clarified. Therefore, it is important to consider tuberculosis in any member of an at-risk community with renal dysfunction in whom no specific renal diagnosis has been made.

Unfortunately, the spectrum of disease processes that produce a picture of interstitial nephritis is ill understood, let alone the mechanisms outlined here in cases associated directly or indirectly with tuberculous infection. Interstitial nephritis has never had the glamour of glomerulonephritis and has received much less attention. There is now a case for a radical reevaluation of this group of interstitial diseases to move them to a level of understanding comparable to that of glomerular disease and to pinpoint the complex etiological, genetic, and immunological processes that cause them.

DISCLOSURE
The authors declared no competing interests.

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Focal segmental glomerulosclerosis in IgA nephropathy: a result of primary podocyte injury?

H. Terence Cook[1]

Segmental sclerosis is frequently seen in IgA nephropathy and is an adverse prognostic indicator in the Oxford classification. Hill and colleagues have studied patients with IgA nephropathy and show that the segmental sclerotic lesions have features that suggest they are due to primary podocyte injury. They confirm the validity of the Oxford classification in predicting outcome and also show that categorizing the type of FSGS is of prognostic significance, with collapsing and cellular forms having the worst outcome.

Kidney International (2011) **79,** 581–583. doi:10.1038/ki.2010.521

Segmental glomerulosclerosis is characterized by a segmental increase in glomerular matrix with obliteration of capillary lumens and is a common morphological feature in biopsies, either as the only manifestation of glomerular injury or in combination with other pathology. Because the lesions usually affect only some glomeruli, this is termed focal segmental glomerulosclerosis (FSGS). There are at least two mechanisms by which such lesions develop. They may form secondary to an initial lesion of glomerular inflammation or necrosis as, for example, occurs in ANCA-associated glomerulonephritis, in which it is common to see biopsies with both active necrotizing lesions and segmental glomerulosclerosis. Or these lesions may form as a consequence of podocyte injury, as has been elegantly shown in the work of Kriz and co-workers by detailed analysis of animal models.[1] They have demonstrated that loss of podocytes with denuding of the glomerular basement membrane is followed by an adhesion to Bowman's capsule and then the formation of a sclerotic lesion. In some cases of primary FSGS there is evidence for a circulating toxin that damages the podocyte, whereas in other settings the podocyte damage may be secondary to hemodynamic changes as a response to loss of functioning nephrons.

Segmental sclerotic lesions are commonly seen in glomeruli in immunoglobulin A (IgA) nephropathy. In the recently published Oxford classification of IgA nephropathy,[2] the presence of segmental sclerosis (S) was one of the four features that were found to predict an adverse outcome. The others were mesangial hypercellularity (M), endocapillary

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hypercellularity (E), and tubulointerstitial fibrosis (T). The classification therefore gives a score for each of these variables, with M, E, and S having a value of 0 or 1 depending on whether the feature was present or absent, and T being given a score of 0, 1, or 2 corresponding to 0–25%, 26–50%, and >50% tubulointerstitial fibrosis. This international collaborative study showed that each of these variables had independent value in predicting clinical outcome. It is worth noting that in scoring segmental sclerosis the authors counted adhesions together with segmental sclerosis, since this improved interobserver agreement.

I think that many renal pathologists have assumed that the sclerotic lesions seen in IgA nephropathy form mainly as a consequence of healing of inflammatory lesions and thus act as a measure of previous inflammation. However, two related papers by Gary S. Hill and his co-workers in Paris in this issue of *Kidney International*[3,4] provide evidence that in many cases the sclerotic lesions in IgA nephropathy are more like those in primary FSGS. They have also examined the validity of the Oxford classification in their cohort of patients.

They studied 128 biopsies, which represented all their adult patients with IgA nephropathy and adequate biopsies over a 6-year period. This was a homogeneous group none of whom was treated with immunosuppressive agents after biopsy. As they report in the first paper,[3] the authors carried out a detailed analysis of the histological and immunohistochemical features of focal and segmental sclerosis in the biopsies. Firstly, they showed that it was very common to find foci where the glomerular tuft was adherent to Bowman's capsule without any inflammation in the underlying glomerular tuft. This was present in 41% of their cases of IgA nephropathy compared with only 8% of cases of lupus glomerulonephritis that they examined. In primary FSGS the figure was 69%. Thus, in terms of adhesions, IgA nephropathy behaves more like primary FSGS than like an immune complex glomerulonephritis. Secondly, the authors carried out a detailed study in a small subset of their cases looking at immunohistochemical markers of podocytes and parietal epithelial cells. In summary, they showed that at the site of capsular adhesions there was loss of podocyte markers such as GLEPP-1 and nephrin. In larger sclerotic lesions there was not only loss of podocyte markers but also accumulation of cells overlying the lesions that stained with markers of parietal epithelial cells such as cytokeratins or PAX2. These detailed studies suggest that, at least in some instances, the segmental sclerotic lesions in IgA nephropathy may represent a primary podocyte injury progressing to sclerosis rather than occurring secondary to post-inflammatory scarring. This would fit with *in vitro* evidence suggesting that when mesangial cells are stimulated by IgA from patients with IgA nephropathy they release mediators that lead to podocyte injury,[5,6] and also with the fact that excretion of podocytes in the urine reflects disease progression.[7]

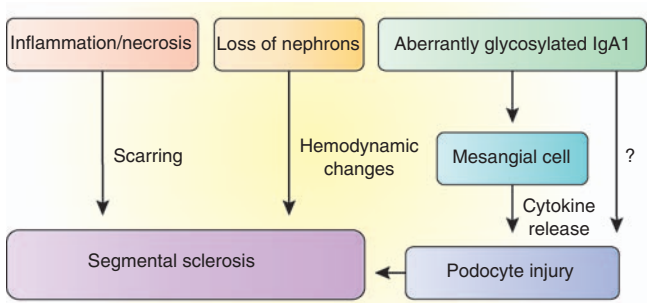

Figure 1 | Possible pathways by which segmental glomerulosclerosis develops in immunoglobulin A (IgA) nephropathy.

