

# Immunology and Diseases of the Kidney

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The emphasis of this paper is the review of several aspects of renal disease which have immunologic overtones and clinical relevance. The pathogenesis of several subtypes of glomerulonephritis will be discussed, the immunologic implications of amyloidosis will be noted, and the relation between immune mechanisms and tubulointerstitial disease will be mentioned. The discussion will then be completed by an analysis of the prognosis of the aforementioned renal diseases, and by an attempt to place contemporary therapeutic modalities in a proper perspective.

Before treating each of these subjects, it is worth acknowledging the important contribution which evaluation of renal biopsy tissue has made to our understanding of the relation between immune mechanisms and renal disease. The availability of fresh tissue from biopsies in living patients has allowed adequate evaluation by immunofluorescent microscopy and electron microscopy (EM). Each of these techniques has provided important and complementary information about the nature of fine structural damage induced by immune mechanisms.<sup>1</sup>

## **Immune Complex Disease.**

### *Proliferative Glomerulonephritis.*

Figure 1 is an immunofluorescent stain for IgG in the glomerulus of a patient with acute post-streptococcal glomerulonephritis. A fluorescing antibody against IgG has been layered over a quick-frozen biopsy specimen and become attached to the IgG. The positive fluorescent lumps are thought to represent deposits of antigen-antibody

complexes adjacent to the capillary basement membranes and in the mesangium (the supporting stalk) of the glomerulus. It is assumed that these histologic abnormalities reflect the following series of pathogenic events: an antigenic derivative of the streptococcus has entered the circulation; an antibody response has developed; soluble immune complexes have been formed in a state of antigen excess; the complexes have precipitated in the glomerulus; complement components have been fixed; and the complement cascade activated with resultant production of inflammation and damage to the glomerulus. Under certain circumstances immunofluorescent stains may identify complexes containing IgM and IgA as well as various components of the complement system and fibrinogen.<sup>1</sup>

Figure 2 is a light microscopic view of a glomerulus from another patient with acute post-streptococcal glomerulonephritis. This picture is the light microscopic correlate of the immunofluorescent preparation described above. The features of a diffuse proliferative glomerulonephritis including swelling of the tufts, a marked increase in cellularity (primarily mesangial cells), occlusion of the capillary loops, and an influx of polymorphonuclear leukocytes are present. It is likely that the leukocytes have been attracted by leukotactic factors released by activation of the complement cascade.<sup>1</sup>

Figure 3 is an EM preparation showing part of the ultrastructure of a glomerulus from the biopsy of a patient with poststreptococcal glomerulonephritis. The pathologic findings include fusion of the foot processes of the epithelial cells and deposition of large, electron-dense deposits adjacent to the sub-endothelial surface of the basement membrane. It is thought that these deposits represent the immune complexes which have been discussed above. Post-

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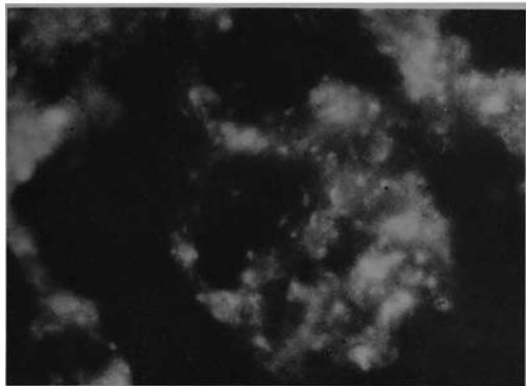


Fig 1—Immunofluorescent microscopic preparation (anti-IgG) of a portion of a glomerulus from a patient with poststreptococcal glomerulonephritis. Note the "lump-bumpy" pattern. ( $\times 1500$ ).

