning nephrons.

The tip lesion variant of FSGS has segmental lesions involving the glomerular tip, which is the outer quarter of the tuft adjacent to the origin of the proximal tubule ([Fig. 28-5B, E](#)). The tip lesion variant of FSGS was first described by Howie and Yoshikawa and their colleagues.^{[208] [209] [210] [211] [212] [213]} The initial peripheral consolidation usually has obliteration of capillary lumens by foam cells, swollen endothelial cells, and an increase in collagenous matrix material (sclerosis). Hyalinosis may occur but is less frequent than in NOS and perihilar FSGS. Visceral epithelial cells adjacent to the consolidated segment are enlarged and contain clear vacuoles and hyaline droplets. These altered visceral epithelial cells often are contiguous, if not attached, to adjacent parietal epithelial cells and tubular epithelial cells at the origin of the proximal tubule which also have irregular enlargement and vacuolation. The tip lesion may project into the lumen of the proximal tubule. Some lesions are less cellular with a predominance of matrix and collagenous adhesions to the Bowman capsule at the origin of the proximal tubule. Although initially peripheral, these lesions may expand toward the glomerular hilum as they progress.

The collapsing variant of FSGS has segmental or global collapse and podocyte hypertrophy or hyperplasia ([Fig. 28-5C, F](#)). Collapsing lesions are characterized by an infolding and wrinkling of glomerular capillary walls and increase in collagenous matrix that results in obliteration of capillary lumens and an increased distance between the collapsed segment and the Bowman capsule. Collapsing lesions have a greater tendency to be global than other variants of FSGS, which may be a reflection of the tendency for rapid progression of this variant. The proportion of glomeruli with lesions that have this pattern of injury varies from all to a few. Both peripheral and perihilar segments may be involved. The hypertrophied podocytes typically contain hyaline droplets and vacuoles. When podocyte hyperplasia is pronounced, the result could be called a crescent, but

current convention among most renal pathologists is to not use the term "crescent" for this process in collapsing FSGS. Relative to the extent of glomerular sclerosis, tubulointerstitial injury is more severe in collapsing glomerulopathy than in typical FSGS. Tubular epithelial cells often have larger resorption droplets, extensive proteinaceous casts, and marked focal dilation of lumens (microcystic change). There also is more extensive interstitial infiltration by mononuclear leukocytes.

In addition to occurring as a primary (idiopathic) process,^{[200] [201]} the collapsing variant of FSGS is the major pathologic expression of human immunodeficiency virus (HIV) nephropathy,^{[205] [214] [215]} and also occurs associated with intravenous drug abuse. In renal transplants, collapsing FSGS occurs as both recurrent and de novo disease.^{[216] [217]}

Unfortunately, the term "cellular" FSGS has been used for a variety of patterns of injury, including collapsing FSGS and tip lesion FSGS. Thus, one must be careful when reading the literature to determine exactly what pattern of FSGS is meant when this term is used. Nevertheless, there does appear to be a cellular form of FSGS that does not have the

features of collapsing FSGS or tip lesion FSGS. This variant has segmental consolidation of glomerular tufts by hypercellularity internal to the GBM, usually with conspicuous foam cells. Any segment can be affected, but, if only peripheral segments are involved, the process should be considered the tip lesion variant. Podocyte hypertrophy or hyperplasia may occur adjacent to the endocapillary lesions. Adhesions may or may not be present. Other glomeruli may have lesions typical of NOS FSGS.

FSGS is by definition a focal process and the limited number of glomeruli in a renal biopsy specimen may not include any of the segmentally sclerotic glomeruli that are present in the kidney. In this instance, focal tubulointerstitial injury or glomerular enlargement, which often accompanies FSGS, can be used as a surrogate marker. For example, FSGS should be considered in renal biopsy specimens of patients with the nephrotic syndrome when there is relatively well-circumscribed focal tubular atrophy and interstitial fibrosis with slight chronic inflammation, even when there are no light microscopic glomerular lesions, no immune deposits, and no ultrastructural changes other than foot process effacement. Diagnostic segmental sclerosis that is adequate for diagnosis may be present only in the tissue examined by immunofluorescence or electron microscopy.

