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References for Further Reading


Immunologic mechanisms in renal disease

—An overview—

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Introduction Evidence that immunologic mechanisms play a role in human renal disease is derived from a number of observations. First, the characterization of certain experimental models, which are similar immunologically and morphologically to human glomerulonephritis has provided a firm basis for this contention. Secondly, the recognition of deposits of immunoglobulin (Ig) and complement components within renal extracellular matrices and basement membranes is compelling evidence for the participation of humoral immunity in these diseases. Thirdly, the presence of certain serologic abnormalities—antinuclear antibodies in lupus erythematosus, anti-basement membrane antibodies in anti-glomerular basement membrane (GBM) nephritis, and immune complexes and complement component changes in a variety of diseases—provides additional support for this view. The reason for the association of complement-deficient states with certain types of glomerulonephritis has not been determined. Finally, cell mediated immunity has been shown to have a dominant role in tubulointerstitial nephritis associated with homograft rejection, but its participation in the other forms of human glomerulonephritis is much less clear. However, cell mediated injury has been implicated in certain experimentally-induced forms of renal disease—acute serum sickness, anti-GBM nephritis, and tubulointerstitial disease.

In this review, emphasis will be placed primarily on the pathogenesis of glomerular disease; the
mechanisms for immune injury to tubular structures are similar in many respects but will not be discussed. No attempt will be made to review exhaustively the contributions of all workers since this is beyond the scope of this discussion.

Structural Characteristics of the Glomerular Capillary

The glomerular capillary is a unique structure consisting of endothelial and epithelial cells with an interposed glomerular basement membrane (GBM). In the peripheral region of the capillary, filtration of various molecules occurs—controlled in part by the hemodynamic factors that determine glomerular filtration as well as characteristics of the molecule, specifically its size and charge. In the more centrolobular part of the glomerulus the mesangium is bounded by the reflections of the GBM and the overlying endothelial cell which separates it from the capillary lumen. The mesangium consists of mesangial cells and extracellular matrix material. Studies in rats by Schreiner and his associates have demonstrated the presence of another cell within this region—a bone marrow derived Ia positive phagocytic cell present in very small numbers. The mesangial cells and matrix are in close contiguity to element of the juxta-glomerular apparatus particularly the lacis cells.

The peripheral capillary and mesangium are common regions for immunologic injury—especially related to the deposition of immune complexes but also the interaction of antibody with structural or planted in situ antigens. Inflammatory cells and monocytes also may be recognized adjacent to or within these regions.

Antigenic and Macromolecular Components of Renal Basement Membranes

The human glomerular capillary wall contains arrays of distinct antigens identified by immunohistochemical techniques (Table 1) (reviewed in). These antigens are distributed with a characteristic topography (Fig. 1). For example, certain antigens (Types IV and V collagen, fibronectin) are present along the internal aspect of the GBM in contiguity with similar sites in the mesangium, whereas other antigens (e.g. antigenic sites reactive with human anti-GBM antibody) are located within the GBM exclusively. Antigenic heterogeneity of basement membranes is suggested further by studies using monoclonal antibodies developed in mice against human or rat basement membrane. The reactivity of these antibodies reveal a number of different immunohistochemical phenotypes reflecting non-characterized antigenic components.

Studies by Kanwar and Farquhar have demonstrated the presence of negatively-charged sites in the lamina rara externa and interna and these have been shown to be related to heparan sulfate proteoglycan (Fig. 1). Similar sites are present within the mesangial matrix—containing both heparan and chondroitin sulfate. The surface of the visceral epithelial cell is also negatively charged but this is related to the presence of a sialic acid glycoprotein, the glomerular polyanion—more recently called Podocalyxin.

Thus there appears to be a remarkable heterogeneity and complexity of basement membrane components. In addition, studies from our laboratory have demonstrated that various human anti-GBM antibodies react differently with fetal GBM suggesting the presence of more than one antigenic determinant.

The presence of plasma proteins in basement membrane has been demonstrated by immunohistochemical techniques and direct immunoassay. Recently, it has been demonstrated that proteins

Table 1 Components of human glomerular basement membrane.