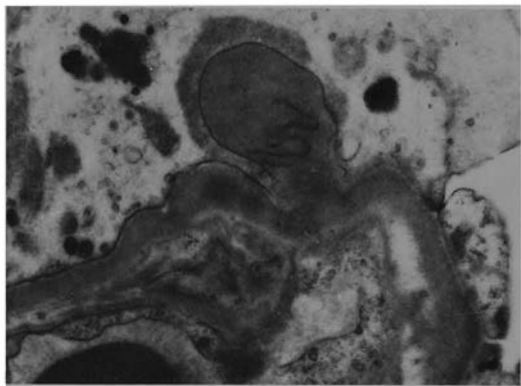


Fig 3—Electron microscopic preparation of a portion of a glomerulus from a patient with acute poststreptococcal glomerulonephritis. Note the large subepithelial electron-dense deposit, "hump" ( $\times 32,000$ ).

streptococcal glomerulonephritis is characteristically associated with large "humplike" deposits in the subepithelial position, but this finding is not absolutely diagnostic because a similar locus of depositon has been noted in other immune-complex-mediated renal diseases such as syphilis with nephritis.<sup>2</sup>

Subsequently, it will become evident that immune complexes may localize on either side of the basement membrane. The reason a deposit may locate in a given site (either subepithelial, subendothelial, or intramembranous) is not entirely defined. Current theory holds that the location of immune-complex deposits may depend upon their physical characteristics, with smaller deposits

(formed by combination of antigen with low affinity antibody) localizing in a subepithelial site and large complexes localizing subendothelially.<sup>1</sup> There is also evidence to suggest that complement-binding sites may be present in the region of the epithelial cell foot processes.<sup>3</sup> Complexes which have fixed complement prior to traversing the basement membrane may be snared by attachment of the complement with these receptors.

Figure 4 is the light microscopic view of two glomeruli from a patient with a staphylococcal abscess

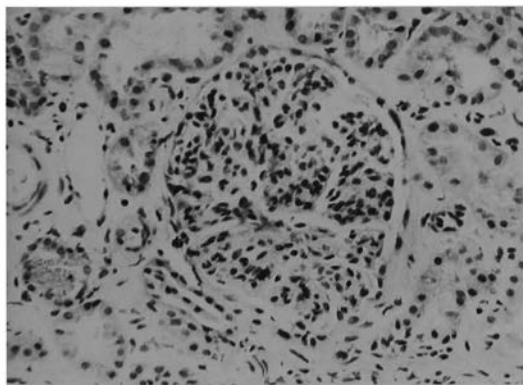


Fig 2—Light microscopic preparation (H & E) of a portion of a renal biopsy from a patient with diffuse proliferative glomerulonephritis following a streptococcal infection ( $\times 200$ ).

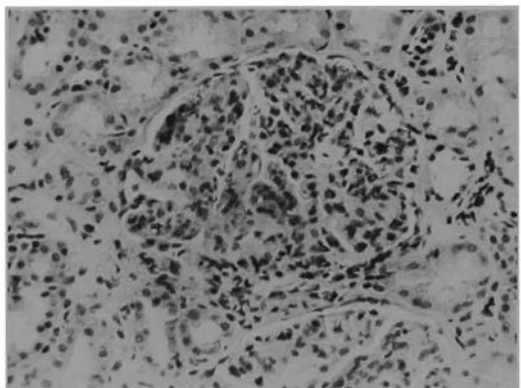


Fig 4—Light microscopic preparation (H & E) of a portion of a renal biopsy from a patient with "shunt nephritis" secondary to staphylococcal infection. Note that glomerulus in the center and the portion of the glomerulus at the lower margin both show proliferative changes ( $\times 200$ ).

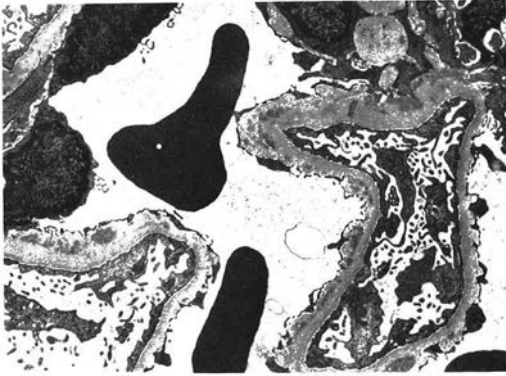


Fig 5—Electron microscopic preparation of a portion of a glomerulus from a patient with systemic lupus erythematosus and a diffuse proliferative lesion by light microscopy. Note the large subendothelial deposits ( $\times 10,000$ ).