The focal segmental glomerular scarring that is observed in FSGS, especially NOS FSGS, is not specific. Many injurious processes can cause focal glomerular scarring and must be ruled out before making a diagnosis of FSGS. For example, hereditary nephritis causes progressive glomerular scarring that can mimic FSGS. This is revealed by identification of the ultrastructural changes that are characteristic of hereditary nephritis. FSGS, for example, caused by IgA nephropathy, lupus nephritis, antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis, can result in focal

segmental glomerular scarring that is histologically indistinguishable from that caused by FSGS. Findings by immunofluorescence and electron microscopy, and by serology, can reveal a glomerulonephritic basis for focal glomerular scarring.

IMMUNOFLUORESCENCE MICROSCOPY

Nonsclerotic glomeruli and segments usually have no staining for immunoglobulins or complement. As in patients with minimal change glomerulopathy, as well as individuals with no renal dysfunction, a minority of patients with FSGS will have low-level mesangial staining for IgM in nonsclerotic glomeruli. Low-level mesangial C3 staining is less frequent and low-level IgG and IgA are rare. The presence of substantial staining of nonsclerotic glomeruli for immunoglobulins, especially if immune complex-type electron dense deposits are present, points toward the sclerotic phase of a focal immune complex glomerulonephritis rather than FSGS.

Sclerotic segments typically have irregular staining for C3, C1q, and IgM ([Fig. 28-6](#)). Other plasma constituents are less frequently identified in the sclerotic areas. Epithelial resorption droplets stain for plasma proteins.

ELECTRON MICROSCOPY

The ultrastructural features of FSGS are nonspecific. As already mentioned, however, electron microscopy plays an important role in the diagnosis by helping to identify other

Figure 28-6 Immunofluorescence micrograph showing irregular segmental staining for C3 corresponding to a site of segmental sclerosis. (Fluorescein isothiocyanate [FITC] anti-C3, ×3000.)

causes of glomerular scarring that can be mistaken for FSGS by light microscopy alone.

Foot process effacement in FSGS affects sclerotic and nonsclerotic glomeruli, and usually is more focal than in minimal change glomerulopathy. Occasional glomerular capillaries have focal denudation of foot processes. Nonsclerotic glomeruli and segments should have no immune complex-type electron dense deposits. One must be careful not to confuse electron dense insudative lesions with immune complex deposits. These lesions equate with the hyalinosis seen by light microscopy and result from the accumulation of plasma proteins within sclerotic areas. Thus, if the electron dense material is present in sclerotic but not in nonsclerotic glomerular segments, it should not be considered to be evidence of immune complex-mediated glomerular disease. On the other hand, well-defined mesangial or capillary wall electron dense deposits in nonsclerotic segments indicate immune complex-mediated glomerulonephritis with secondary scarring, which should be confirmed and further characterized by immunofluorescence microscopy.

In a specimen with collapsing FSGS, the most important ultrastructural assessment is for the presence or absence of endothelial tubuloreticular inclusions. Endothelial tubuloreticular inclusions are identified in over 90% of patients with HIV infection and

collapsing glomerulopathy, but in fewer than 10% of patients with idiopathic collapsing glomerulopathy or collapsing glomerulopathy associated with intravenous drug abuse. The only other settings in which endothelial tubuloreticular inclusions are numerous is one in patients with systemic lupus erythematosus and in patients treated with interferon alfa.

Pathogenesis

The pathogenesis of FSGS is poorly understood. The advanced segmental lesions are essentially segmental scars composed predominantly of collagen. The pathogenesis must involve an injurious factor (the etiology) that initiates a sequence of events that ultimately causes the segmental glomerular scarring. As with many patterns of glomerular

injury, it is likely that multiple different etiologies can initiate shared pathogenic pathways that can ultimately result in segmental glomerular sclerosis. In addition, different sets of etiologic factors may initiate the different pathogenic pathways that lead to the different structural variants of FSGS.

