Glomerulonephritis

WILLIAM F. FALLS, JR., M.D.

Medical Service, Veterans Administration Hospital, and Department of Medicine, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

In this paper the histologic picture of the most common disorders usually classified under the heading of glomerulonephritis will be reviewed, and the subject of angiitis will be briefly addressed. A special effort will be made to relate renal biopsy findings to the immunologically mediated pathogenetic process which is thought to be operative in each case. Where it seems appropriate, a few comments will also be made on clinical and pathological correlations. The specific entities to be covered include: diffuse proliferative glomerulonephritis; focal proliferative glomerulonephritis; membranous glomerulonephritis; antibasement membrane antibody disease; rapidly progressive glomerulonephritis (crescentic disease); membranoproliferative glomerulonephritis; lipoid nephrosis (nil disease); focal, segmental, and global sclerosis; polyarteritis nodosa; hypersensitivity angiitis; and Wegener granulomatosis. Few comments will be made about therapy because that subject is covered elsewhere in this issue. The review will be concluded by a discussion of the prognostic value of information gleaned from careful biopsy evaluation.

Two types of immunologic injury to the kidney have been clearly defined in experimental models and are thought to have distinct clinical counterparts.[1] These are immune-complex mediated disease and antibasement membrane antibody disease. The former is the most common and will be considered first.

Immune-Complex Glomerulonephritis

The pathogenesis of several glomerulonephritic patterns to be discussed subsequently seems to be of this type. In the classic immune-complex model, the following sequence of events is thought to occur: an antigenic substance gains access to the bloodstream and is delivered to immunologically competent cells which begin making antibody in response to the challenge; as antibody is released into the circulation, it combines with antigen to form complexes. Under certain circumstances of antigen excess, the complexes which are formed are small and soluble and are not phagocytized in the reticuloendothelial system; these activate the complement cascade via the classic pathway ($C_1 \rightarrow C_4 \rightarrow C_2 \rightarrow C_3$), and the entire aggregate of antigen, antibody, and complement components precipitates in the region of the glomerular basement membrane. The terminal components of the complement system include substances which increase vascular permeability and are leukotactic. An increase in the permeability of the capillary wall leads to leakage of protein into Bowman space and the influx of leukocytes may cause proteolytic destruction of portions of the glomerular capillary wall; in response to this assault, endothelial and mesangial cell proliferation occur. Thus, any antigen capable of stimulating an antibody response is a potential cause of immune-complex mediated injury. As we shall see, numerous inciting antigens have been identified, but the pattern of injury may vary considerably, probably depending on the nature of the antigen and the responsiveness of the host.[2]

Our understanding of the nature of immunologic injury to the glomerular capillary has been enhanced greatly by the development of immunofluorescent staining techniques. In this process a quick-frozen renal biopsy section is treated with a fluorescent-tagged antibody against a specific class of human globulin, complement component, or fibrinogen.

Correspondence and reprint requests to Dr. William F. Falls, Jr., Renal Section, VA Hospital, Richmond, VA 23249.

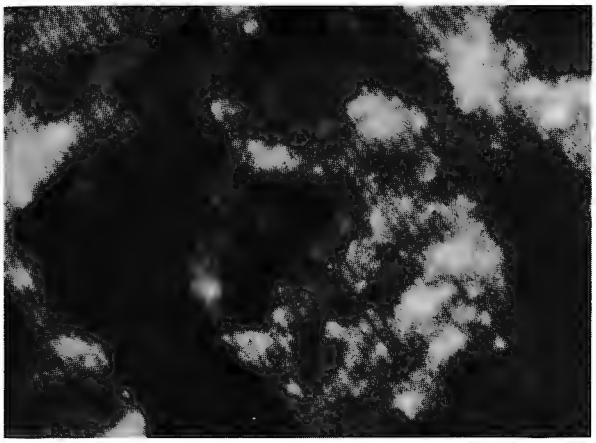

Fig 1—Immunofluorescent microscopic preparation (anti-IgG) of a portion of a glomerulus from a patient with poststreptococcal glomerulonephritis. Note "lumpy-bumpy" pattern. (× 1500).

