children transplanted for other diseases. No recur­
rences were observed and no evidence of thrombotic
microangiopathy was seen in the surgically removed
kidneys or in renal biopsies. It is our opinion that in
the HUS associated with Shiga toxin, renal trans­
plantation is indicated and has a very low risk of
recurrence. Graft outcomes are not different from
those seen in other diseases. Cyclosporin is known to
increase the risk of recurrent or de novo thrombotic
microangiopathy. It is therefore of interest that 12 of
the 19 children in our series received cyclosporin
in their immunosuppressive protocol. No thrombotic
microangiopathy was observed.

These findings subsequently have been confirmed by
a follow-up report from Minneapolis [21] and a large
French–German collaborative study. They found no
recurrences in HUS associated with diarrhoea, but a
substantial risk in the atypical sporadic or familial
forms.

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The diagnostic trash bin of focal and segmental glomerulosclerosis—an
effort to provide rational clinical guidelines

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In the age of evidence-based medicine, physicians are
facing the task of integrating their individual clinical
expertise and the best external evidence. To meet these
goals for the treatment of a patient with proteinuria,
normal renal function and the histological diagnosis
of focal and segmental glomerulosclerosis (FSGS)
turns out to be rather difficult, as the published evi­
dence, concerning the efficacy of immunosuppressive
therapy, is extremely confusing. The chance of
obtaining complete remission by steroid therapy has

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been reported to range from 0 to 70% [1,2]. This extreme variability immediately suggests that maybe different disease entities are subsumed under a single histological term.

It is interesting to note that sometimes nephrologists base their diagnosis and medical management of patients with glomerular diseases on the histological classification, ignoring important clinical features. Many other members of the medical profession have realized for a long time that tissues in general only have a limited spectrum of reactions to the huge variety of insults they may be confronted with. In inflammatory hepatic diseases, histological evaluation of liver tissue is only one part of the diagnostic workup, and hepatologists rarely treat a patient based on the pathologist’s report. In nephrology, unfortunately, the situation is often completely different: the final diagnosis is often made near the morgue, i.e. in the basement of the hospital by a pathologist who all too often is left alone by the clinician with little or no information on the patient’s actual status or medical history. Therefore, one should accept the pathologist’s report for what it actually is: the description of an injury pattern rather than the diagnosis of a disease entity. If so, it quickly becomes evident that additional clinical information is important to arrive at the correct diagnosis.

If FSGS is a uniform pattern of injury, that results from a variety of insults, therapeutic regimens have to be individualized.

Rennke and Klein [3] proposed the differentiation between two major disease complexes, both of which are characterized histologically by FSGS on biopsy. Whereas the primary form is a disease of the glomerular capillary wall, possibly at the level of the visceral epithelium, secondary FSGS results from a variety of conditions that promote glomerular capillary hypertension and increased transcapillary flow rates (see Table 1). Clinically, both entities are proteinuric conditions. An increase of urinary protein excretion is caused by a disturbance of the glomerular permselective properties, which determine the ability of the glomerular filter to restrict the passage of macromolecules from the blood into Bowman’s space. Large and/or anionic molecules are filtered less readily than smaller and/or cationic compounds (glomerular size and charge selectivity). The initial event in primary FSGS is a loss of charge selectivity. If the disease is severe, size selectivity can also be impaired. In the latter patients, the rate of response to steroid therapy is markedly reduced and prognosis is worse [4,5]. In secondary FSGS, the initial damage is also a loss of charge selectivity. In addition, however, as proteinuria increases, size selectivity is impaired gradually over time in these patients. Treatment with an angiotensin-converting enzyme (ACE) inhibitor is able to stabilize renal excretory function only as long as proteinuria is due to an isolated charge selectivity defect as is the case in microalbuminuric patients with diabetic nephropathy. In later stages, appropriate therapy improves size selectivity, but proteinuria is only reduced and the speed of loss of excretory kidney function is slowed, but not prevented [6].