Some of the same pathogenic events that cause segmental scarring and focal glomerular injury in proliferative or necrotizing glomerulonephritis are probably operative in producing the sclerosis of FSGS. In this regard, the over-production of transforming growth factor- β 1 (TGF- β 1) in glomeruli due to acute inflammatory lesions may cause glomerular sclerosis.^[218] In experimental models of glomerular inflammation, the administration of antibodies to TGF- β or other inhibitors of TGF- β results in a decrease in matrix accumulation and a reduction in the severity of glomerular scarring.^[219] Whether these events occur in human disease is yet to be proved, although there is increased expression of TGF- β in many different types of renal disease, including FSGS.^[220] Several mechanisms are associated with the fibrosis of renal disease. Extracellular matrix proteoglycans such as decorin and biglycan that may have a pathogenic role in fibrosing diseases may do so by regulation of TGF- β .^[221]

FSGS also results from the loss of nephrons, which causes compensatory intraglomerular hypertension and hypertrophy in the remaining glomeruli. The compensatory capillary hypertension results in both epithelial and endothelial cell injury, as well as mesangial alterations that lead to progressive focal and segmental sclerosis.^{[222] [223] [224] [225] [226] [227] [228] [229]} This process, at least in experimental animals, is made worse by increased dietary protein intake and is ameliorated by both protein restriction and antihypertensive therapy. Several other abnormalities also may play a role in the pathogenesis of FSGS, including disorders of lipid metabolism, such as the urinary loss of lecithin-cholesterol acyltransferase,^{[230] [231] [232] [233]} abnormalities of the coagulation pathway, and alterations in T cell function.^[234] The role of growth factors in addition to TGF- β and platelet-derived growth factor certainly may participate in these lesions.

Whether the loss of nephron number leads to glomerular sclerosis in human remains controversial. There are well-documented examples of patients who have had either congenital absence or surgical removal of a kidney before the development of FSGS.^[235] As would be expected, patients with a greater degree of loss of renal mass have a greater incidence of secondary FSGS. However, data from long-term studies of individuals donating a kidney for renal transplantation have not demonstrated an increased incidence of hematuria or proteinuria when compared to siblings.^{[236] [237]} Long-term studies of men who have had a unilateral nephrectomy due to trauma indicate that there is only a small increase in mild proteinuria and systolic hypertension when compared to age-matched controls.^{[238] [239]}

Glomerular enlargement accompanied by the development of FSGS also occurs in the setting of hypoxemia, for example, in patients with sickle cell anemia, congenital pulmonary disease, or cyanotic congenital heart disease. Obesity appears to predispose to FSGS.^{[240] [241] [242] [243]} Weight loss and the administration of an ACE inhibitor decreased protein excretion by 80% to 85%.^[242] Patients with sleep apnea may have proteinuria that is more functional in nature, but with little or no evidence of glomerular scarring or epithelial injury observed on biopsy.^{[244] [245]}

Exciting new data suggest that some examples of primary FSGS are a consequence of injury to the podocyte.^{[246] [247] [248]} Podocytes are highly differentiated postmitotic cells whose function is based on their architecture. Several proteins have now been detected on the podocyte, and their role in various diseases is becoming clearer. Thus, in collapsing forms of focal sclerosis, podocytes undergo irreversible ultrastructural changes. This is in contrast to minimal change disease and membranous nephropathy where mature podocyte markers are retained at normal levels. In collapsing FSGS and HIV nephropathy, there is disappearance of all of these markers, suggesting a dysregulated podocyte phenotype in these diseases.^[249] In fact, podocyte proliferation is seen in some examples of FSGS, which may be a consequence of the decrease in cyclin-dependent kinase inhibitors P27 and P57.^[250] The effacement of foot processes may be a consequence of the overproduction of oxygen radicals and accumulation of lipid peroxidase.^[251] In theory, the loss of visceral epithelial cells could result in focal areas of GBM denudation with diminished barrier function.