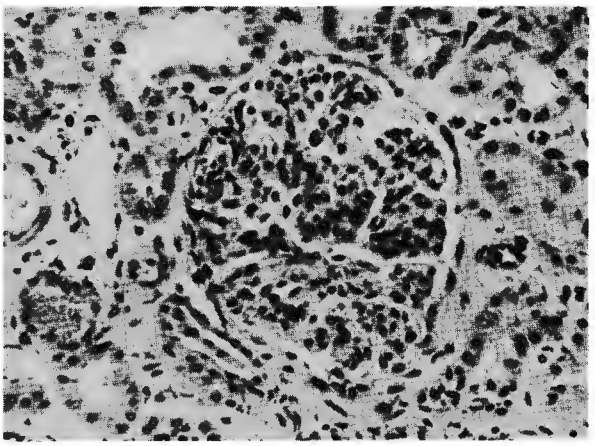

Fig 2—Light microscopic preparation (H & E) of a portion of renal biopsy from a patient with diffuse proliferative glomerulonephritis following streptococcal infection (×200).

When this preparation is viewed with fluorescent microscopy, a clear picture of the area of protein deposition is obtained. In the case of immune-complex mediated disease, a "lumpy-bumpy" pattern will be observed and is the hallmark of this type of injury.

Diffuse Proliferative Glomerulonephritis

Figure 1 is a photomicrograph of the immunofluorescent staining for IgG in a patient with acute poststreptococcal glomerulonephritis. Note the coarse, granular deposition of the immunofluorescent material in the area of the capillary basement membrane and the mesangium. Figure 2 is the light microscopic correlate of this lesion and shows the characteristic picture of diffuse, proliferative glomerulonephritis. The glomerulus is swollen and the capillary loops are occluded by proliferating mesangial and endothelial cells; there is marked hypercellularity and an influx of foreign inflammatory cells is noted. Figure 3 is a high-power view of an electron micrograph which demonstrates the classic appearance and location of the electron-dense deposits which are thought to represent the deposited complexes. Note that the deposits are quite large, "hump-like," and located in a subepithelial position; the foot processes in the area of the deposit have become fused. This phenomenon of foot process fusion has been found to correlate closely with the presence of proteinuria.

The immunofluorescent and light microscopic picture described above is typical of the aggressive type of immune-complex mediated disease characterized by poststreptococcal glomerulonephritis but is by no means specific to it. A similar light microscopic appearance may be seen in some patients with lupus erythematosus, bacterial endocarditis, nephritis associated with infected ventriculojugular shunts, cryoglobulinemic nephropathy, and other antigenic insults.[2] Diffuse proliferative glomerulonephritis secondary to lupus erythematosus can usually be distinguished from poststreptococcal disease because the electron-dense deposits in lupus are usually located on the subendothelial surface of the basement membrane (Fig 4) and discrete viruslike particles may also be evident.[2] The site of deposition in other diseases is

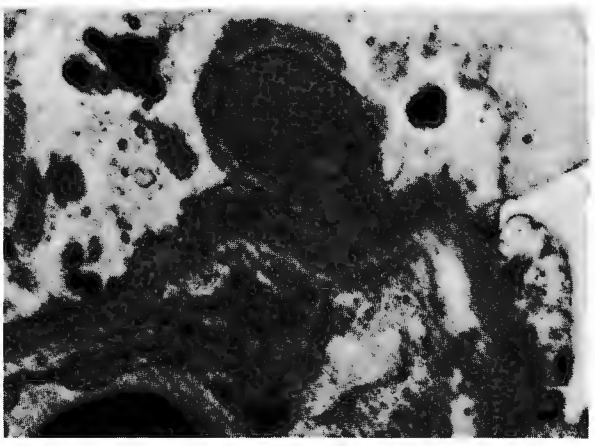

Fig 3—Electron microscopic preparation of a portion of a glomerulus from a patient with acute poststreptococcal glomerulonephritis. Note large subepithelial electron-dense deposit, "hump" (× 32,000).

