

# Idiopathic Focal Segmental Glomerulosclerosis

By H. William Schnaper

**Idiopathic focal segmental glomerulosclerosis (FSGS) is a primary glomerular disease that essentially represents a form of chronic, progressive renal fibrosis for which there is no discernible cause. Often presenting with or eventually manifesting the nephrotic syndrome, this disease is increasing in incidence in both children and adults. Therapy continues to be a challenge, although some patients clearly respond to corticosteroids or cyclosporine with a decrease in, or remission of, proteinuria. A favorable response is associated with a decreased likelihood of progression to kidney failure. Given our clinical experience and recent advances in understanding the genetics of FSGS, a stochastic model of disease pathogenesis can be proposed.**

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**I**N 1957, RICH<sup>1</sup> described a novel lesion in a group of children with the nephrotic syndrome who had died. The lesion appeared to begin with thickening of basement membranes and progressed to complete obliteration of the normal glomerular architecture by hyaline deposits. This was a surprising finding because these patients had experienced symptoms typical of what was then called *lipoid nephrosis*. Indeed, unlike the findings in other patients with progressive glomerular disease who died, there was no evidence of inflammation, crescent formation, or malignant arteriolar sclerosis. Subsequent reports by Heptinstall, Hayslett, Churg, White, and others (reviewed by Hyman and Burkholder<sup>2</sup>), and an extensive clinicopathologic analysis by Habib and Kleinknecht,<sup>3</sup> further defined the histopathology. The lesions consisted of extracellular matrix (ECM) accumulation that was focal because the glomeruli were not involved uniformly, and segmental because only part of each glomerulus was affected. Thus, the generally accepted descriptor for this condition became *focal segmental glomerulosclerosis* (FSGS).

Our understanding of this entity has progressed little since these initial descriptions. Although our ability to treat FSGS has improved over time, the treatments are empiric. We have little knowledge of the etiology or mechanisms of this disease. Indeed, it is perhaps more accurate to refer to FSGS as “these diseases” because the marked heterogeneity of clinical presentation and course suggests that more than one etiology is involved. Further, there are no animal models that accurately recapitulate the histology and course of idiopathic FSGS, so our knowledge is based largely on inference or clinical observations. Here, we explore how our clinical experience may elucidate aspects of FSGS. In our discussion, idiopathic FSGS refers to a lesion that occurs without obvious causes such as hyperfiltration, human immunodeficiency virus infection, or other renal disease.

## CLINICAL PRESENTATION: NEPHROSIS AND PROTEINURIA

FSGS may present at any age. The pediatric incidence was reported to peak in children at ages 2 to 3,<sup>4</sup> but other studies suggest that the incidence may increase with age in both children<sup>5</sup> and adults.<sup>6</sup> A preponderance of males also has been reported in one study,<sup>4</sup> but not confirmed. FSGS is the most common acquired cause of chronic kidney failure in children<sup>7</sup> and is a significant contributor to end-stage kidney disease in adults as well. The incidence, at least in North America, appears to be increasing in both children<sup>8,9</sup> and adults.<sup>10</sup>

Frequently, FSGS presents with nephrotic syndrome, defined variably by the classic tetrad of proteinuria, hypoalbuminemia, edema, and hypercholesterolemia,<sup>11</sup> or by the presence of edema and nephrotic-range proteinuria. The latter has been defined as greater than 3 gm/d in adults, 50 mg/kg/d<sup>3</sup> or 40 mg/m<sup>2</sup>/hr<sup>12</sup> in children, or an increased urine protein:creatinine ratio variably reported as being between 2<sup>13</sup> and 3.5.<sup>14</sup> However, a significant number of patients present with isolated proteinuria or with proteinuria and hematuria (see later section on Clinical Manifestations: Signs and Symptoms). The cause of proteinuria is uncertain. As is true for minimal change nephrotic syndrome (MCNS), proteinuria in FSGS occurs without apparent disruption of the glomerular filtration bar-