A permeability factor has been described in some patients with FSGS. In a seminal study by Savin and colleagues,^[243] 33 patients with recurrent FSGS after transplantation had a higher mean value for permeability to albumin than normal subjects. After plasmapheresis, the permeability factor in six patients was reduced and proteinuria significantly decreased. This circulating factor bound to protein A and had an apparent molecular weight of about 50,000 D.^{[252] [253]} Experience with patients with steroid-resistant FSGS in native kidneys suggests that plasmapheresis may diminish proteinuria and stabilize renal function in a minority of patients. In most patients, however, there is no improvement in proteinuria despite loss of the permeability factor after plasmapheresis.^[254] The importance of this permeability factor in the pathogenesis of FSGS remains poorly understood.

HIV-associated FSGS is pathologically identical to idiopathic collapsing FSGS, except for the presence of endothelial tubuloreticular inclusions in the former but not the latter. This close association of HIV infection with collapsing FSGS, as well as experimental evidence of focal glomerular sclerosis in mice transgenic for HIV type I genes,^{[199] [205] [218] [220] [235] [246] [255] [256]} raises the possibility that HIV can be an etiologic agent of FSGS. Whether other viral diseases, including parvovirus B19, cause the idiopathic collapsing variant of FSGS remains to be elucidated.^{[257] [258]} Parvovirus B19 has been found with greater frequency in patients with idiopathic and collapsing FSGS compared with patients with other diagnoses.^[258] The polyomavirus SV40 may also play a role.^[259]

It has long been known that there are familial forms of FSGS.^[260] In a study of 18 families with 45 biopsy-proven cases of FSGS, the disorder appeared to be transmitted in an autosomal dominant pattern. It was associated with HLA alleles, including HLA-DR4, HLA-B12, HLA-DR8, and HLA-DR5.^[261] In fact, a linkage analysis has been performed in one large family with inherited FSGS with localization of a suspected gene on chromosome 19q13.^[262] Even nonfamilial FSGS is associated with specific HLA types. In children of Hispanic origin, FSGS has been linked to HLA-DR8,^{[263] [264]} and B8 is associated with DR3 and DR7 in children of Germanic origin.^[265] In adults, FSGS is found with an increased incidence of HLA-DR4,^[266] and HLA-B53 in some patients with FSGS is associated with heroin.^[267]

Recent genetic case studies of familial FSGS have led to the identification of podocyte proteins and have highlighted the important role of podocyte proteins in the glomerular filtration barrier. For instance, positional cloning has led to the identification of a gene that encodes a podocyte actin-binding protein called α -actin 4 as the cause of autosomal dominant FSGS.^[268] The same strategy has been used to clone two other genes, *NPHS1* (encoding the protein nephrin) and *NPHS2* (encoding the protein podocin). Mutations in the nephrin gene are responsible for autosomal recessive congenital nephrotic syndrome of the Finnish type.^[269] Earlier familial studies on mutations in *NPHS2* described the early childhood onset of proteinuria, rapid progression to end-stage renal disease, and no recurrence after renal transplantation.^[270] Further studies have shown that mutations in *NPHS2* resulting in familial autosomal recessive FSGS are due to nonsense, missense, frame shift, or premature stop codons.^[271] How frequent are *NPHS2* or podocin mutations in childhood FSGS? The frequency varies from 20% to 33%, depending on the population studied.^{[272] [273] [274]} *NPHS2* mutation also occurs in adult-onset FSGS, specifically in exon 5 of the *NPHS2* gene (R229Q).^[271] Interestingly, the genotype does not necessarily correlate with the phenotype. Some patients appear to be steroid-sensitive, others steroid-resistant, and yet others sensitive to cyclosporine therapy.^[275]

Clinical Features and Natural History

In all forms of primary FSGS, proteinuria of varying degrees is the hallmark. The degree of proteinuria varies from non-nephrotic (1–2 g) to massive proteinuria (>10 g)

associated with all of the morbid features of the nephrotic syndrome. Hematuria occurs in over half of FSGS patients, and approximately one third of patients present with some degree of renal insufficiency. Gross hematuria is more commonly seen in FSGS than in minimal change glomerulopathy.^[276] Hypertension is found as a presenting feature in one third of patients. There are differences in the presentation of FSGS in adults and children.^{[196] [277] [278] [279]} Children tend to present with more proteinuria, whereas hypertension is more common in adults.