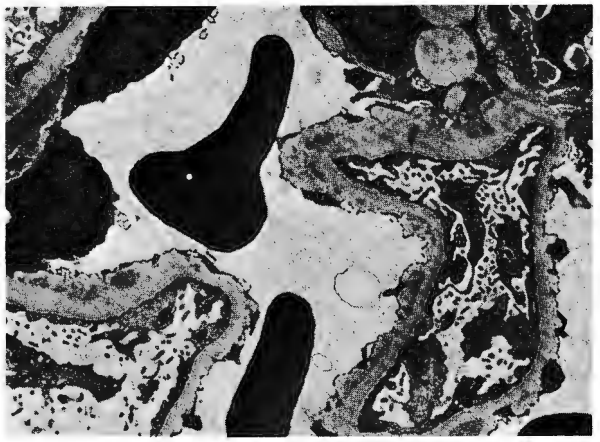

Fig 4—Electron microscopic preparation of a portion of a glomerulus from a patient with systemic lupus erythematosus and a diffuse proliferative lesion by light microscopy. Note large subendothelial deposits (× 10,000).

variable, but in many cases with proliferative lesions they are subendothelial.

In most cases of diffuse proliferative glomerulonephritis associated with lupus, one can find serologic evidence of activation of the classic complement pathway (low serum $C_{1q} \rightarrow C_2 \rightarrow C_4 \rightarrow C_3$).[2] Such changes are variable in other diseases with proliferative lesions and in some cases of poststreptococcal disease there may also be evidence of activation of the alternate complement pathway. In this circumstance C_3 is activated directly, bypassing the earlier components. A number of substances are known to activate C_3 directly. These include endotoxin, properdin, and IgA-containing complexes.

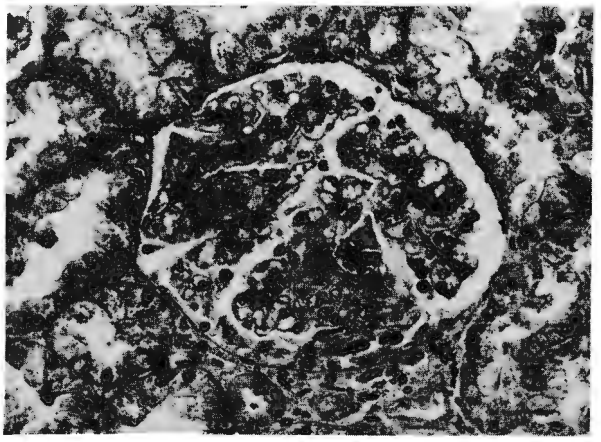

Fig 5—Light microscopic preparation (H & E) of a portion of a renal biopsy from a patient with systemic lupus erythematosus, showing a focal proliferative lesion (× 400).

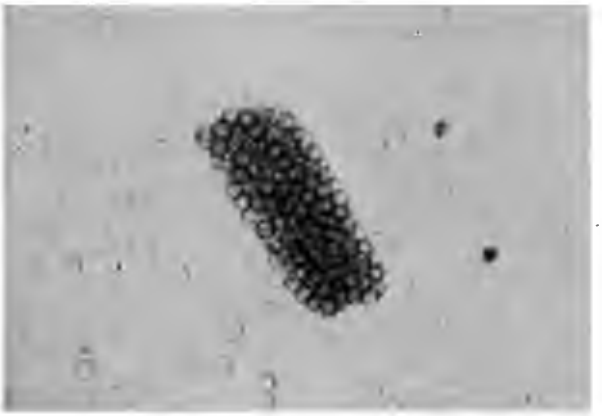

Fig 6—Red blood cell cast in urine sediment from a patient with poststreptococcal glomerulonephritis (× 1,000).

The course of immune-complex mediated proliferative glomerulonephritis is highly variable, depending on the disease process, and may well be related to the supply of antigen. In lupus erythematosus there is an inexhaustible supply of antigen in the form of various nucleoprotein derivatives including double-stranded DNA.[3] As a consequence, lupus glomerulonephritis tends to be an ongoing, progressive disease. On the other hand, poststreptococcal disease tends to be self-limited, particularly in children,[4] perhaps because of the rapid eradication of antigen from the body.