<table>
<thead>
<tr>
<th>Collagen—Types IV and V</th>
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<tr>
<td>Antigen(s) reactive with autoantibodies (e.g. NC-1 domain of Type IV collagen)</td>
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<tr>
<td>Fibronectin</td>
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<tr>
<td>Laminin</td>
</tr>
<tr>
<td>Entactin</td>
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<tr>
<td>Proteoglycan—heparan sulfate</td>
</tr>
<tr>
<td>Anionic plasma proteins</td>
</tr>
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<td>Underlined antigens recognized by monoclonal antibodies (5)</td>
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* Mesangial matrix contains types IV and V collagen, fibronectin, laminin and proteoglycan (heparan sulfate and chondroitin sulfate)
Fig. 1 The distribution of certain basement membrane antigen(s) in the human is illustrated in black. A. Type IV collagen and fibronectin; laminin has a similar distribution but in addition is present along the lamina rara externa. B. Antigen(s) reactive with autoantibodies in anti-GBM nephritis or Goodpasture’s syndrome. There is evidence that the determinant is present in the non-collagenous domain of Type IV collagen. This antigen is apparently not present or displayed in the mesangial matrix. C. Negatively-charged sites in the lamina rara interna and externa (heparan sulfate proteoglycan), the mesangial matrix (heparan and chondroitin sulfate), and along the visceral epithelial cell (sialic acid containing polyanion or prodocalyxin)

Table 2 Immunological mechanisms of renal disease.

1. Deposition of circulating immune complexes
2. Interaction of antibody with an in situ antigen
   a. Intrinsic or structural antigen
   b. Exogenous planted antigen
3. Cell mediated immunity
   a. Tubulointerstitial nephritis induced experimentally or in homograft rejection
   b. Participation in models of immune complex disease and in situ antigen antibody interaction.

with relatively low isoelectric points (albumin, IgG) are present in normal GBM and in increased amounts in diabetic GBM whereas the more cationic species are not (e.g. IgG1, IgG3, IgG4). These findings suggest that the GBM contains intrinsic positive charges which are abrogated by the binding of anionic plasma proteins in vivo.

Immunologic Mechanisms of Renal Disease (Table 2) As discussed above, evidence for the participation of immune mechanisms in the pathogenesis of human renal disease is derived from a variety of experimental, immunohistochemical, morphologic, and serologic studies (reviewed in[13]-[22]). In certain human diseases (e.g. anti-GBM nephritis, lupus nephritis) there appears to be sufficient evidence to implicate a specific process. However, the picture is far from clear in other diseases such as dense deposit disease and other forms of glomerulonephritis. It has been assumed erroneously that all diseases with granular non-linear deposition of Ig reflect the localization of circulating immune complexes. The picture is further confused by a heavy reliance on comparison with experimental models and our incomplete understanding and ignorance regarding the pathogenesis of human glomerulonephritis.

Deposition of Circulating Immune Complexes
The classical model for this form of glomerular or vascular injury is acute serum sickness in the rabbit—extensively studies over two decades ago by Dixon, Germuth and their colleagues[21][22]. Following the administration of a foreign protein antigen (e.g. bovine serum albumin or BSA) there is an initial period of equilibration followed
by a linear logarithmic decline in plasma concentration for a period of approximately 9-12 days and then a rapid clearance from the plasma coincident with the appearance of antibody. During this period of time, antibody appears initially in an environment of excess antigen—leading to the formation of soluble antigen-antibody complexes. These complexes are biologically active and have the ability to fix complement. For reasons which are not completely clear complexes localize within the mesangial and subendothelial regions of the glomerular capillary as well as in vessels in other parts of the body—producing both vasculitis and glomerulitis (Fig. 2). The vasculitis is characterized by infiltration of polymorphonuclear leukocytes whereas the glomerular lesion is associated primarily with mononuclear cell infiltration—as demonstrated by Hunsicker et al.\textsuperscript{23}. If this infiltration is abrogated by antimacrophage serum there is a striking decrease in the amount of proteinuria indicating the importance of these cells in the pathogenesis of glomerular capillary injury.