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rier sufficient to account for the massive protein loss. Both MCNS and FSGS are described as showing decreased staining for glomerular polyanion,<sup>15</sup> one possible explanation for urinary loss of albumin, a negatively charged protein.<sup>16</sup> Guasch et al<sup>17</sup> describe a biphasic curve for glomerular permselectivity in patients with FSGS that includes decreased fractional clearance of smaller molecules, similar to what is observed in MCNS,<sup>18</sup> but also increased fractional clearance of larger macromolecules, suggesting the existence of a shunt mechanism for the clearance of larger proteins. Urinary proteins may include, in addition to albumin, other components of the plasma that may have clinical significance. These include immunoglobulin (Ig)G and opsonizing factors, whose loss may lead to susceptibility to infection by encapsulated bacteria<sup>19</sup>; vitamin D-binding proteins and 25-OH-vitamin D<sub>3</sub>, causing bone demineralization<sup>20</sup>; and iron-binding proteins, leading to anemia.<sup>21</sup>

In addition to protein, the urinalysis in FSGS may be positive for blood and glucose. The latter, if not related to corticosteroid therapy or pre-existing conditions, is a potential cause for concern because it may be a sign of tubulointerstitial damage. Similarly, patients with significant proteinuria would be expected to have a high urine specific gravity. Inability to concentrate the urine secondary to tubular disease may cause a low urine specific gravity that is, like glucosuria, a potential harbinger of progressive renal fibrosis.<sup>22</sup>

#### CLINICAL MANIFESTATIONS: SIGNS AND SYMPTOMS

An important consideration in the presentation of FSGS is the presence or absence of the nephrotic syndrome. In children, a survey of several studies indicates that as many as 80% of patients are nephrotic at presentation.<sup>23</sup> In adults, the percentage may be somewhat lower.<sup>24</sup> In a more recent retrospective study, adults were less likely to present with nephrotic syndrome than were children (55% versus 76%), but over time the incidence of nephrosis increased to greater than 80% in both groups.<sup>25</sup> These figures are subject to interpretation because they could reflect selective referral patterns. Given the changing incidence of FSGS, the numbers in the general population could now differ from the results of these retrospective studies. It has been suggested that patients present-

ing with nephrosis are more likely to progress to chronic kidney failure. Nephrotic patients are more likely to be hypertensive, to have increased serum creatinine levels, or to have hematuria.<sup>26-30</sup> Hypertension and azotemia also are more likely in adults than in children.<sup>28</sup> Although these findings may help define a population of patients, they are not useful for determining whether a patient has FSGS or is likely to progress to renal failure. The only valid diagnostic determinant is the biopsy examination itself. Although all adults presenting with significant proteinuria, or with proteinuria plus hematuria, will undergo biopsy examination, this procedure is deferred in nephrotic children under the age of 10 who have normal serum complement levels, no evidence of collagen vascular disease, and clinical findings consistent with MCNS.<sup>31</sup> Although the clinical findings do not differentiate between MCNS and FSGS, the majority of children under age 10 with this presentation have the former disease. Those who have FSGS usually are found in the subgroup of patients who fail to respond to corticosteroid therapy.

In the absence of nephrosis, FSGS may be found in as many as 30% to 50% of adult patients undergoing a biopsy procedure.<sup>24</sup> The data are less conclusive regarding children who are not nephrotic. Regardless of age, FSGS is a more likely diagnosis in African-American or Hispanic adult<sup>32</sup> or pediatric<sup>33</sup> patients than in their Caucasian counterparts.

#### GENETIC FACTORS IN FSGS

There are numerous reports in the literature of siblings with FSGS, many of these cases being associated with other syndromes. In some instances, an isolated renal lesion was seen in 2 or more siblings after a specific stimulus, or the cases occurred in a temporally clustered manner. These findings suggest that a genetic predisposition led to FSGS after a common inducing event.<sup>23</sup> Varied human leukocyte antigen (HLA) associations have been described,<sup>23</sup> also suggesting a genetic predisposition. More recently, mutations showing Mendelian inheritance patterns have been identified. The most commonly identified cause of hereditary nephrosis leading to the loss of renal function is congenital nephrotic syndrome of the Finnish type.<sup>34</sup> This steroid-resistant form of progressive kidney disease results from a mutation of *NPHS1*, the gene for nephrin. Nephrin is a member of a