Focal Proliferative Glomerulonephritis

Another histologic pattern of immune-complex mediated glomerular injury is demonstrated in Figure 5. This is the pattern of focal (among glomeruli) and segmental (within a glomerulus) glomerulonephritis. By immunofluorescence the deposited globulins tend to be localized more within the mesangial region than along the capillary walls, and IgA may frequently be found along with other immune globulins and complement components. Evidence of alternate complement pathway activity may also be seen and it has been suggested that IgA-containing complexes may set this pathway in motion.[5]

Focal proliferative lesions may be seen in a wide variety of disorders including some patients with lupus erythematosus, Schönlein-Henoch purpura, and Berger disease (IgA nephropathy).[2]

Figure 6 is the photomicrograph of a red cell

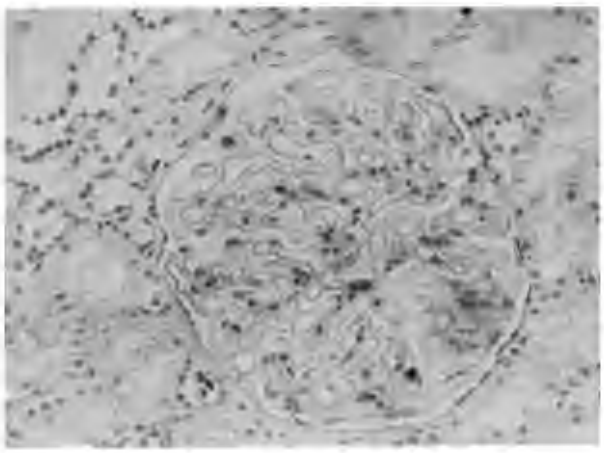

Fig 7—Light microscopic preparation (PAS) of a portion of a glomerulus from a patient with membranous glomerulonephritis (× 200).

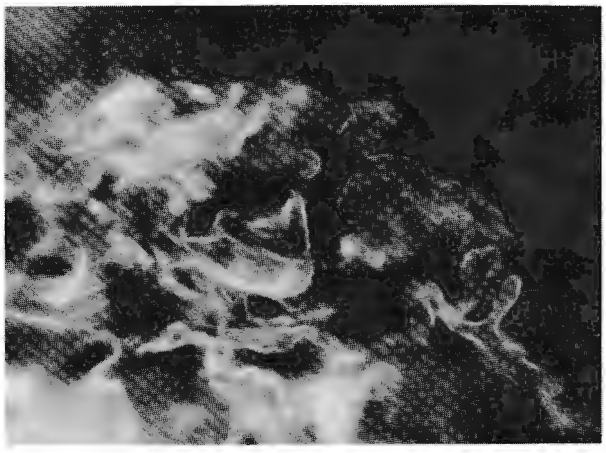

Fig 9—Immunofluorescent preparation (IgG) from a portion of biopsy of a patient with antibasement membrane antibody disease. Note linear pattern of fluorescence. (× 1500).

cast. This structure is considered to be characteristic of inflammatory or necrotizing disease of the glomerulus. It is introduced at this time because, being the most characteristic feature of the urine sediment in patients with glomerulonephritis, it tends to correlate with the type of proliferative lesions which have just been described.

Membranous Glomerulonephritis

In each of the immune-complex mediated disorders mentioned above, the light microscopic picture demonstrated evidence of cellular proliferation and inflammation. Such is ordinarily not the case in membranous glomerulonephritis. Figure 7 demonstrates the typical light microscopic picture of this lesion. The only recognizable abnormality is thickening of the basement membrane. On immunofluorescent and electron microscopic study this membrane alteration is found to be secondary to finely granular deposition of immunoprotein along the subepithelial border of the basement membrane. In addition to IgG and IgM, complement components may be deposited. Why this deposition is not associated with the induction of an inflammatory reaction like that described above is unclear. In animal models similar lesions are associated with small, weak-affinity antibodies[6] and it is possible that this is also true in human disease.

A membranous pattern may be seen in a number of clinical states including: lupus erythematosus, drug intoxication (heavy metals, tridione, penicillamine), solid tumors (carcinoma of the lung and colon), sickle cell disease, hepatitis B infection, and as an idiopathic occurrence.[2] Patients with membranous nephropathy usually present with a nephrotic state characterized by edema, hypoalbuminemia, hypercholesterolemia, heavy proteinuria, and fat-filled macrophages in the urine sediment.