infection of a ventriculojugular shunt which had been made because of hydrocephalus. The lesion is a diffuse proliferative glomerulonephritis and could not be distinguished from the poststreptococcal lesion by conventional light microscopic or immunofluorescent studies. Figure 5 is an EM study showing a large subendothelial deposit from a patient with lupus erythematosus and proliferative glomerulonephritis by light microscopy. The subendothelial region is the favored site of deposition in lupus.<sup>1</sup> Figure 6 shows the light microscopic appearance of a glomerulus from a patient with focal proliferative glomerulonephritis. Note that segments of the glomerular tuft

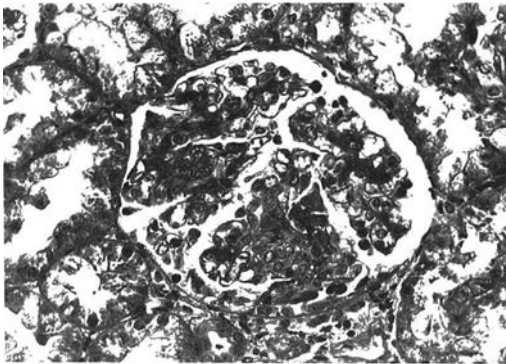


Fig 6—Light microscopic preparation (H & E) of a portion of a renal biopsy from a patient with systemic lupus erythematosus showing a focal proliferative lesion ( $\times 400$ ).

appear to have normal cellularity and that the inflammatory reaction is less severe than in the cases noted earlier. Immunofluorescent and electron microscopic studies would show the immune deposits to be less numerous and to have more of a mesangial location than in the diffuse proliferative lesion. IgA deposition is seen with greater frequency in the mesangium in focal lesions.<sup>1</sup>

After a review of the first six figures it is clear that the classic light microscopic picture of proliferative glomerulonephritis, either diffuse or focal, reflects a disorder of immune-complex deposition in the region of the glomerular capillary basement membrane and mesangium. From observation of the pathologic material it is also easy to envision that the inflammatory process would lead to leakage of albumin, red blood cells, and immunoproteins into the urine with development of an "active" urine sediment. The mediators of inflammation in proliferative lesions are not well understood but are thought to be released by activation of the terminal portion of the complement cascade.<sup>1</sup> Serum levels of early-reacting complement components and  $C_3$  are frequently, but not invariably, reduced in patients with immune-complex-mediated proliferative lesions. The antigenic substances which may be involved in this type of lesion are numerous and will be discussed below.

#### *Membranous Glomerulonephritis.*

Another histologic pattern of renal involvement that is almost certainly mediated by glomerular immune-complex deposition is membranous glomerulonephritis (Fig 7). Note that the only abnormality is marked thickening of the capillary basement mem-

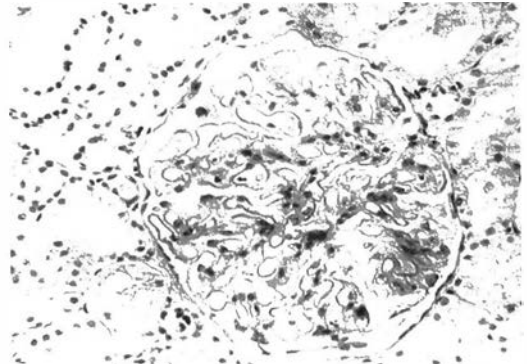


Fig 7—Light microscopic preparation (PAS) of a portion of a glomerulus from a patient with membranous glomerulonephritis ( $\times 200$ ).

brane. Figure 8 demonstrates that the cause of the basement membrane thickening is the presence of numerous dense deposits along the epithelial border of the basement membrane with projections of basement membranelike material interposed between the deposits. Fusion of the epithelial cell foot processes adds to the breadth of the capillary wall and probably has been induced by the marked albumin leak which most of these patients experience. Immunofluorescent studies show a fine granular deposition of IgG and IgM as would be expected from the location of the deposits on EM.<sup>1</sup> On occasion, complement components also may be identified in the glomerular capillaries, but this occurs with much less frequency and in a more scant distribution than in proliferative lesions. Serum complement levels are usually normal in membranous glomerulonephritis. The absence of an inflammatory response may relate to the presence of immune complexes which fix complement poorly, or to an impotent complement system. As might be expected, patients with the membranous lesion usually develop a nephrotic syndrome and tend to have a less "active" sediment than those with a proliferative process.