family of cell-cell adhesion molecules that have an immunoglobulin-like domain structure. Interdigitating between epithelial foot processes, nephrin forms the epithelial slit diaphragm that is the ultimate steric barrier to the glomerular filtration of macromolecules. A mutation more specifically associated with FSGS is found in *NPHS2*, the gene for podocin, another podocyte protein. This mutation occurs in a significant percentage of children with FSGS who experience the onset of nephrosis between ages 3 months and 5 years. Children with this mutation are often refractory to any form of therapy.<sup>35</sup> A third mutation, of the *ACTN4* gene that encodes actinin 4, also has been associated with FSGS.<sup>36</sup> The protein products of all of these genes serve structural functions in the podocyte. Taken together with the observation that other podocyte proteins are disrupted or dysfunctional in acquired renal disease<sup>37</sup> and the finding of podocyturia in some patients with FSGS,<sup>38</sup> these results suggest that podocyte dysfunction plays an important role in the development of proteinuria and/or progression.

Another mutation of interest that is associated with FSGS is found in exons 8 or 9 of the Wilms tumor suppressor gene, *WT1*. This abnormality has been associated with nephrosis in Denys-Drash and Frasier syndromes.<sup>39</sup> The former includes congenital nephrotic syndrome, XY pseudohermaphroditism, and Wilms tumor, associated frequently with diffuse mesangial sclerosis. Frasier syndrome has more typical FSGS and gonadal abnormalities.<sup>40</sup> Interestingly, different members of the same family, with the same mutation, may show very different clinical manifestations or varied severity, ranging from normal phenotype to progressive FSGS. This observation strongly suggests that additional environmental factors or the influence of additional gene products is important in disease expression.

#### HISTOPATHOLOGY OF FSGS

A hallmark of FSGS cited by Rich<sup>1</sup> but not confirmed by all subsequent investigators<sup>41</sup> is the early involvement of juxtamedullary nephrons, with centripetal progression into the cortex. Because the circulation to these nephrons is regulated differently from that to the superficial cortex, it has been proposed that a hemodynamic factor may be important in the development of FSGS, consistent with experimental animal data subsequently devel-

oped by Ikoma et al.<sup>42</sup> These findings also correlate well with hemodynamic studies in animal models of progressive glomerular disease. The juxtamedullary location has led clinicians to emphasize the importance of obtaining tissue from this region when performing a biopsy procedure.<sup>11</sup>

The sine qua non of FSGS is the presence of increased amounts of ECM, usually including both normal basement membrane components such as type IV collagen and laminin, and components not normally seen such as atypical ECM isoforms or fibrillar collagens (types I and III).<sup>43-45</sup> The exact nature of the sclerotic lesion continues to be a topic of discussion. Clearly, a process occurs by which an area of the glomerulus that previously was open to perfusion becomes solidified by some combination of mesangial matrix, glomerular basement membranes, and collapsed vascular structures.<sup>46</sup> True capillary collapse, as opposed to obliteration by accumulated extracellular matrix, likely represents the loss of podocytes that support the capillary structure and may represent a particularly aggressive form of FSGS.<sup>47,48</sup> Insudation of serous material may lead to the accumulation of acellular, hyaline deposits, leading some investigators to describe the lesion as *focal sclerosis and hyalinosis*. Kriz and Lemley<sup>49</sup> have proposed that these synchiae represent a reactive process by which adhesions permit plasma proteins to be extruded directly into the tubulointerstitium, thus playing a significant role in stimulating progressive tubulointerstitial fibrosis.

Within the glomerulus, the sclerotic lesion often starts near the hilum, progressing outward from the mesangial stalk into the glomerular tuft. A study suggests that the 2-dimensional representation obtained from biopsy sections underestimates the number of glomeruli affected in a given patient. When 3-dimensional reconstructions were undertaken, some apparently unaffected glomeruli were found to be involved in segments that were not in the plane of the original section.<sup>50</sup> Thus, the FSGS lesion may be more diffuse than we appreciate on routine biopsy examination.

