The Glomerular Basement Membrane in Long-Term Allografts with Heavy Proteinuria

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The early failure of a transplanted kidney is a well known event which most often is provoked by tissue incompatibility. The late failure of renal allografts, so-called chronic rejection which leads to a slowly decreasing graft function is less well known from a pathogenetic viewpoint. Early reports by Porter and his group stressed arterial damage as the most important morphologic lesion in chronic rejection. However, in recent years, glomerular disease has also attracted attention.

It is generally agreed that lesions of the glomerular basement membrane (BM) (eg deposits) can reflect pathogenetic mechanisms. We have therefore carried out an electronmicroscopic study of the basement membrane in allograft kidneys with severe glomerular lesions. The aim of the study was to gain more precise information about the ultrastructure and location of BM abnormalities in late occurring glomerular transplant disease.

The study is part of a more extensive investigation of late failures in patients who received kidney transplants between 1964 and 1971. Excluding early deaths and graft failures 125 recipients with grafts functioning from one to more than eight years were available for analysis. The criteria for selection of cases for further studies were the presence of proteinuria of more than 3 g per day with or without steadily declining graft function. According to these criteria transplant disease developed in 22 patients. Renal biopsies for electronmicroscopy were available in 14 of these cases. Protein excretion varied between 4 and 21 g per day and serum albumin was between 4 g and 1 g per 100 ml. Half of these patients developed a typical nephrotic syndrome. During the period of investigation the graft had to be removed from 6 of the patients.

By light microscopy all the morphological features typical of glomerulonephritis were present. Endothelial, mesangial and epithelial cell proliferation were present in various degrees and mesangial thickening was severe in most cases. However, the lesions occurred in a very variable and haphazard
manner making it impossible to compare the glomerular disease with any known type of native kidney glomerulonephritis. IgG, IgM and complement were demonstrated by immunofluorescence in all cases. In many the fluorescence was very strong. The pattern was most often a combination of a finely linear and a finely granular deposit. Other classes of immunoglobulins and other proteins were sometimes detected.

On electron microscopy the amount of mesangial matrix was increased in nearly all cases and peripheral mesangial interposition was very frequent. The ultrastructure of the basement membrane was either normal or showed different kinds of abnormalities, which we have divided into five main types (Figures 1-4).

Type 1 was an electron-lucent, flocculent material which usually occurred in a subendothelial position. This lesion has been described by several investigators in allografts. Immunopathologic studies by others have suggested the presence of immunoglobulins and complement in this lesion.

Type 2 abnormal basement membrane structure was an electron-dense granular material with a structure similar to that earlier described in so-called deposits in many types of native kidney glomerulonephritis. In acute

![Image](image_url)

**Figure 1.** Abnormal basement membrane structure (ABMS) type 1 in a peripheral capillary loop. An electron-lucent, flocculent substance (arrowed) is present below the endothelium (EN). Epithelial cells are indicated by EP. x 49,000
post-streptococcal nephritis it has been found as localized 'humps' in a sub-
epithelial position. In Goodpasture's syndrome which is thought to be caused 
by anti basement-membrane antibodies, this kind of granular material has 
been found in a subendothelial location.

In our allografts the position of this material was very variable; it could 
be seen subepithelial, intramembranous or subendothelial, but was found 
most often in a mesangial position. Subepithelial humps were never seen. In 
two cases a pattern identical with that of native kidney membranous glomeru-
lonephritis was seen. They were subepithelial patches of electron dense 
granular material between 'spikes' of normal looking BM. This pattern has 
not previously been described in allografts. One of the patients had non-
glomerular disease in his own kidneys.

Type 3 were small vesicular particles 300-600 Å in diameter surrounded 
by a triple-layered membrane. They usually occurred in large clusters in the 
BM, the mesangial matrix or the urinary space.

Type 4 were larger vesicular particles 700-2000 Å in diameter, also sur-
rrounded by triple-layered membranes. 