#### *Antigens Associated with Immune Complex Disease.*

There are a large number of disorders in which antigen-antibody complex deposition is recognized or suspected as being the cause of renal disease.<sup>1</sup> Exogenous antigens, particularly drugs and foreign proteins, may induce an immune-complex glomerulonephritis with the appearance of either a proliferative

or a membranous lesion. A number of bacterial organisms including the streptococcus, staphylococcus, pneumococcus, and treponema pallidum have induced a complex-mediated nephritis which is usually proliferative in pattern. Plasmodium malariae may cause either a proliferative or membranous nephritis. It is suspected that numerous viral agents may incite immune-complex-mediated renal disease. Both hepatitis-B virus and the Barr-Epstein virus have been clearly identified as providing the antigenic stimulus for an immune-complex-mediated disorder. The former has been incriminated as inducing proliferative and membranous lesions as well as a generalized arteritis.

Perhaps the best defined of all immune-complex-mediated renal diseases is that associated with systemic lupus erythematosus. It is clear that in this disorder endogenous cellular antigen (DNA, RNA, and numerous derivative substances) provides an inexhaustible source of antigen for complex formation. Diffuse proliferative, focal proliferative, and membranous nephropathy have been identified in patients with systemic lupus.

Recently, considerable excitement has been generated by the discovery of other endogenously-produced antigens which may cause renal disease in man. A derivative of tubular brush border has been identified as the antigenic component of an immune-complex-induced membranous glomerulonephritis in patients with sickle cell anemia.<sup>4</sup> The nephrotic syndrome secondary to a membranous lesion has been recognized in some patients with solid tumors of the lung and colon; in a patient with the latter neoplasm carcinoembryonic antigen has been identified as part of the complex on the basement membrane.<sup>5</sup> Immune-complex glomerulonephritis may be seen with some frequency in patients with cryoglobulinemia, particularly those in whom there is a mixed IgG-IgM cryoglobulin with rheumatoid factor activity.<sup>6</sup>

After reviewing all of the known causes of immune-complex-mediated renal disease one is left with an unrecognized antigen as the stimulus for the disease process in most cases of the idiopathic nephrotic syndrome. This includes patients with focal proliferative, diffuse proliferative, or membranous lesions. The offending antigen is also unknown in such syndromes as Wegener's granulomatosis and Henoch-Schönlein purpura. Within the next few years the inciting antigens will be identified in many of these disorders and may well prove to be viral agents.

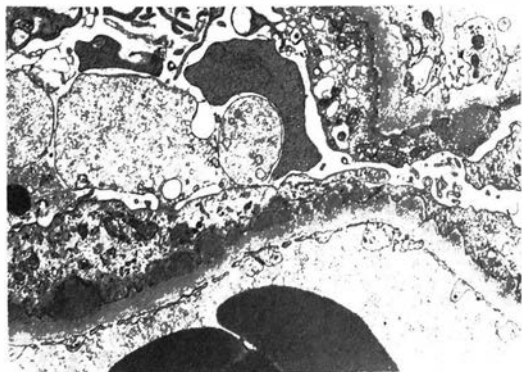


Fig 8—Electron microscopic preparation of a portion of a glomerulus from a patient with membranous glomerulonephritis. Note the numerous subepithelial deposits. ( $\times 15,800$ ).