Immunofluorescence microscopy usually is negative or is positive only for IgM in a granular pattern. IgG and IgA deposits are rare. The C3 complement component sometimes is detected. Mild mesangial hypercellularity may be observed and, if extensive, could foretell disease that is poorly responsive to treatment.<sup>51-53</sup> A more omi-

nous sign is the presence of tubular atrophy/drop-out or interstitial inflammatory cells.<sup>4,29</sup>

The classification of FSGS relative to that of other glomerulopathies has not been resolved entirely. It belongs to a group of glomerular lesions in which there is no evidence of inflammation or other process to disrupt the glomerular filtration barrier. These patients have been included within the category of idiopathic nephrotic syndrome by some investigators but because that appellation may include diseases in which the nephrosis results from idiopathic chronic glomerulonephritis, we and others have used the term *primary nephrotic syndrome*<sup>3,11</sup> to denote the lack of a morphologically apparent cause of the proteinuria. As noted previously, along with other forms of primary nephrotic syndrome, FSGS may show immunoglobulin deposition (particularly IgM) or mild mesangial hypercellularity. If excessive, these findings indicate the likely presence of another disease. Habib and Kleinknecht<sup>3</sup> have suggested that MCNS, FSGS, and related disorders essentially are one disease, with the lesion being capable of changing from one diagnosis to another over time. An alternative interpretation is that they are different diseases with partial overlap. In favor of MCNS and FSGS representing a continuum of disease, both are associated with massive proteinuria but do not show significant abnormalities of the glomerular filtration barrier on light microscopy. Thus, FSGS could be viewed as the eventual result of unrelenting proteinuria in steroid-resistant MCNS. Against this interpretation, some patients with steroid-resistant MCNS can experience years of proteinuria without any evidence of progression; in the era before the common use of corticosteroid therapy for MCNS, it was not a disease uniformly associated with progression (note that early descriptions by Rich<sup>1</sup> and others included a worse prognosis as one of the characteristics delineating FSGS from MCNS). We have proposed a schema in which all cases of idiopathic FSGS associated with nephrosis are subsumed within the category of primary nephrotic syndrome, as indicated in Figure 1. By this classification, primary nephrotic syndrome includes MCNS and its variants such as IgM nephropathy and mild mesangial hypercellularity, along with FSGS. Another group, outside of the primary nephrotic syndrome circle, includes patients with FSGS that is secondary to systemic disease or that occurs as a late event after other,

histologically defined renal lesions. These additional cases can be considered to suggest that glomerulosclerosis, idiopathic or otherwise, is a final common pathway of progressive nephron loss.

#### TREATMENT

Although the diagnosis of idiopathic FSGS carries with it significant concern regarding long-term kidney function, therapy can influence outcome positively.<sup>54-57</sup> Therefore, aggressive treatment is indicated in an effort to avoid end-stage kidney disease. Unfortunately, clinical heterogeneity despite a relatively undifferentiated histopathologic finding means that it is not possible to determine in advance which patients are most at risk for the development of chronic kidney failure. The main determinant of how aggressively to approach treatment is thus the perceived balance between the risk for progression and that of toxic effects of the therapy. Until recently, the primary treatment has been corticosteroids. Although FSGS is less responsive than MCNS, some patients do respond. In adults, treatment with 60 mg/d for up to 9 months will induce remission or at least decrease proteinuria in as many as 50% of patients. Even a partial response is associated with a better long-term prognosis for renal function. The treatment appears to influence outcome rather than simply to identify patients likely to avoid renal failure because historic controls indicate that a majority of the responders might have progressed otherwise.<sup>55</sup>

In children, high-dose corticosteroid therapy was the first treatment that appeared to influence outcome significantly. This regimen involves intravenous boluses of methylprednisolone, 30 mg/kg to a maximum of 1,000 mg, every other day for 6 doses and with decreasing frequency thereafter. A favorable response was observed in 75% to 80% of children who had failed to respond to conventional oral corticosteroids.<sup>54</sup> However, other investigators who have used somewhat modified versions of this protocol have found it to be less effective, although more so than conventional steroids,<sup>58</sup> and it is associated with side effects that include those of osteopenia and immune suppression.<sup>59</sup> Alkylating agents have proven effective in combination with corticosteroids,<sup>60,61</sup> but have not been subjected to controlled trials when used alone.