So far I have discussed segmental sclerosis in two categories—post-inflammatory and secondary to podocyte injury—but morphologically it is possible to recognize several patterns of segmental sclerosis, as was described by the pathologists who devised what is commonly referred to as the Columbia classification of FSGS.[8] They recognized four distinct morphological variants—collapsing, tip, cellular, and perihilar—and categorized the remaining forms as 'not otherwise specified.' In the second paper,[4] Hill and colleagues have categorized the types of segmental sclerosis seen in their biopsies according to a modified version of this classification. They looked at the clinical outcomes in their 128 patients and asked how progression of disease relates to the pathological features identified in the Oxford classification and also how the different types of FSGS are related to outcome. With regard to the Oxford classification, they show that in univariate analysis all of the four features—mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental sclerosis (S), and tubulointerstitial fibrosis (T)—were significantly more likely to be present in patients with a bad outcome, defined as doubling of serum creatinine or need for dialysis. In multivariate analysis mesangial hypercellularity was associated with bad outcome and tubulointerstitial scarring with rate of decline of renal function, with endocapillary hypercellularity almost reaching statistical significance. The authors conclude that their study confirms the validity of the Oxford criteria in a cohort with somewhat more advanced disease.

When they looked at the different types of segmental sclerosis, they found that they were able to classify almost all their cases using slightly modified Columbia criteria. One of the questions they had to deal with was to try to distinguish those lesions that are just post-inflammatory from those that are secondary to podocyte injury, and this was why they modified the criteria. In order to avoid including post-inflammatory scarring, they required that, at a minimum, the sclerotic lesions should also have either overlying epithelial proliferation or hyalinosis lesions. Their results show that they were able to successfully classify most of the biopsies with segmental sclerosis using this system. They show that patients with FSGS have a much worse renal survival than patients without FSGS, and also that the different types of FSGS they can identify have different effects on outcome, with the cellular and collapsing forms having particularly bad outcomes. In passing, it is worth noting

that they draw attention to the difficulties in deciding whether hypercellularity in Bowman's space represents a true crescent or proliferation of parietal epithelial cells—this may confound attempts to assess the prognostic significance of extracapillary proliferation.

There are some points that will need to be addressed in further studies. Firstly, as is noted above, the authors attempt to make the distinction between a post-inflammatory scar and an area of what they would call 'true' FSGS on the basis of the presence of hyalinosis lesions and/or epithelial hyperplasia. However, they do not provide evidence that these are valid criteria for making the distinction. Secondly, as they admit, they do not show that there is agreement between different pathologists in classifying the different types of FSGS. Thirdly, since their criteria for the cellular form of FSGS require the presence of endocapillary hypercellularity, it is clear that these biopsies would have been scored in the Oxford classification as E1, and so further analysis will be necessary to ask how this should be incorporated into the Oxford schema. Finally, as they themselves point out, 80% of their biopsies showed some form of FSGS, which is a higher proportion than previously reported. Thus, their results will need to be validated in other groups of patients.

In conclusion, these papers[3,4] should make us reconsider the significance of segmental sclerosis in IgA nephropathy. It is likely that there are at least three ways that segmental sclerosis may occur in glomeruli in IgA nephropathy (Figure 1): firstly, by post-inflammatory scarring; secondly, due to compensatory hemodynamic changes following loss of nephrons; and thirdly, as these papers emphasize, by primary podocyte damage, perhaps secondary to mediators released from mesangial cells. If a significant percentage of segmental sclerotic lesions represent the consequence of primary podocyte damage, it may lead us to consider new pathogenic mechanisms and may also have therapeutic consequences. In addition, we may need to refine the way in which we assess segmental sclerosis in determining the prognostic implications of histology. It is reassuring that the studies reported here support the conclusions of the Oxford classification, but they raise the possibility that the utility of the classification could be further enhanced by the distinguishing of different types of segmental sclerosis. That possibility will require confirmation of the results in other larger cohorts.

DISCLOSURE
The author declared no competing interests.

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Non-HLA antibodies in kidney allograft rejection: convincing concept in need of further evidence

Heinz Regele[1]

Mostly indirect evidence suggests an important pathogenic role for non-HLA anti-endothelial cell antibodies (AECAs) in both acute and chronic rejection. The lack of standardized screening assays for AECAs unfortunately hampers the systematic collection of data in multicenter trials. Diagnostic tests based on commercially available platforms could pave the way for testing larger patient cohorts, but they still suffer from some important limitations.

Kidney International (2011) **79,** 583–586. doi:10.1038/ki.2010.517

BACKGROUND

The clinical management of patients with circulating alloantibodies in renal transplantation is almost exclusively focused on antibodies against ABO blood group antigens and the human leukocyte antigen (HLA) system. There is solid and universally accepted evidence for an important role of anti-HLA antibodies in both early/acute and late/chronic rejection of renal allografts. We now possess a number of different cell-based assays (cytotoxic or flow cytometric cross-match) and solid-phase assays (enzyme-linked immunosorbent assay, HLA-coated beads) that reliably detect potentially alloreactive antibodies (Figure 1). The recently

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