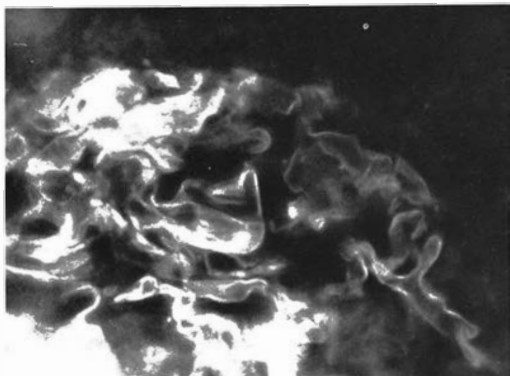


Fig 9—Immunofluorescent preparation (IgG) from a portion of a biopsy of a patient with antibasement membrane antibody disease. Note the linear pattern of fluorescence ( $\times 1500$ ).

#### Antibasement Membrane Antibody Disease.

Figure 9 is an immunofluorescent stain showing homogeneous linear deposition of IgG along the basement membrane of the glomerulus. This pattern is thought to represent the attachment of antibasement membrane antibody to some antigenic component in the basement membrane. The antibody is usually IgG although linear deposition of IgM and complement have also been described in some cases. In many patients, circulating antibody can be demonstrated by allowing the patient's serum to react with sections of normal human kidney. The mechanism whereby deposition of antibasement membrane antibody leads to renal damage is uncertain, but that severe damage can be induced is amply demonstrated by Figure 10 which shows a proliferative lesion of both the mesangial and epithelial cells. Proliferation of the latter with crescent formation is apparently induced by the leakage of large molecular weight fibrin precursors into Bowman's space through tears in the basement membrane.<sup>1</sup>

An occasional epithelial crescent can be found in virtually any type of renal disease, but involvement of essentially the entire glomerular population is seen in two circumstances: rapidly progressive glomerulonephritis and Goodpasture's syndrome. Many patients with the clinical picture of idiopathic, rapidly progressive glomerulonephritis and most patients with Goodpasture's syndrome (lung hemorrhage and nephritis) will display evidence of antibasement membrane antibody as the cause of renal damage. The offending antibody in Goodpasture's syndrome

cross-reacts with pulmonary basement membrane and is thought to induce the pulmonary as well as the renal disease. The stimulus for production of antibasement membrane antibody is uncertain, but damage to pulmonary or glomerular basement membrane by viral agents or chemical irritants with uncovering of hidden antigenic sites has been suggested as a mechanism.<sup>1</sup> As might be expected, patients with antibasement membrane antibody disease and crescent formation frequently have very "active" urine sediments and may be nephrotic.

#### Glomerulonephritis and Activation of the Alternate Complement Pathway (Membranoproliferative Glomerulonephritis).

In general terms, when the complement system is activated in the disorders discussed above, it is probably brought about by the classic pathway ( $C_1 \rightarrow C_4 \rightarrow C_2 \rightarrow C_3$ ). Recently, however, evidence has begun to accumulate suggesting that activation of the latter part of the complement cascade via the so-called "alternate pathway" may be of importance in inducing renal damage.<sup>1</sup> Activation of the "alternate pathway" has been noted in some cases of post-streptococcal glomerulonephritis, but the most provocative evidence for a role of this pathway has been observed in patients with the pattern of membranoproliferative or mesangiosclerotic glomerulonephritis.

West and his associates originally described a group of children with heavy proteinuria: "active" urine sediments; low circulating  $C_3$  levels; light mi-

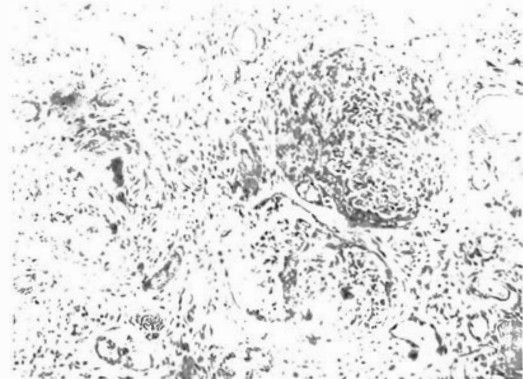


Fig 10—Light microscopic preparation (H & E) from the renal biopsy of a patient with antibasement membrane antibody disease. Note the marked crescent formation and interstitial inflammatory reaction ( $\times 80$ ).