The clinical distinction between primary and secondary FSGS is difficult. It is nonetheless essential, since immunosuppressive therapy is indicated only in the former condition. A patient with rapid onset of a full blown nephrotic syndrome is likely to suffer from primary FSGS, whereas a slowly developing proteinuric condition in a patient with a typical medical history, that includes conditions summarized in Table 1, is more likely to have secondary FSGS. Evaluation of biopsy material also provides some distinguishing features. The ultrastructural finding of relatively mild segmental foot process fusion over the non-sclerosed segments with lesser degrees of visceral cell hypertrophy and hyperplasia is indicative of secondary FSGS. In a systematic study of podocyte alterations in primary and secondary forms of FSGS, d’Agati and co-workers noted that the mean percentage of the glomerular surface area affected by foot process fusion was significantly less in obesity (42±24%) and reflux nephropathy (mean 25%) compared with primary FGS (65±23%) [7]. The greatest degree of foot process effacement was observed in the clinically most malignant forms of FSGS, the collapsing (82±24%) and cellular (87±21%) variants. Unfortunately, with regard to this parameter, remarkable overlap between the two forms is seen. Serum protein (and especially albumin) concentrations can additionally provide valuable information for the differential diagnosis. Some years ago, Praga et al. compared 19 patients with massive (5–10 g/day) proteinuria and normal serum albumin concentration (>35 g/l) and 16 patients with similar protein excretion but persistent hypoalbuminaemia (proteinuria 6–14 g/day, serum albumin concentration <30 g/l) [8]. In the normalbuminaemic group, he found healed crescentic glomerulonephritis, reflux nephropathy, scarred IgA nephropathy, unilateral renal agenesis and obesity, whereas patients with hypalbuminaemia suffered from membranous glomerulonephritis or minimal change glomerulopathy. Treatment with captoril reduced proteinuria only in patients with normoalbuminaemia, indicating that

Table 1. Classification of focal and segmental glomerulosclerosis

<table>
<thead>
<tr>
<th>1. Primary (idiopathic) FSGS</th>
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<tr>
<td>2. HIV- or heroin-associated FSGS</td>
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<tr>
<td>3. Secondary FSGS</td>
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<tr>
<td>A. With reduced renal mass such as in</td>
</tr>
<tr>
<td>Oligomeganephronia</td>
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<tr>
<td>Unilateral renal agenesis</td>
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<td>Renal dysplasia</td>
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<td>Reflux nephropathy</td>
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<td>Massive surgical ablation</td>
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<td>Renal allograft failure</td>
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<tr>
<td>Any advanced renal disease with reduction in functioning nephrons</td>
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<tr>
<td>B. With initially normal renal mass such as in</td>
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<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Obesity</td>
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<td>Cyanotic congenital heart failure</td>
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</table>
these patients actually suffer from secondary FSGS. Why these subjects maintain normoalbuminaemia despite heavy urinary protein loss, similar to what is seen in patients on continuous ambulatory peritoneal dialysis (CAPD), is unclear, but several hypotheses can be proposed. The most likely explanation is that tubular catabolism of albumin contributes to albumin loss in patients with primary FSGS. Consequently, hepatic albumin synthesis can no longer cope with such an additional burden and maintain serum albumin levels. The general failure of ACE inhibitors to reduce proteinuria in acute primary nephrotic states has been confirmed in animal studies [9]. Nevertheless, even in this condition, ACE inhibitors reduce urinary protein excretion in a certain proportion of patients [10]. We interpret this response as evidence that an additional component of secondary FSGS is present in these subjects. Reduction of proteinuria by ACE inhibitors can be used to quantify the degree of chronic non-specific damage. This estimate can provide useful information before immunosuppressive therapy is considered.

In summary, a variety of clinical parameters help to distinguish primary and secondary FSGS and therefore enable clinicians to identify those patients who are most likely to benefit from immunosuppressive therapy or administration of an ACE inhibitor. In patients with primary FSGS, the finding of selective proteinuria, i.e. of an isolated defect in glomerular charge selectivity, helps to identify candidates in whom immunosuppressive treatment has the greatest likelihood of success.

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