Vesicular structures similar to our types 3 and 4 have been observed in
a few cases in allografts before and they have then been called virus-like particles. However, several facts point against this interpretation and it seems more probable that they are either degradation products or the result of abnormal basement membrane synthesis.

Type 5 had irregular membranous shapes 0.2μ in diameter either ring shaped or with open ends. In high magnification, the wall when cut at right angles is about 250 Å thick and consists of two parallel layers with a narrow space in between. When cut obliquely the wall sometimes appears cross-banded and when cut tangentially a granular pattern is seen. The nature of

![Figure 3. ABMS type 3. A cluster of vesicular structures with a dense content, 300-600 Å in diameter are located outside a process of an epithelial cell (EP). x 59,000](image)

this type of particle is difficult to judge. These particles have not been described earlier in allografts, but a few authors have seen similar structures in other diseases, eg in diabetes and in ischaemic obsolescent glomeruli.

The frequency and distribution of BM lesions in these biopsies was very variable and all 5 types of abnormal BM structures could be present in one glomerulus.
SUMMARY

In allotransplant disease several pathogenetic factors can be of importance. They include immunopathological mechanisms resulting from persistence of factors which operated against the original kidneys, or from histoincompatibility between graft and host. Immunological attack without relation either to incompatibility or original disease, that is a de novo glomerulonephritis, may also occur. Furthermore, ischaemic glomerular damage may be caused by the intimal thickening of the arteries and the influence of treatment itself.

Eight of our patients had non-glomerular native renal disease, so that transmission of disease can be ruled out. Of the remaining patients only one seemed to represent transmission of a rapidly progressive glomerulonephritis. Some of the lesions described here can occur also in non-immunological diseases, but many data in this as well as in earlier investigations point toward an immunological pathogenesis of late allograft failure. The antigen is unknown. It could be identical with a histocompatibility antigen, but there are also other possibilities.

In conclusion it can be stated that the severe transplant disease described here displays ultrastructural BM lesions of a rather complicated nature. The
The pathogenesis of this glomerular disease cannot be stated with confidence at the present, but in all probability several different mechanisms, immunological as well as non-immunological, are operating.

OPEN DISCUSSION

F P BRUNNER (Basle): I would like to ask Dr Olsen whether the changes seen in the first biopsies had been seen in other patients without proteinuria? We have found the same thickening of the basement membrane on routine biopsy of many transplants, without proteinuria.

OLSEN: I think you are referring to our type 1 appearance. This has been reported many times in allografts and also, in very few cases, in isografts. But I don't think that exactly similar material has been seen outside the transplant situation.

BRUNNER: Could you comment whether you found the same lesion without proteinuria?

OLSEN: We have only examined biopsies on patients with late disease and severe proteinuria. When they had a normal graft function we did not biopsy them.

K LANGE (New York): Why in your type 1 and type 2 biopsies, do you want to exclude the interpretation of glomerulonephritis, transmitted from the patients' original disease?

OLSEN: I think you are referring to the case of ours which we regarded as a transmitted glomerular nephritis, where we had exactly the same electron-microscopic picture in the native kidney as in the graft: namely extensive subendothelial deposits of our type 2. In addition the immunofluorescence picture in those two kidneys was quite similar. I can add that the proteinuria occurred rather early in this case, a few months after transplantation. No such similarity was present in any other case.

J S CAMERON (London): Your finding of an extramembranous deposit is very interesting and very important. Could you tell us whether either of the two patients who showed this pattern had received horse antilymphocyte globulin, either recently or distantly?

POSBORG PETERSEN (Co-author): I'm the clinician in this paper. None of
these patients received ALG. On the question of transmission, of course this
is always hard to ascertain if you are not able to demonstrate anti-GBM cir-
culating in the serum. However, as mentioned in this paper half of our patients
did not have glomerulonephritis as the disease in their native kidneys.