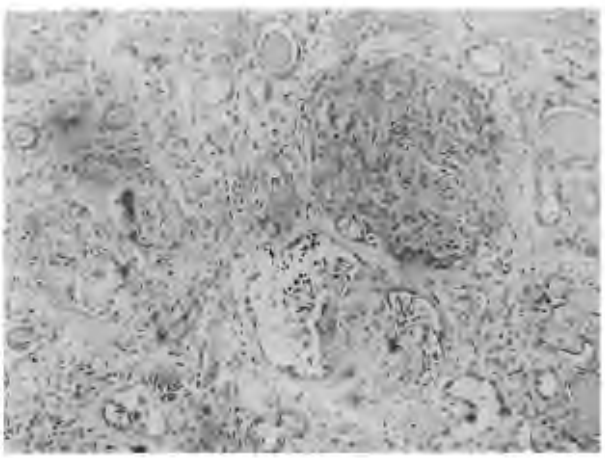

Fig 8—Light microscopic preparation (H & E) from renal biopsy of a patient with rapidly progressive glomerulonephritis. Note marked crescent formation by proliferating glomerular epithelial cells (× 80).

Antibasement Membrane Antibody Disease

The second, well-established type of injury to the glomerular capillary is that caused by circulating antibasement membrane antibody.[1] In this disorder antibodies, usually of the IgG class, develop against

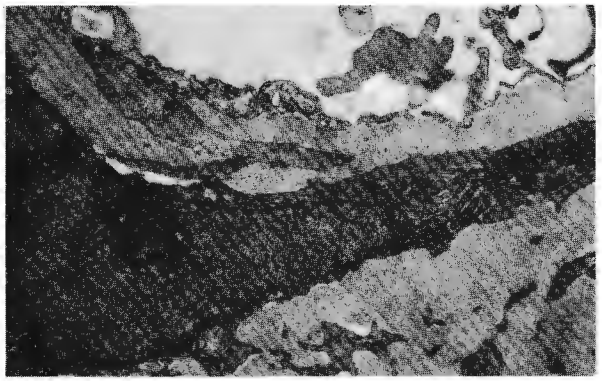

Fig 10—Electron microscopic representation of basement membrane reduplication in a patient with type I membranoproliferative glomerulonephritis. (× 14,000).

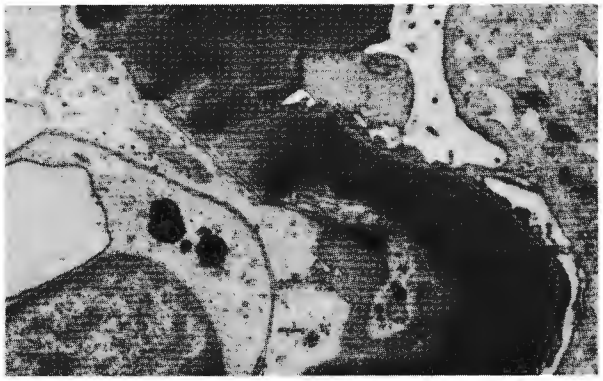

Fig 11—Electron micrograph from a patient with membranoproliferative glomerulonephritis type II. Note the homogeneous electron-dense deposit throughout the basement membrane. (× 15,000).

some antigenic component of the basement membrane. These abnormal antibodies enter the circulation and are carried to the kidney where they attach to antigens on the basement membrane. This reaction of antigen and antibody activates the complement cascade, probably via the classic pathway, and induces an inflammatory reaction in a manner analogous to that described earlier. Under certain circumstances there may be cross-reactivity of the glomerular antibasement membrane antibody with other basement membranes in the body, particularly the lung. It is this sharing of antigenic determinants that is thought to lead to lung hemorrhage and glomerulonephritis in Goodpasture syndrome.[7]

Rapidly Progressive Glomerulonephritis (Crescentic Disease)

A histologic picture of marked proliferation of both visceral and parietal epithelial cells, leading to extensive crescent formation (Fig 8) associated with a rapidly progressive, downhill clinical course may be seen under a number of different clinical circumstances.[8] It is classically seen in the kidneys of patients with Goodpasture syndrome and in this setting immunofluorescent staining invariably shows a linear deposition of antibody (Fig 9). A crescentic pattern may also be seen in patients with rapidly progressive glomerulonephritis without lung hemorrhage. In this circumstance only about 40% of the patients show an immunofluorescent pattern which is indicative of antibasement membrane antibody disease.[2] The remainder show a "lumpy-bumpy" fluorescent pattern indicative of an immune-complex pathogenesis. This is confirmed by electron microscopy which demonstrates electron-dense deposits. The common denominator of the crescentic pattern seems to be damage to the glomerular basement membrane of such a magnitude that fibrinogen and other components leak into Bowman space where the coagulation process is activated. This, in turn, stimulates proliferation of epithelial cells and attracts an influx of macrophages.[9] The picture of crescent formation and immune-complex deposition may also be seen in diffuse proliferative lupus and certain of the angiitic processes to be discussed later.