microscopic evidence of cellular proliferation, increased mesangial matrix, and a tendency to lobulation of the glomerular tufts; glomerular  $C_3$  deposition with little or no accompanying IgG or IgM by immunofluorescence; and a circulating activator of  $C_3$  ( $C_3$  nephritic factor).<sup>8</sup> The patients were considered to be a unique group and designated as having membranoproliferative glomerulonephritis with hypocomplementemia. Subsequently, it has been recognized that patients with membranoproliferative lesions are not a homogeneous group; and they have now been subdivided into two groups, primarily on the basis of EM features. Type I patients show evidence of splitting and reduplication of the basement membrane and have electron dense deposits. The activation of early complement components and the infrequent demonstration of circulating  $C_3$  nephritic factor in this group suggest the presence of a classic immune-complex-mediated disease. Type II patients, on the other hand, show a marked homogeneous increase in density of the glomerular capillary basement membrane without evidence of deposits (dense deposit disease).<sup>1</sup> Circulating  $C_3$  nephritic factor is usually present and early reactive complement components are normal. The nature of the dense transformation of the basement membrane is uncertain and the pathogenesis of this disorder remains to be defined.

#### Lipoid Nephrosis of Childhood (Nil Disease).

Another disorder which classically has been considered with the glomerulonephritides is lipoid nephrosis of childhood or nil disease. This is the most common cause of the nephrotic syndrome in childhood. The only recognizable histologic abnormality in patients with this disturbance is fusion of the foot processes recognizable on EM (Fig 11). The etiology of this disorder is uncertain, but renewed interest in the possibility of its being an immunologic disease has been kindled by the discovery of a similar lesion in several patients with Hodgkin's disease who have the nephrotic syndrome. Since current thought suggests that Hodgkin's disease may be a T-cell disturbance, it has been suggested that nil disease reflects a disturbance of cellular immunity.<sup>9</sup>

#### Focal Segmental Sclerosis.

A subgroup of children with the idiopathic nephrotic syndrome who do not respond well to the therapeutic agents mentioned below has been described recently. This group frequently has mild microscopic hematuria as opposed to the children with typical nil

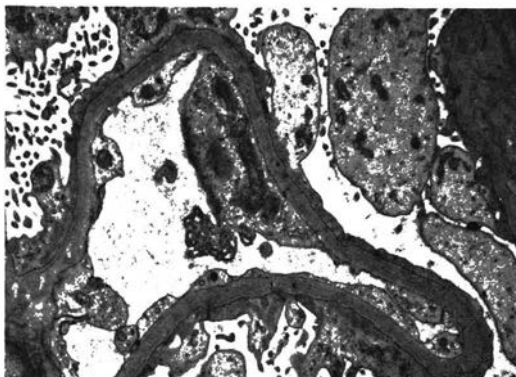


Fig 11—Electron microscopic preparation of a portion of a renal biopsy from a patient with "nil disease." Note the normal appearing basement membrane, the absence of deposits, and the presence of fused foot processes ( $\times 14,000$ ).

disease who show no "activity" of the urinary sediment. Segmental sclerosis beginning in the juxtamedullary glomeruli and progressing to become a diffuse generalized involvement with ultimate global sclerosis has been identified in these children.

#### Amyloidosis.

Amyloidosis of the kidney is an interesting cause of the nephrotic syndrome which, on clinical grounds, may be confused with the glomerular diseases previously mentioned and which has a close relationship to the body's immune systems. On light microscopy the glomerular mesangium may appear infiltrated with a homogeneous material and the basement membrane may be thickened. Such a pattern may be confused with diabetic nephropathy or a late stage of immune-complex-mediated nephropathy which has led to significant sclerosis; staining with Congo red and viewing the sections under polarized light will demonstrate the typical apple-green birefringence if amyloid fibrils are present, however. The amyloid fibril also gives a characteristic appearance by EM as demonstrated in Figure 12.

Exciting recent work has provided a clearer understanding of the nature of amyloid. The amyloid fibrils seen in patients with B-cell dyscrasias, either multiple myeloma or primary amyloidosis, are thought to be composed of light-chain derivatives of the paraprotein produced by the abnormal B cells.<sup>10</sup> An entirely unique protein (AA protein) has been identified as composing the amyloid of patients with secondary amyloidosis related to chronic infection or

familial Mediterranean fever.<sup>10</sup> The reason that these different proteins have similar refractive properties and give a similar appearance on EM relates to the fact that they share the same beta-pleated arrangement of their amino acid components.