Differences in clinical manifestations correlate with different pathologic phenotypes of FSGS. For example, patients with perihilar FSGS accompanied by glomerular hypertrophy more commonly have non-nephrotic-range proteinuria than FSGS patients who do not have glomerular hypertrophy. Additionally, there are differences in the clinical presentation of the collapsing variant of FSGS and the glomerular tip lesion variant of FSGS. For example, the collapsing variant often has more severe proteinuria and renal insufficiency but less hypertension than the typical variant, and the glomerular tip lesion variant often presents with rapid onset of edema similar to minimal change glomerulopathy.

Weiss and co-workers^[280] first reported six patients with a collapsing variant of FSGS, and larger series of such patients have subsequently been studied.^{[200] [201]} Patients with collapsing FSGS have substantially more proteinuria, a lower serum albumin, and higher serum creatinine than patients with perihilar FSGS. The development of proteinuria, edema, or hypoalbuminemia may occur rapidly over the course of days to weeks, in contrast to the more insidious development of proteinuria in most patients with typical FSGS. Moreover, patients with collapsing FSGS more frequently have extrarenal manifestations of disease a few weeks before onset of the nephrosis, such as episodes of diarrhea, upper respiratory tract infections, or pneumonia-like symptoms that are usually ascribed to a viral or other infectious process. However, the systemic symptoms of fever, malaise, and anorexia occur in fewer than 20% of patients at the time of onset of nephrosis.

The clinical presentation of the glomerular tip lesion variant differs from that of both perihilar FSGS and collapsing FSGS. Patients with glomerular tip lesion FSGS tend to be older white males, in sharp contrast to the younger black male prevalence in collapsing FSGS. The proteinuria in these patients usually is severe and the onset is abrupt with sudden development of edema and hypoalbuminemia. The rapidity of onset of the disease process is similar to the clinical presentation of minimal change glomerulopathy.^{[207] [211] [281]} Glomerular tip lesion patients may develop reversible acute renal failure, especially at the time of initial presentation when the degree of proteinuria, edema, and hypoalbuminemia is at its peak. This also is similar to minimal change glomerulopathy and rarely occurs with typical FSGS.

It is difficult to ascribe a survival by year for the aggregate group of patients with FSGS. In general, patients with perihilar FSGS have a better long-term outcome than those with collapsing FSGS. Because a greater number of patients with glomerular tip lesion respond to corticosteroid therapy, the long-term outcome for patients with this histologic

variant may be better than that for patients with typical FSGS. Some authorities do not believe there is an association between the pathologic variants of FSGS and the long-term course.^[282]

The degree of proteinuria is a predictor of the long-term clinical outcome. Non-nephrotic-range proteinuria correlates with a more favorable renal survival of over 80% after 10 years of follow-up.^{[283] [284]} In contrast, patients who have more than 10 g of proteinuria per day have a very poor long-term renal survival, with the majority of patients reaching end-stage renal disease within 3 years.^{[285] [286]} This rapid decline in renal function has been termed "malignant FSGS" due to the morbid nature of the nephrosis and the rapidity of the deterioration in renal function.^[284] Patients with FSGS and protein excretion that measures between non-nephrotic-range and massive proteinuria have a variable long-term renal outcome. In general, they have a relatively poor outcome, with half of these patients reaching end-stage renal disease by 10 years.^{[196] [279] [287]}

One of the most useful prognostic indicators for patients with FSGS is whether they attain a remission of their nephrotic syndrome.^[278] Patients who have a remission of nephrosis have a substantially greater renal survival than those who do not.^{[278] [283] [284] [288] [289]} According to Korbet and associates^{[196] [279]} fewer than 15% of patients with complete or partial remission progress to end-stage renal disease within 5 years of follow-up. Up to 50% of patients not attaining remission progress to end-stage disease within 6 years of follow-up.