Glomerulonephritis in Which the Pathogenesis is Not Clearly Defined: Membranoproliferative (Mesangiosclerotic Glomerulonephritis)

Great interest is currently being focused on lesions included under this heading[10]; its classification is in a state of almost daily flux. On light microscopy the glomeruli from patients with this type of lesion show a lobular pattern which is associated with an increase in both the cellular and acellular components of the mesangium. This type of lesion may be seen in a variety of disease states including lupus erythematosus and non-resolving poststreptococcal glomerulonephritis. It is nonspecific in and of itself. Typical membranoproliferative lesions have also been described in children and adolescents who usually present with a nephrotic syndrome accompanied by varying numbers of red blood cells and red blood cell casts in the urine sediment. Early on, attention was drawn to the fact that many of these children had low levels of circulating C_3 and some had evidence of

Fig 12—Electron microscopic preparation of a portion of a renal biopsy from a patient with "nil disease." Note normal-appearing basement membrane, the absence of deposits, and the presence of fused foot processes (× 14,000).

activation of the alternate complement pathway as manifested by the presence of properdin in the glomerular mesangium.[2] Careful evaluation of biopsies with silver staining techniques revealed extensive reduplication of the basement membrane. Electron microscopic study confirmed this finding and suggested that the new basement membrane was laid down by proliferating mesangial cells burrowing beneath the cytoplasm of the endothelial cells (Fig 10). Subsequent evaluation of a larger number of cases has revealed the presence of some IgG deposits and early-reactive complement components in the mesangium. These patients have been classified as having membranoproliferative glomerulonephritis, type I

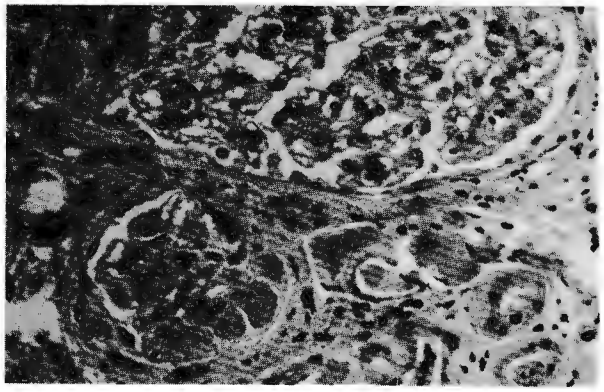

Fig 13—Light microscopic representation (PAS) of renal biopsy section from a patient with focal, segmental sclerosis. Note the peripheral hyaline lesions in lower glomerulus while upper glomerulus is relatively spared. (× 200).

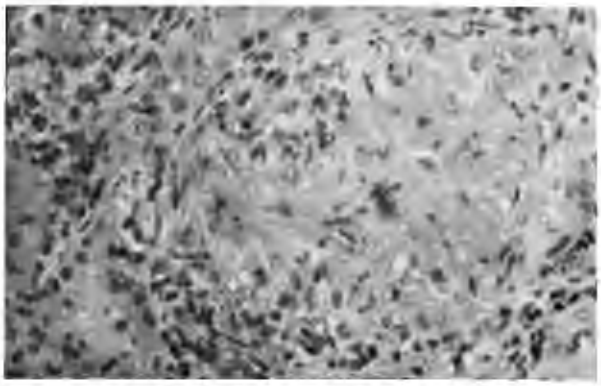

Fig 14—Light microscopic view of necrotic glomerulus (H & E) from a patient with Wegener granulomatosus. (× 500).

and are thought to have a variant of a classic immune-complex mediated disease. At present there is no clue as to the nature of the inciting antigen or antigens.