#### **Tubulointerstitial Disease.**

Investigation of the immunologic aspects of tubulointerstitial disease has been overshadowed by the tidal wave of studies evaluating the mechanisms of immunologic glomerular damage. Interest in the interstitium has been rekindled, however, by the discovery of an association between the ingestion of certain drugs and the development of interstitial nephritis. It is now evident that a molecular moiety of several members of the penicillin family may act as a hapten, combine with an endogenous protein to make a complete antigen, stimulate an antibody response, and ultimately result in precipitation of immune complexes in the region of the tubular basement membranes with incitement of a diffuse interstitial inflammatory reaction.<sup>11</sup> Autoantibodies to tubular basement membrane have also been demonstrated and incriminated as the cause of interstitial infiltration in lupus erythematosus, the transplanted kidney, and the crescentic disease of Goodpasture's syndrome and rapidly progressive glomerulonephritis (Fig 10).<sup>1</sup> Studies in animals have suggested that chronic pyelonephritis may be perpetuated by cellular immune mechanisms originally activated by the release of antigenic substances from tissues damaged by invading pathogenic bacteria.<sup>1</sup>

#### **Prognosis and Treatment.**

Having reviewed the current thoughts about the pathogenesis and histologic appearance of immunologically related renal disease, we ought now to attempt to apply this information in a fashion that will be beneficial to a given patient. Such application is practical in two major areas, prognosis and treatment. The importance of a renal biopsy in obtaining tissue for evaluation is obvious. Its importance in obtaining practical prognostic and therapeutic information which will help the patient is variable. For example, a renal biopsy is not likely to be helpful in the management of the patient with obvious interstitial disease as manifested by leukocytes and a relatively scant amount of albumin in the urine. If the disease is drug induced, it will probably resolve spontaneously with discontinuation of the offending agent.

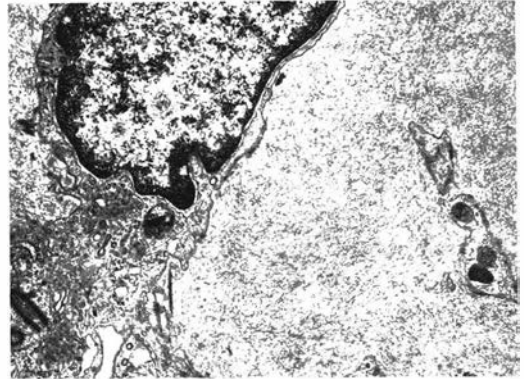


Fig 12—Electron microscopic preparation of a portion of a glomerulus showing amyloid fibrils ( $\times 24,000$ ).

It is among patients with an unexplained nephrotic syndrome that evaluation of an adequate renal biopsy is most helpful.

#### *Prognosis.*

Patients with focal proliferative glomerulonephritis, lipoid nephrosis, and membranous glomerulonephritis have a relatively good prognosis either treated or untreated. Lupus patients with a focal proliferative lesion may live for years without showing evidence of deterioration in renal function. Many children with nil disease undergo a spontaneous remission and when deterioration in function occurs, it usually progresses very slowly. Patients with drug-related or tumor-related membranous nephropathy may have remission of their disease with removal of the offending antigen; those with an idiopathic membranous lesion, or lupus and a membranous lesion, may spontaneously remit or remain nephrotic with an unchanged creatinine clearance for years.<sup>1</sup>

On the other hand, patients with diffuse proliferative lesions unrelated to a specific infecting organism, particularly those with lupus erythematosus, have a poor prognosis. Most patients with ant basement membrane antibody disease and marked crescent formation will reach the terminal stage within two years.

Patients with membranoproliferative glomerulonephritis tend to have an intermediate prognosis with most showing progressive deterioration in renal function to its terminal stage in 5 to 12 years.<sup>1</sup> Amyloid patients and patients with segmental sclerosis also demonstrate an intermediate prognosis.