**Glomerular Localization of Complexes** The mechanisms leading to or promoting the glomerular localization of these complexes or any macromolecule are incompletely understood (Table 3). The properties of the complex itself—size, antibody avidity, charge, and plasma concentration—are important determinants of this process\textsuperscript{18,20-22}. Thus small complexes containing antibody of relatively low avidity or affinity tend to localize in the peripheral capillary whereas larger-sized complexes

<table>
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<th>Table 3 Determinant of glomerular localization of macromolecules or immune complexes.</th>
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<tr>
<td>1. Properties of the complex</td>
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<tr>
<td>Size</td>
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<tr>
<td>Antibody avidity</td>
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<tr>
<td>Charge</td>
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<tr>
<td>Plasma concentration—controlled in part</td>
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<tr>
<td>by the mononuclear phagocytic system</td>
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<td>2. Characteristic of the glomerulus</td>
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<tr>
<td>Mesangial sequestration</td>
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<tr>
<td>Electrostatic charge</td>
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<tr>
<td>3. Hemodynamic determinants</td>
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<td>4. Biologically active mediators</td>
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<td>Angiotensin II, prostaglandins</td>
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Fig. 2 Deposition of immune complexes in the subendothelial and mesangial zones with formation of immune deposits (D) containing Ig and complement components.
count the overall reticuloendothelial system as an important variable in this process.

The demonstration that the glomerular capillary wall contains negatively charged molecules has lead to important studies regarding the influence of charge on immune complex localization. Thus, Gallo et al. demonstrated that passive administration of cationic immune complexes resulted in diffuse localization within the subendothelial and subepithelial regions—loci that are rich in the glycosaminoglycan, heparan sulfate. Similarly, Border and his associates demonstrated that active immunization with cationic BSA leads to the development of a membranous disease with peripheral capillary localization of immune complexes. Using this model in normal and C6 deficient rabbits Groggel et al. demonstrated a requirement for terminal complement components in the development of capillary injury—that appeared to be independent of mononuclear cells and neutrophils.

In addition, cationized human IgG binds to negatively-charged sites of the rat glomerular capillary after in vivo perfusion—and in this locus can bind passively—administered or actively-induced antibody resulting in glomerulonephritis.

As indicated above, the mesangial zone is a common sites for the deposition of immune complexes. There is abundant evidence, based largely on morphologic studies using various tracers, that this region is normally perfused by plasma (evidence reviewed in 3). However, the inaccessibility of the mesangium has not permitted appropriate physiologic studies in order to define the rate or extent of plasmic flow. The uptake of macromolecules is conditioned by the various factors indicated above related to localization of immune complexes. In addition certain experimental manipulations are known to affect mesangial kinetics. For example, induction of proteinuria by aminonucleoside or anti-GBM antibody results in increased localization of macromolecules within the mesangial zone. The mechanism of this phenomenon is unknown but may reflect increased mesangial perfusion in nephrotic states.

Macromolecules enter the mesangial zone at the endothelial-mesangial interface. However, the exit of complexes from the mesangium or degradation is much less clear. Phagocytosis by mesangial cells and infiltrating monocytes has been clearly demonstrated in a number of experimental situations. In addition the presence of a small number of positive phagocytic cells also has been demonstrated in this region. Another route of egress is by way of the glomerular stalk to the hilum of the glomerulus although the route thereafter is more obscure—possibly into the interstitium or the lymphatics. It is also possible that complexes or macromolecules may enter the mesangial zone in one region and return to the circulation by way of another.

The role of various hemodynamic factors in the localization of immune complexes in human renal disease is unknown. However, certain clinical observations suggest an influence. For example, it has been shown in both human and experimental situations that renal artery stenosis protects the kidney in immune complex disease. Administration of angiotensin II has been shown to result in an increase in mesangial sequestration of macromolecules.

**Immune Complex Disease as a Cause of Chronic Glomerulonephritis** The repetitive administration of an antigen over a period of weeks to a rabbit ultimately leads to a spectrum of morphologic changes similar to that observed in various forms of chronic glomerulonephritis in human beings. The early observations of Dixon, Germuth, and their respective associates alluded to above have led to many of our concepts regarding the pathogenesis of glomerulonephritis. The antibody response of the animal plays a role in the ultimate clinical and morphologic picture—in that non-antibody producers or aggressive antibody producers had no or minimal disease whereas rabbits producing small amounts of antibody and maintained by repetitive antigen administration in antigen excess had more severe disease.

Although most of the models of experimental renal disease involve the administration of a foreign antigen, the immune complex disease occurring in female NZB/NZW mice (and more re-
recently described mouse strains) reflect the interaction of host antigens (e.g. native-DNA etc.) with antibody. The spectrum of immune complex lupus nephritis in these mice is typical of that observed in human lupus erythematosus. This fascinating disease has been studied extensively by a number of workers as reviewed by Steinberg and his associates at the National Institutes of Health.