Membranoproliferative glomerulonephritis, type II, on the other hand, seems to be a more specific, homogeneous disease entity, albeit poorly understood. This disorder is also seen more frequently in younger individuals who usually present with a nephrotic syndrome. The light-microscopic biopsy picture is indistinguishable from the lobular pattern with basement membrane reduplication seen in type I. A distinctive dense deposition involving all of the basement membranes is seen with electron microscopy (Fig 11),[10] however, and positive immunofluorescent staining is seen only for complement. The staining is intense and seems to involve the same areas as the electron-dense deposits. These abnormal histologic changes accompany a blood chemical picture which is characterized by low C_3 levels, normal early-reacting complement components, and the presence of an abnormal circulating globulin component which is capable of activating C_3 directly (C_3 nephritic factor).

Type II membranoproliferative glomerular nephritis is felt to be mediated via alternate pathway complement activation alone. For reasons that are not clear, type II disease has been observed with some frequency in patients with partial lipodystrophy and glomerulonephritis. Both type I and type II may show recurrence in the transplanted kidney.

Lipoid Nephrosis of Childhood (Nil Disease)

Most young children who have a nephrotic syndrome display no recognizable abnormality on light

or immunofluorescent microscopy of their renal biopsy. The only recognizable change is fusion of the epithelial cell foot processes (Fig 12) which can be observed on electron microscopic section. This histologic pattern correlates with an essentially normal urine sediment. If cellular elements are present in more than very scant numbers, some other process must be considered. A similar lesion has been noted to occur in some patients with active Hodgkin disease and to disappear with successful treatment of the underlying disorder. This observation, taken in conjunction with the recognition that Hodgkin disease is a T-cell related malignancy, has invited speculation that the idiopathic nephrotic syndrome of childhood may also be a manifestation of abnormal T-cell function.[11] Such conjecture is interesting but entirely unproven.

Focal, Segmental, Global Sclerosis

Those young children with a nephrotic syndrome who have neither a spontaneous remission nor a favorable response to steroid therapy probably have this disorder. In most cases the initial involvement is deep in the juxtamedullary glomeruli, and centrifugal progression occurs throughout the entire cortex. In the focal lesion, some glomeruli are involved by segmental areas of mesangial sclerosis or hyalinization which are easily noted on light microscopy (Fig 13). Immunofluorescent studies may show spotty, nonspecific staining for IgG and complement, and electronmicroscopy demonstrates an increase in mesangial matrix material with an occasional mesangial deposit. In patients with global sclerosis the changes are similar but involve the entire glomerulus. The etiology of this disorder is uncertain, but an immune-complex mechanism is suggested by the finding of immunoglobulins in the sclerotic lesions and its occurrence in association with hepatitis B infection.[12]

Angiitis

The angiitic processes are probably immunologically induced and for our purposes may be divided into three groups, depending on the size of vessels involved and the presence or absence of granulomatous change.

Polyarteritis nodosa: Histologically this disorder is characterized by necrotizing, inflammatory lesions of medium-sized and large arteries. The hallmark of this process in the kidney is the presence of ischemic necrosis and infarction. Deposits of immune globulin, complement, and fibrin may be seen with immunofluorescent stains of the vessel walls. Clinically, patients with this disturbance present with a picture of hypertension, mononeuritis multiplex, central nervous system disturbances, and progressive renal insufficiency with an active urinary sediment.

Hypersensitivity angiitis: This is an angiitic process which involves small vessels including arterioles, venules, and the capillary loops of the glomerulus. Segmental necrosis of glomerular tufts may be seen on light microscopy and there may be nonspecific deposition of immune globulin and complement noted by immunofluorescence and light microscopic studies. Vasculitis of the skin is a frequent accompaniment of the renal lesions. This type of angiitis has been reported as a manifestation of hypersensitivity to a number of drugs. Hepatitis B infection has also been described in association with this disorder.[13]

Granulomatus arteritis: Wegener granulomatosis, the prototype of this disturbance, is characterized by the presence of necrotizing granulomas in the respiratory tract and a necrotizing, proliferative lesion of the renal glomerulus (Fig 14). Immunoglobulins and fibrin are deposited in a nonspecific glomerular pattern and crescents may be seen with frequency. Although thought to be of immunologic origin, the antigenic stimulus for this disease is unknown.[14]

Prognosis of Immunologically Mediated Renal Injury

The question, Why do a biopsy? frequently arises. Information from tissue examination should be of value in determining the proper diagnosis, prognosis, and treatment. We have pointed out the diagnostic value in the histologic review above. The prognostic information to be gained may be substantial and is outlined below.