As in other forms of glomerular injury, a high entry serum creatinine level is associated with poor long-term renal survival.^{[283] [285] [290] [291]} Patients with a serum creatinine of over 1.3 mg/dL have a poorer renal survival than those with lower serum creatinine, irrespective of the level of proteinuria (10-year renal survival of 27% vs. 100%).^[196] Entry serum creatinine by multivariate analysis may be more important

than proteinuria as a predictor of progression to end-stage renal disease.^{[283] [284] [286] [287] [290] [291]}

Controversy abounds regarding whether there is a poorer long-term prognosis in black patients compared to white patients. In children, Ingulli and Tejani noted that within 8.5 years of follow-up, 78% of black patients but only 33% of white patients progressed to end-stage renal disease.^[291] The racial predilection for poor long-term prognosis has not been corroborated in adult patients with nephrosis.^{[283] [284]}

Some pathologic discriminators correlate with long-term clinical outcome. Neither the degree of scarring within the glomerulus nor the number of glomeruli that are totally obsolescent is predictive of long-term renal outcome.^{[207] [282] [291] [292]} As in most forms of glomerular disease, interstitial fibrosis and tubular atrophy correlate with poor prognosis. Substantial controversy has surrounded the prognostic value of discriminating between

different types of FSGS. Most investigators agree that there is a much more rapid deterioration in renal function with collapsing FSGS than typical FSGS.^{[197] [200] [293]}

Another controversial issue is the prognostic significance of the location of the sclerosis within the glomerular tuft. The original descriptions of the glomerular tip lesion by Howie and Brewer^{[210] [211] [212]} suggested that this variant of FSGS has a better response to corticosteroid therapy and a more benign clinical course than typical FSGS. Other investigations have not confirmed an improved long-term renal survival with glomerular tip lesions. These latter studies, however, included very few patients with glomerular tip lesions in the cohort of patients who were studied.^{[207] [213] [282]}

The prognostic significance of mesangial hypercellularity associated with FSGS also is controversial. Some studies have identified a correlation between mesangial hypercellularity and poor outcomes, such as poor response to steroids,^{[294] [295]} more frequent relapses,^[326] and more progression of renal insufficiency.^[296] However, other studies have not confirmed the more rapid loss of renal function.^{[213] [282]}

Laboratory Findings

Hypoproteinemia is common in patients with FSGS, with total serum protein reduced to varying extents. The serum albumin concentration may fall to below 2 g/dL, especially in patients with the collapsing and glomerular tip variants of FSGS. As in other forms of the nephrotic syndrome, levels of immunoglobulins are typically depressed, and levels of lipids are increased, especially serum cholesterol. Serum complement components are generally in the normal range in FSGS. Circulating immune complexes have been detected in patients with FSGS,^{[142] [297]} although their pathogenic significance has not been determined. Serologic testing for HIV infection should be obtained for patients with FSGS, especially those with the collapsing pattern.

Treatment

Other than the ISKDC, there have been no prospective randomized treatment trials for FSGS. Thus, available data are based entirely on anecdotal series using different treatment protocols, different definitions of remission, response, relapse, and resistance, and different lengths of therapy.^{[278] [283] [288] [298]} One review of studies suggested that only 15% of patients with FSGS responded to treatment, in sharp contrast to those with minimal change glomerulopathy.^[299] More optimistic reports have been obtained by groups in Toronto and Chicago^{[278] [279]} that suggest that 30% to 40% of adult patients may attain some form of remission with corticosteroid treatment. A compilation of these studies by Korbet^[196] suggests that of 177 patients who received a variety of different forms of therapy, 45% attained complete remission, 10% attained partial remission, and 45% had no response.^{[278] [283] [288] [298] [300]}