Indeed, the only drug that has proven effective in controlled trials is the calcineurin inhibitor cy-

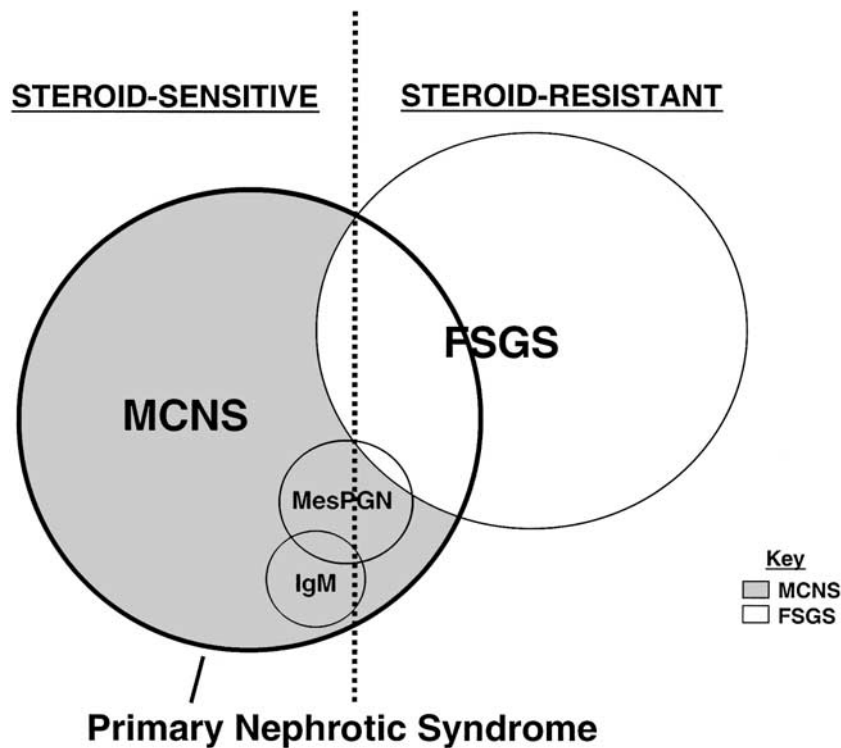


Fig 1. The spectrum of primary nephrotic syndrome and related disorders. The shaded area includes what typically is referred to as MCNS and its variants. The circle with the thick line circumscribes all cases of what we have termed *primary nephrotic syndrome*. Although it includes many cases of FSGS, the portion of FSGS outside of primary nephrotic syndrome includes patients with FSGS secondary to other primary renal diseases such as chronic glomerulonephritis, human immunodeficiency virus infection, or obstructive uropathy (see text). In contrast to MCNS and FSGS, mesangial IgM nephropathy and mild mesangial hypercellularity usually are not considered to represent distinct entities, but rather to reflect events related to the primary disease. Collapsing glomerulopathy has been omitted pending determination of whether it represents a truly distinct entity. Given the increasing frequency of idiopathic FSGS, the circles in the diagram cannot be considered to represent the current relative incidence or prevalence of these diseases. MesPGN, mild mesangial hypercellularity. Data from Schnaper and Robson<sup>11</sup>.

cyclosporine. In a study that included mostly adults but also some children, 70% of patients entered complete or partial remission, compared with 4% of a control group. The dose was titrated to achieve a 12-hour trough level of 125 to 225  $\mu\text{g/L}$ .<sup>57</sup> Given in high doses to offset binding to the excess plasma lipids in nephrosis, cyclosporine decreased both proteinuria and disease progression (relative to historic controls) in a group of high-risk patients.<sup>56</sup> Even with maintenance of acceptable drug levels, chronic cyclosporine nephrotoxicity may occur; many clinicians monitor patients who receive prolonged treatment through follow-up kidney biopsy examination for the purpose of determining both efficacy of the treatment and evidence of toxicity. Other calcineurin inhibitors have been tested, in-

cluding tacrolimus,<sup>62</sup> but have not been subjected to a controlled trial.