Another model that has resulted in considerable controversy is one initially described by Heymann 25 years ago. The administration of a crude tubular antigen, termed FX1A, to a rat leads to the evolution of membranous nephropathy over a period of weeks to months. Although there was initial evidence supporting the role of circulating immune complexes in this process, more recent studies suggest that this disease is a consequence of in situ antigen-antibody interaction.

Interaction of Antibody with an In Situ Antigen

(Table 4) Intrinsic or Structural Antigens

The recognition that circulating antibody can interact directly with the kidney was first recognized at the turn of the century. Although intensively studied during the last two decades, the model is incompletely understood. Two phases in this disease are recognized. In the heterologous phase anti-GBM antibody made in one animal is administered to an animal of a different species and promptly binds to the GBM. After a period of time, the autologous phase appears in which the recipient animal develops antibody to the fixed heterologous IgG—compounding the initial injury.

A number of mechanisms lead to glomerular capillary injury resulting in proteinuria. Activation of complement has been recognized to play a role in some models—although there is considerable variation depending upon the animal used and the type of antibody employed. The complement-dependent injury is a consequence of polymorphonuclear leukocyte infiltration related to the generation of chemotactic substances such as C5a—since this injury is in part inhibited by complement depletion using cobra venom factor or neutrophil depletion using nitrogen mustard.

Table 4 Interaction of antibody with an in situ antigen.

1. Intrinsic or structural antigen
   a. Basement membrane or matrix component
      (1) Type IV collagen, laminin
      (2) Antigen(s) involved in experimental anti-GBM nephritis or Steflay's nephritis (non-collagenous domain of Type IV collagen)
      (3) Antigen(s) involved in human anti-GBM nephritis or Goodpasture's syndrome (non-collagenous domain of Type IV collagen)
   b. Subepithelial antigen(s)—Passive Heymann's Nephritis and possibly other forms of membranous nephropathy

2. Exogenous planted antigen
   a. Aggregated IgG in mesangium
   b. Concanavalin A on endothelium
   c. Cationized antigen on negatively-charged (heparan sulfate proteoglycan) sites in basement membrane
   d. Heterologous antibody on the basement membrane or in epimembranous deposits

Recently, Groggel et al. have demonstrated a requirement for the terminal complement sequence for the mediation of proteinuria and decreased renal function in the heterologous phase of anti-GBM nephritis in the rabbit. This injury was independent of C3 deposition and leukocyte infiltration and was not observed in C6 deficient rabbits. Therefore, complement plays a role in at least two ways: the generation of chemotactic substances leading to leukocyte infiltration and activation of the terminal complement sequence. The mechanism of injury induced by the latter process is unknown. Thus, complement-independent mechanisms are related to monocyte infiltration as described above, as well as other mechanisms that have not been defined.

Monocytes have been recognized in diseased glomeruli by morphologic techniques in glomerular cultures during the autologous phase of anti-GBM nephritis. In an accelerated model of anti-GBM nephritis in the rat, Schreiner et al. demonstrated that the proteinuria appearing during the initial 24 hours correlated with polymorphonuclear
leukocyte infiltration, whereas the proteinuria that developed between 48 and 96 hours was associated with infiltration mononuclear cells; at both time periods rat IgG was present on the GBM in this accelerated model.

In a passive model of the autologous phase of anti-GBM nephritis (produced by injection of a subnephritic dose of horse anti-rabbit GBM antibody into rabbits followed 15 hours later by rabbit anti-horse Ig), depletion of monocytes by antimacrophage serum strikingly diminished monocyte infiltration, proteinuria, and histologic injury. It is likely that macrophage accumulation is dependent on immune adherence to the Fc portion of the IgG molecule. There is also evidence for infiltration of cells resembling lymphocytes during the heterologous phase of anti-GBM nephritis.

The precise structural antigens against which anti-GBM antibodies are directed have not been defined. As described above, the GBM contains a number of defined antigens—including type IV collagen and laminin—and it is probable that most anti-GBM antisera contain antibodies to these and other known antigens as well as undefined components.

Administration of anti-laminin antibody to rats frills to induce acute proteinuria inspite of fixation of the antibody to GBM and the development of glomerular alteration. Low grade proteinuria did develop after 2 weeks unassociated with deposition of autologous rat IgG. Studies in mice following the administration of antibody to laminin or type IV collagen revealed basement membrane changes and relatively low grade proteinuria.