In children, the initial treatment of FSGS is similar to that of minimal change glomerulopathy, because so many pediatricians treat patients without having histologic confirmation of the disease process. Thus, the ISKDC recommended using an initial course of prednisone of 60 mg/day/m², up to 80 mg/day for 4 weeks. This should be

followed with 40 mg/day/m², up to 60 mg/day, administered in divided doses for 3 consecutive days out of 7, for 4 weeks, and then tapered off for 4 more weeks. Similar to the adult patients with minimal change glomerulopathy, a longer course of therapy at higher doses of prednisone may be necessary to induce remission. Thus, in those series where there is an increased remission rate,^{[190] [278] [283] [288] [298] [301] [302]} prednisone treatment was continued for 16 weeks to achieve remission. In adult patients, median time for complete remission was 3 to 4 months.^[193]

Among patients with a positive response to corticosteroid treatment, a portion will relapse. Guidelines for retreatment of this group of patients are similar to those of relapsing minimal change glomerulopathy. In patients whose remission prior to relapse was prolonged (> 6 months), a repeat course of corticosteroid therapy may again induce a remission. In steroid-dependent patients who develop frequent relapses, repeated high-dose corticosteroid therapy results in unacceptable cumulative toxicity. Thus, alternative strategies such as the addition of cyclophosphamide or cyclosporine may be useful. In some patients, reestablishment of remission may result when cyclophosphamide is administered for 8 to 12 weeks at a dose of 2 mg/kg/day.^[279]

In patients with the glomerular tip lesion variant of FSGS, a trial of corticosteroids is appropriate because many patients have a decline in protein excretion.^{[209] [281] [282]}

The practice of using higher doses of corticosteroids to reach remission has resulted in alternative therapeutic approaches in patients who are resistant to oral prednisone. In these forms of therapy, prednisone-resistant FSGS has been treated with methylprednisolone boluses of 30 mg/kg/day to a maximum of 1 g given every other day for six doses, followed by this same dose on a weekly basis for 10 weeks; subsequently, similar doses are given on a tapering schedule. In addition to these large doses of methylprednisolone, oral prednisone is given.^{[303] [304]} Some patients are also given alkylating agents. With this treatment protocol, 12 of 23 children entered remission, and 6 had decreased urinary protein losses.

These very high doses of corticosteroids in children, and the duration of daily prednisone for up to 6 to 9 months in adults, are not without enormous short- and long-term side effects. In studies in which long-term, high-dose corticosteroids are administered, few analyses have been undertaken of the development of osteoporosis, the short- and long-term risk of infection, and the development of cataract, diabetes, or other long-term sequelae. Thus, the available data do not allow for careful understanding of risk-benefit ratios. Until the use of very large doses of Solu-Medrol (methylprednisolone) is

subject to controlled clinical trials, the utility of this potential yet dangerous approach must be viewed with caution. There are some authorities who feel that most treatment of FSGS with corticosteroids is hazardous.^[305]

Attempts at alternate-day steroid therapy have not been successful except in elderly populations. The Toronto group^[306] demonstrated that patients over the age of 60 years achieved a 40% remission rate using up to 100 mg of prednisone on alternate days for 3 to 5 months. This therapy was well tolerated in this population without obvious side effects during the study period. Alternate-day prednisone most likely works in this population because of an increased susceptibility to the immunosuppressive effects of corticosteroids and altered glucocorticoid kinetics in the elderly.

Alternatives to Corticosteroid Therapy

Several studies have failed to document the effectiveness of cytotoxic drugs in the treatment of FSGS.^{[288] [307]} In one review, only 23% of 247 children with FSGS were steroid-responsive, and 70 patients were treated with cytotoxic drugs. Of these, 30% responded. In the final analysis, fewer than 20% of the 247 children were in remission. The use of cytotoxic drugs has been evaluated in only one series of adults.^[288] Although their use correlated with longer remissions and fewer relapses, no other study has corroborated these results.