#### PROGNOSIS

At one time, FSGS was felt to progress uniformly to chronic uremia and the need for end-stage kidney disease therapy. However, it has become apparent that clinical findings and prognosis are heterogeneous.<sup>25,63</sup> The Southwest Pediatric Nephrology Study Group reported that a significant number of children with FSGS retained normal or near-normal function several years after diagnosis.<sup>4</sup> The absence of nephrosis may be a highly favorable index of disease activity. In one study, 47% of nephrotic adults progressed to end-stage kidney disease within 10 years, whereas only

8% of patients who were not nephrotic similarly progressed.<sup>55</sup> Such a striking difference is not always seen. A study of children identified 3 groups of patients: those who were nephrotic at presentation, those who presented with asymptomatic proteinuria but eventually developed the nephrotic syndrome, and those who were never nephrotic. The incidence of chronic renal insufficiency was similar in the 3 groups.<sup>30</sup> Regardless of the conclusions of these studies, because patients with asymptomatic proteinuria without nephrosis subsequently may become nephrotic or progress to end-stage without becoming nephrotic, it is not possible to predict outcome confidently from the symptoms at presentation.

One differentiating factor, already noted with corticosteroid treatment of adults,<sup>55,64</sup> is response to therapy. In children, Arbus et al<sup>65</sup> noted 3 clinical patterns after corticosteroid treatment of FSGS. Those who responded to steroids fared well, but those who never responded, or who developed resistance to treatment within 18 months, had a poorer prognosis. Other factors associated with greater likelihood of progression include hypertension, interstitial inflammation and fibrosis,<sup>4,30,55</sup> or African-American or Hispanic ethnicity.<sup>32,33</sup> Massive proteinuria has been associated with progression of steroid-resistant nephrotic syndrome,<sup>66</sup> although the pathogenetic significance of the proteinuria remains unresolved.<sup>67</sup>

Kidney transplantation is associated with 2 problems that are relatively specific for FSGS. One of these is recurrence related to the presence of a circulating factor that enhances glomerular permeability.<sup>68</sup> In children with FSGS in whom preemptive transplantation has been attempted to avoid hemodialysis, a very high incidence of perioperative complications has been noted. These have been attributed to graft loss from thrombosis and may represent an effect of the nephrotic state rather than of FSGS per se.<sup>69</sup> For this reason, most pediatric centers now choose to dialyze all children with FSGS for a period of time before proceeding to transplant, using either coagulation studies or an index of active nephrosis such as lipid abnormalities or serum albumin to determine whether the likelihood of thrombotic complications has diminished.

#### WHAT DO WE KNOW ABOUT PATHOGENESIS?

What is FSGS? Three paradigms may be postulated: (1) idiopathic FSGS is the primary manifestation of a specific renal disease; (2) FSGS is a defined lesion that occurs after stimulation of specific events that can be triggered by a variety of associated causes such as MCNS (which also is not well-defined pathogenetically); and (3) FSGS is a final common pathway of glomerular obliteration that occurs after myriad lesions of the kidney. In support of the first possibility, some patients, particularly children, present with a characteristic set of clinical findings and a rapidly progressive course. In addition, the increasing number of single genetic mutations associated with idiopathic FSGS suggests that a direct cause of the lesion may be found in specific cases. The second possibility is supported by the observation that FSGS may begin as a steroid-sensitive lesion, followed in some cases by a supervening, steroid-resistant process. Further, the marked heterogeneity of clinical presentation and course appears to indicate that the totality of FSGS includes more than one disease. The third possibility is supported by the observation that FSGS has been found associated with such disparate antecedent nephropathies as those associated with chronic glomerulonephritis,<sup>69</sup> transplant nephropathy,<sup>70</sup> sickle cell disease,<sup>71</sup> and obstructive nephropathy.<sup>72</sup> In this interpretation, idiopathic FSGS simply may denote one or more circumstances in which the proximate stimulus for chronic, progressive glomerular disease has not been identified yet.

All of the earlier paradigms may be relevant, with FSGS being a heterogeneous syndrome that may involve various models of pathogenesis. Clearly, a biopsy specimen represents a snapshot of the kidney and does not permit us to view the mechanism or the rate at which changes in histology are occurring. In this respect, the clinical data that we obtain from the patients may be as helpful as histology in characterizing the events involved in FSGS. Of critical importance is the response to therapy because this characteristic likely differentiates 2 underlying mechanisms. Thus, it is noteworthy that in a disease not classically attributed to inflammation, the only effective therapies that have been found are anti-inflammatory. However, as noted previously, some patients initially are steroid

sensitive but then become steroid resistant. Again, this observation suggests that there are 2 potential mechanisms, one that is blocked by steroids and a second, supervening mechanism that is steroid unresponsive.