Steblay's Nephritis A variant of this disease was described by Steblay a number of years ago. He observed that sheep immunized with heterologous GBM in adjuvant developed a progressive severe form of glomerulonephritis as a consequence of fixation of autologous IgG to the sheep's own basement membrane. This autoimmune disease probably reflects breaking of tolerance induced by immunization with basement membrane antigens—some of which are similar and others dissimilar to antigens of the sheep—resulting in production of autoantibodies and severe anti-GBM nephritis. A similarity of the Steblay antibody to that seen in human anti-GBM nephritis has been observed.

Human Anti-GBM Nephritis and Goodpasture's Syndrome The presence of circulating or bound antibody to GBM is the hallmark of human anti-GBM nephritis or, if associated with pulmonary hemorrhage, Goodpasture's syndrome. The cause of this loss of tolerance to the antigen(s) is unknown. The disease occurs especially in young adults, presents a clinical picture of rapidly progressive glomerulonephritis and is often severe leading to renal failure. Recent studies by Wieslander et al. have demonstrated that the putative antigen is collagenase-resistant, has a molecular weight of 26,000 and may be located in the non-collagenase region of type IV collagen. However, studies from our laboratory have demonstrated that various human anti-GBM antibodies react differently—some identifying basement membrane antigens in the fetal kidney and others not reacting at all. Recently, however
it has been possible to uncover certain basement membrane antigens by acid-urea denaturation of tissues—indicating that certain antigenic determinants are hidden.

In certain patients who receive renal homografts for familial nephritis, anti-GBM nephritis has been observed in the transplanted kidney. The formation of antibodies in these patients after transplantation and the inability to detect the nephritogenic antigen in the patients' own kidney suggests that there may be a genetic deletion in this structural component. There is some evidence that the defect may be X-linked. In addition, recently we have observed that certain of these antigens may be detected in the epithelial basement membrane of normal denatured skin sections, but not in that of male patients with Alport’s syndrome. The epidermal basement membrane of skin from female patients showed gaps of non-reactivity supporting X-linked inheritance.

Experimentally-induced Membranous Nephropathy It has been recognized for some time that the infusion of heterologous antibody to a proximal tubular brush border antigen (FXIA) into rats leads to the relatively rapid development of epimembranous deposits (passive Heymann’s nephritis). Largely through the efforts of Couser and his colleagues as well as Van Damme et al., this disease has been shown to develop as a consequence of in situ interaction of heterologous antibody with an antigen located in the glomerular capillary wall (Fig. 4A). Although no inflammatory cells participate in the injury leading to increased glomerular permeability to protein, a complement-dependent mechanism plays a role since the proteinuria at 4-5 days is inhibited following complement depletion with cobro venom factor. When sheep gamma 2 anti-rat FXIA IgG is administered to a rat it becomes “planted” in the subepithelial region—where it is able to combine with passively-administered or actively-induced rat anti-sheep IgG resulting in proteinuria. This latter injury is also cell-independent and complement dependent. There is considerable evidence that the membranous nephropathy in active Heymann’s nephritis (or autologous immune complex nephritis) represents a similar in situ mechanism rather than reflecting the deposition of circulating immune complexes.

The nature of the glomerular antigen and the relationship to the tubular brush border has been obscure. However, Kerjaschki and Farquhar have isolated a large glycoprotein with a molecular weight of 33,000 (gp 330) and have recently localized this antigen to coated pits on epithelial cells.

![Figure 4](image-url)
Maaker and Singh\textsuperscript{(43)} have isolated a larger antigen (gp600)—and suggest that gp330 is a subunit of this molecule.

\textit{Exogenous Planted Antigens} Experimental studies have demonstrated that it is possible to plant an antigen in the glomerulus. The subsequent interaction with an actively-produced or passively-administered antibody then can be evaluated. Conceptually, this may be a potentially relevant mechanism in human disease although there is no incontrovertible proof at present that it is operative in man.

The demonstration of this process in experimental animals generally requires a contrived protocol. This is essential since it is necessary to exclude the antigen from the circulation after planting it in the glomerulus—in order to avoid formation of circulating immune complexes after passive administration or active formation of antibody.