As knowledge accumulates, we may feel obliged

to perform a biopsy on every patient with chronic renal disease who is progressing toward its terminal stage in order to determine his or her ultimate candidacy as a transplant recipient. Antibasement membrane antibody disease, membranoproliferative glomerulonephritis, and focal segmental sclerosis have been recognized as recurring in grafted kidneys, ultimately leading to their failure. Indeed, it is now considered inappropriate to transplant a patient with antibasement membrane antibody disease if circulating antibodies can be demonstrated in his or her serum.<sup>1</sup>

#### *Treatment.*

Much has been written about the treatment of immunologically related renal diseases. Unfortunately, except for the management of two disorders, nil disease and Wegener's granulomatosis, there is little agreement and much bias about specific treatment. Diuretics are of great symptomatic value in edematous states but have no effect on basic pathogenic mechanisms. The agents which have been used as possible inhibitors of immune mechanisms include corticosteroids, antimetabolites, and alkylating agents. Each of these drugs has significant toxicity, particularly when used over a prolonged period, and their modes of action remain uncertain. The natural history of many of the immunologically related renal diseases is variable and capricious. Consequently, controlled studies, involving numerous patients and extending over a long period of time, are needed to establish the efficacy of any drug regimen. These studies have not been done. Outlined below is a personal assessment of the state of the art of immunotherapy in renal disease.

As already mentioned there seems to be uniform agreement that therapy is effective in those patients with nil disease and those with Wegener's granulomatosis. In lipid nephrosis the administration of corticosteroids will enhance the rate of remission, and the duration of remission after relapse can be prolonged by supplementing the steroids with cyclophosphamide or chlorambucil. Nil disease in Hodgkin's disease will subside with treatment of the lymphoma. Cyclophosphamide is effective in producing a sustained remission in the renal disease of Wegener's granulomatosis, a disorder which was formerly uniformly lethal.<sup>12</sup>

Treatment in a patient with immune-complex-mediated diffuse proliferative or focal glomerulonephritis is most effective if it can be directed at

eradication of a recognizable inciting antigen. Obviously, this is most successful if the antigen is derived from an infectious agent such as a staphylococcus or a spirochete. If the antigen cannot be removed as in lupus erythematosus, one must carefully weigh the potential benefits of therapy against the possibility of significant drug toxicity. It is my impression that most authorities would tend not to treat a focal proliferative lesion in lupus but would be aggressive in the management of a patient with a diffuse proliferative lesion. In the latter case, one might use a combination of steroids and either azothioprine or cyclophosphamide in doses sufficient to return serologic indicators of disease activity such as C<sub>3</sub> levels or anti-DNA antibody levels to normal.<sup>13</sup>

The management of membranous glomerulonephritis of either the idiopathic type or that associated with lupus erythematosus is equally perplexing. Controlled studies done in Great Britain in the 60s suggested that no therapy was effective in the idiopathic membranous lesion.<sup>14</sup> However, recent uncontrolled retrospective analysis<sup>15,16</sup> and an ongoing American cooperative study<sup>17</sup> suggest that prolonged steroid administration may be helpful.

Therapy for patients with crescentic disease has included steroids, azothioprine, cyclophosphamide, and anticoagulation agents. Isolated cases treated with these agents have shown good responses, but there have been no controlled studies to substantiate this fact. Steroids have been advocated as being of value in membranoproliferative lesions,<sup>18</sup> but here again there have been no comparisons with a comparable untreated population.

There seems to be no specific treatment for amyloidosis. However, amyloid deposition may be inhibited by treatment of an underlying myelomatous state or by correction of a smoldering infectious process.<sup>1</sup> Success has been reported recently in reducing proteinuria in amyloid disease secondary to familial Mediterranean fever by the administration of colchicine.<sup>10</sup>

#### **Summary.**

The relation between the immunologic systems and renal disease has been briefly reviewed and several pathogenic immunologic mechanisms have been correlated with the histologic pictures which they produce; this information has then been related to contemporary thoughts about prognosis and therapy. Much has been learned, but there is obviously much



more to be done, particularly in the areas of prevention and treatment.

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