The ISKDC carefully examined the role of cyclophosphamide in the treatment of children with FSGS. For 3 months, cyclophosphamide was used in combination with a 12-month course of every-other-day prednisone therapy. When this regimen was compared to prednisone alone, there was no improvement in response between patients treated with cyclophosphamide and those receiving prednisone alone.^[308]

Patients resistant to prednisone may be induced into remission with cyclosporine. A randomized trial demonstrates the utility of cyclosporine in patients with steroid resistance, resulting in remission in the majority of patients.^[309] This study compared 46 cyclosporine-treated, steroid-resistant FSGS patients to 45 control patients. Of the 46 patients, 9 achieved complete remission, whereas none of the controls did. Partial remissions were observed in 40% to 70% of the cyclosporine-treated patients, and in 17% to 33% of the control patients. These results are statistically significant when both complete and partial remissions are considered. Withdrawal of treatment results in relapse in over 75% of patients.^[299]

How long should patients be treated with cyclosporine? In a study by Meyrier and colleagues, when patients remained in remission for over 12 months, cyclosporine was slowly tapered and eventually removed without subsequent relapse.^[193] Unfortunately, long-term treatment with cyclosporine was associated with increases in tubular atrophy and interstitial fibrosis.^[193] The degree of tubulointerstitial disease was positively correlated with the initial serum creatinine, the number of segmental scars on initial biopsy, and on a cyclosporine dose of more than 5.5 mg/kg/day. Thus, there is a clear trade-off in the use of cyclosporine over the long term in the well-established development of interstitial fibrosis and tubular atrophy.

ACE inhibitors and angiotensin receptor blockers (ARBs) have been evaluated in the treatment of FSGS. ACE inhibitors have been shown to decrease proteinuria and the rate of progression to end-stage renal disease.^{[310] [311] [312] [313]} These results have been obtained not

only in the presence of diabetes but also in cases of nondiabetic renal disease. In patients with sickle cell disease, glomerulomegaly, and FSGS, ACE inhibitors decreased proteinuria acutely while maintaining the GFR and renal plasma flow.^[240] In general, these studies suggest that ACE inhibitors, and perhaps angiotensin II receptor antagonists, would provide a substantial ameliorative effect in nephrotic symptoms of FSGS. In fact, in patients with glomerulomegaly and resultant non-nephrotic-range proteinuria, an ACE inhibitor or angiotensin II receptor antagonist sufficiently decreases proteinuria and potentially decreases hyperlipidemia, edema, and other manifestations of persistent loss of protein in the urine in this population with excellent long-term prognosis. Regardless of other forms of anti-inflammatory or immunosuppressive therapy employed, the beneficial effects of these agents indicates that they should be added, despite the well-known side effects of hyperkalemia and reduction in GFR, especially in patients with serum creatinine of over 3 mg/dL.

Other forms of treatment have been used. Plasmapheresis or protein absorption strategies to remove circulating factors responsible for FSGS have led to remission of recurrent FSGS, but do not appear to be beneficial in the primary disease.^{[254] [314]} Anecdotal cases suggest that mycophenolate mofetil may be useful in some patients as well.

In summary, patients with primary FSGS remain frustrating patients to treat. Enthusiasm for the use of high-dose, prolonged corticosteroid therapy in adults and children has prompted the use of this therapy in many FSGS patients. Only a prospective randomized trial that carefully evaluates this approach will determine its precise effectiveness. In patients who have protein excretion of less than 3 g/day or with glomerulomegaly found on biopsy, a trial of ACE inhibitors or angiotensin II receptor antagonists is warranted. In those patients who have nephrotic-range proteinuria, careful supportive care and consideration of a trial of oral corticosteroids in adult patients may be an acceptable approach after the patient is carefully informed of the risks and potential benefits of 12 to 16 weeks of daily corticosteroid therapy. Alternating a trial of cyclosporine may be warranted at a dose of 5 mg/kg/day for less than 12 months. In all of these patients, an ACE inhibitor may provide a substantial reduction in proteinuria and a potential long-term benefit that may be equal to or greater than that of immunosuppressive therapy.