As noted earlier, the course of a patient with an immune-complex mediated diffuse proliferative lesion is variable and relates to the underlying disease process. In those patients with an idiopathic lesion or in lupus the prognosis is usually poor. Patients with membranous lesions secondary to a recognized antigen which can be withdrawn or eradicated frequently show remission or improvement. Thirty percent of patients with an idiopathic nephrotic syndrome secondary to membranous nephropathy may have a spontaneous remission whereas the course of the remainder tends to be indolently downhill with a continued nephrotic syndrome. Patients with crescentic disease either related to an antibasement membrane

antibody or to circulating immune complexes do poorly. The prognosis in both types of membranoproliferative lesions is one of slow progression to end-stage disease in 10-12 years. The prognosis in nil disease is excellent with a high incidence of spontaneous remissions. Focal and global sclerotic lesions are associated with a slow but inexorable deterioration in renal function. The prognosis for untreated polyarteritis nodosa and Wegener granulomatosis is very poor. A similar prognosis is seen with small vessel angiitis unless it is drug-related in which case withdrawal of the offending agent may be accompanied by improvement.

In summary, the histopathology of the more common glomerulonephritic and angiitic lesions which may be seen on renal biopsy has been reviewed. Their diagnostic and prognostic implications have been discussed. Undoubtedly, the future will bring alterations in the presently outlined classifications as our understanding of the underlying immunologic pathogenetic mechanisms expands.

Acknowledgment: This work was funded by the Veterans Administration (MRIS 2737). The author is deeply indebted to Dr. Peter Schatzki of the Veterans Administration Hospital, Richmond, Virginia, and Dr. William J. S. Still of the Medical College of Virginia, Richmond, Virginia, for their assistance in the preparation of the pathologic material presented in the illustrations.

REFERENCES

1. McCluskey RT, Klassen J: Immunologically mediated glomerular, tubular, and interstitial renal disease. *N Engl J Med* 288:564–570, 1973.

2. Brenner BM, Rector FC Jr (eds): *The Kidney*. Philadelphia, WB Saunders Company, 1976, vol 2, pp 838–940, 941–1078.

3. Agnello V, Koffler D, Kunkel HG: Immune complex systems in the nephritis of systemic lupus erythematosus. *Kidney Int* 3:90–99, 1973.

4. Perlman LV, Herdman RC, Kleinman H, et al: Post-streptococcal glomerulonephritis. A 10-year follow-up of an epidemic. JAMA 194:63–70, 1965.

5. Clarkson AR, Seymour AE, Thompson AJ, et al: IgA nephropathy: A syndrome of uniform morphology, diverse clinical features and uncertain prognosis. *Clin Nephrol* 8:459–471, 1977.

6. Germuth FG Jr, Rodriguez E: *Immunopathology of the Renal Glomerulus. Immune Complex Deposit and Antibasement Membrane Disease*. Boston, Little Brown and Company, 1973.

7. Wilson CB, Dixon FJ: Anti-glomerular basement membrane antibody-induced glomerulonephritis. *Kidney Int* 3:74–89, 1973.

8. Beirne GJ, Wagnild JP, Zimmerman SW, et al: Idiopathic crescentic glomerulonephritis. *Medicine* 56:349–381, 1977.

9. Atkins RC, Holdsworth SR, Glasgow EF, et al: The macrophage in human rapidly progressive glomerulonephritis. *Lancet* 1:830–832, 1976.

10. Jones DB: Membranoproliferative glomerulonephritis. *Arch Pathol Lab Med* 101:457–461, 1977.

11. Sherman RL, Susin M, Weksler MR, et al: Lipoid nephrosis in Hodgkin's disease. *Am J Med* 52:699–706, 1972.

12. Jenis EH, Teichman S, Briggs WA, et al: Focal segmental glomerulosclerosis: *Am J Med* 57:695–705, 1974.

13. Gocke DJ, Hsu K, Morgan C, et al: Vasculitis in association with Australia antigen. *J Exp Med* 134:330S–336S, 1971.

14. Wolf SM, Fauci AS, Horn RG, et al: Wegener's granulomatosis. *Ann Intern Med* 81:513–525, 1974.