Another finding that may differentiate among causes of FSGS is the presence or absence of nephrosis. The alert reader will have noted that the schema in Figure 1 does not include patients without nephrosis. Given that nonnephrotic patients may have a lower incidence and/or rate of progression to end-stage disease, it is likely that the nephrotic and nonnephrotic groups represent patients with different diseases.

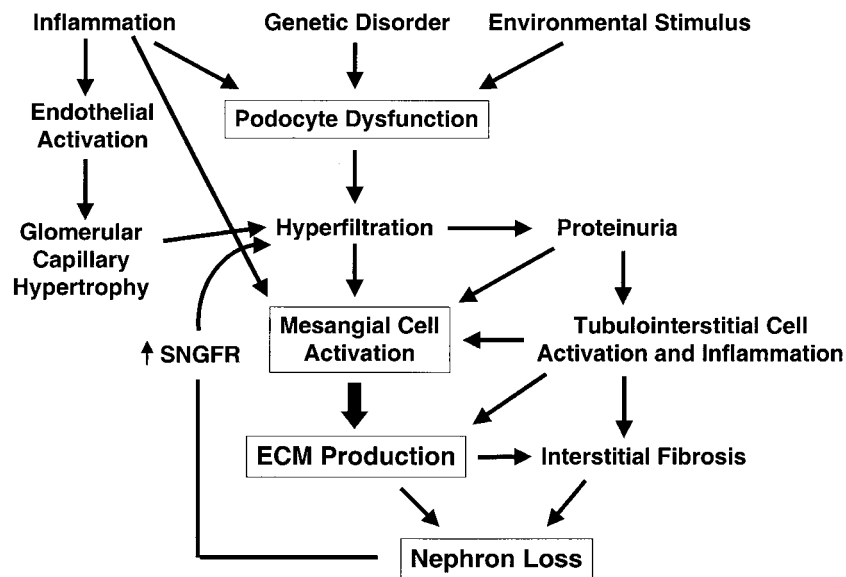
In those idiopathic FSGS patients who present with full clinical manifestations of the nephrotic syndrome, it is not clear how different the nephrotic syndrome is from the nephrosis in MCNS. As noted previously, both diseases involve proteinuria that occurs without obvious disruption of the glomerular filter. Podocyte effacement/fusion could be a result rather than a cause of proteinuria.<sup>73</sup> The permselectivity curves generated in FSGS and MCNS are similar but not identical. One potential indication that the mechanisms of nephrotic proteinuria differ is that the permeability factor described by Savin et al<sup>74</sup> has not been found in patients with MCNS. It should be noted that there is at present no evidence directly connecting the glomerular permeability factor to the sclerotic process in FSGS. Thus, the mechanisms of proteinuria and of fibrosis may be distinct.

Regardless of the mechanism of fibrosis, it is apparent that some patients have an aggressive disease that has a high risk for early-onset chronic kidney failure. Because we have been unable to differentiate among these patients solely on the basis of the initial biopsy examination and presentation, it is important to develop new paradigms for differentiating among patients who are not likely to progress, who are likely to progress unless they receive aggressive therapy, or who are likely to progress even after receiving aggressive treatment. For example, specific gene mutations might prove to be resistant to treatment, or microchip array analysis of RNA expression patterns might be used prospectively to define these groups. Such identification would permit clinicians to maximize therapy but avoid unnecessary toxicity to their patients.

Another consideration related to differentiation among possible clinical subgroups is whether

FSGS in early childhood is different from that found in adults. Children have slightly different symptoms from adults, but these may be more useful for differentiating among classes of patients than in individual cases. The likelihood of progression and incidence of nephrosis also may be different. Ethnicity appears to have an impact on both incidence and rate of progression of disease in FSGS. The impact of age and ethnicity, along with data such as the variable clinical manifestations in patients with identical WT1 gene mutations, strongly support the notion that FSGS is a multifactorial disease, in which a multiplicity of conditions determine outcome.

A potential pathogenetic scheme can be proposed for idiopathic FSGS based entirely on clinical (human) data (Fig 2). The mutations associated in a Mendelian fashion with FSGS involve largely podocyte-specific genes, suggesting a critical role for the visceral epithelial cell. In addition to genetic influences, responsiveness to corticosteroids suggests that inflammation could affect the filtration barrier, or affect the podocyte directly. Loss of podocyte architecture and of cell-cell or cell-matrix adhesion would permit ballooning of the glomerular capillary and hyperfiltration. Activation of endothelial cells could lead to glomerular capillary hypertrophy, a particularly common finding in obese patients with FSGS.<sup>75</sup> Hypertrophy could lead to hyperfiltration. Because convection contributes to transglomerular passage of macromolecules,<sup>76</sup> hyperfiltration alone may cause at least some proteinuria. Passage of macromolecules into the mesangium, inflammation, and perhaps paracrine signals from the podocyte then activate mesangial cells, leading to the increased production of mesangial cell matrix. Proteinuria also delivers biologically active molecules from the plasma to the tubulointerstitium, activating epithelial-to-mesenchymal transdifferentiation and the generation of further inflammatory molecules and profibrotic cytokines such as transforming growth factor  $\beta$  (TGF- $\beta$ ). Tubular damage may lead to activation of the renin-angiotensin system, also increasing mesangial cell activation through TGF- $\beta$  production and the direct action of angiotensin II on the mesangial cell, which further stimulates TGF- $\beta$  production. Tubulointerstitial fibrosis leads to nephron loss. Remaining nephrons respond with a compensatory increase in single-nephron glomerular filtration rate, further increasing hyperfiltration



**Fig 2.** Proposed scheme for the development of FSGS. Inflammation, a gene mutation or an environmental stimulus, singly or in concert, causes podocyte dysfunction. Loss of normal podocyte architecture permits ballooning of the glomerular capillary, changing the restrictive capacity of the glomerular filtration barrier, engendering hyperfiltration, and stretching the mesangial cell. Endothelial activation leads to capillary hypertrophy, and proteinuria delivers biologically active macromolecules to the mesangium. Along with these stimuli, possible production of activating mediators by the injured podocyte and direct effects of inflammatory mediators contribute to further mesangial cell activation. The mesangial cell secretes ECM components, leading to the mesangial accentuation often observed in FSGS. Simultaneously, delivery of biologically active molecules to the renal tubule and the tubulointerstitium initiates inflammation, interstitial fibrosis, and nephron loss. SNGFR, single-nephron glomerular filtration rate.

and proteinuria.<sup>77</sup> It should be noted that because uninephrectomy does not cause significant proteinuria and glomerulosclerosis, hyperfiltration must be extreme to cause progressive renal disease (clinical and experimental data reviewed by Schnaper<sup>23</sup>). Nonetheless, it could play a role in the maintenance of progression. Combined, these events define a process that is driven by genetics and inflammation at the outset, but that eventually becomes self-sustaining.

Foidart et al<sup>78</sup> have suggested that ECM accumulation occurs when cells de-differentiate toward a more primordial state. Maintenance of a differentiated state is an active process that includes the effects of cytokines, growth factors, and cell-ECM and cell-cell interactions.<sup>79</sup> Surrounded by a developing scar, podocytes and mesangial cells may lose these stimuli and become more fibroblastoid in appearance and function.<sup>80</sup> If this fibroblastoid transformation affects the tubular epithelium,<sup>81</sup> the result will be tubulointerstitial fibrosis and the accelerated loss of functioning nephrons.

The focality and segmental nature of this process in idiopathic FSGS suggests that maintenance of normal structures is regulated highly, with local breakdown of that maintenance permitting the initiation of a process that leads ultimately to scar formation. At the level of the whole organism, the apparent temporal clustering of cases within families suggests that there may be specific stimuli for the disease that are capable of activating a genetic program leading to ECM accumulation. Identifying such influences would be an essential step in addressing the etiology of FSGS. In the absence of an exact animal model, progress will continue to rely on the ongoing collaboration among geneticists, experimental pathologists, and clinicians. We have much to learn.

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