In a model of acute mesangiitis, aggregated human IgG is administered to an animal (e.g., rabbit or rat) and following localization within the mesangium the kidney is transplanted to another animal and then rabbit antiseraum to IgG is passively administered and binds to the antigen in the mesangium\textsuperscript{(43)} (Fig. 4B). This results in acute mesangial injury with infiltration of polymorphonuclear leukocytes. When concanavalin A (Con A) is infused it binds to endothelial surfaces; the subsequent administration of anti-Con A antiseraum leads to in situ antigen-antibody interaction\textsuperscript{(44)}.

In the same vein, studies by Oite et al. have demonstrated that renal perfusion of a cationized protein (ferritin or IgG) leads to binding to negatively-charged sites in the capillary wall\textsuperscript{(38,39)}. The systemic passive administration of antibody or its active formation by the animal—leads to glomerulonephritis as a consequence of in situ binding of antibody to the planted cationized antigen.

\textit{Cell Mediated Immunity (CMI)} As described above, humoral mechanisms (antibody-mediated) have been shown to play a crucial role in the pathogenesis of various forms of glomerulonephritis. In earlier studies there was little information regarding the relative importance of CMI in the development and progression of renal injury. It is accepted that T cell regulatory mechanisms are necessary for immune responsiveness to certain antigens and the ultimate development of antibody. What is at issue is whether cell-mediated mechanisms participate in the development of nephritis. Within the last 10-15 years a number of observations have supported a role for cellular immunity in the development of renal disease (reviewed in\textsuperscript{(49,50)}).

1) Monocytes have been demonstrated within diseased glomeruli of experimental animals and patients by a number of investigators using standard light and electron microscopic techniques (reviewed in\textsuperscript{(113-149,60)}).

2) The incisive experiments of Schreiner et al.\textsuperscript{(49)} and Hunsicker et al.\textsuperscript{(23)} have shown glomerular infiltration of monocytes respectively in an accelerated form of anti-GBM nephritis in rats and in acute serum sickness in rabbits. The infiltration was responsible for the development of proteinuria. This macrophage-dependent injury was abrogated by pretreatment with antimacrophage serum\textsuperscript{(49)}.

3) Compelling evidence for CMI was derived from studies by Bhan et al.\textsuperscript{(51-70)} who administered sensitized lymphocytes to rats with fixed heterologous anti-GBM antibody or immune complexes localized to the mesangium. This maneuver led to morphologic changes in glomeruli and monocyte infiltration.

4) Cyclosporin A, which is thought to act on proliferating T cells, has been shown by Neild et al.\textsuperscript{(53)} to inhibit glomerular injury in acute serum sickness in rabbits. Further, in acute post-streptococcal glomerulonephritis we have demonstrated recently the presence of small numbers of T cells as well as monocytes within glomeruli. The surface phenotype of these cells appear to distinguish tissue obtained early (OKT4>OKT8) from late (OKT8>OKT4) in the course of the disease.

5) A number of studies have been carried out evaluating the responsiveness of lymphoid cells in patients to GBM antigens using assays measur-
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ing leukocyte migration inhibition and lymphocyte blastogenesis (reviewed in\(^{45}\)). The antigens have included collagenase digested GBM and TBM, fetal kidney homogenates, trypsinized GBM, and glycosidase-treated membranes. These studies have demonstrated variable results in nephritic patients and in some instances positive results in non-nephritic diseases. The studies of Fillet et al.\(^{70}\) demonstrated responsiveness only to glycosidase-treated GBM in patients with proliferative glomerulonephritis. All of these studies may be criticized because of the impurity and recognized heterogeneity of the antigenic materials. In addition, there is no proof that the responses identified play a role in the development or progression of glomerulonephritis. Nevertheless, these observations are important since they likely reflect systemic cellular autoimmune responses that develop as a consequence of glomerular injury.

6) The production of tubulointerstitial disease in mice, rats and guinea pigs after immunization with xenogeneic tubular basement membrane is characterized by the presence of anti-TBM antibodies and an interstitial mononuclear infiltrate. A review of the various model systems is beyond the scope of this paper but the reader is referred to other sources\(^{1470-72}\). Susceptibility to induction of the disease is linked to the major histocompatibility complex. The relative importance of antibodies vs CMI has been unclear although both processes appear to be operative in the rat and guinea pig. In the mouse, Neilson et al. have shown that the nephritis is not dependent on the generation of anti-TBM antibodies but that susceptibility is largely a consequence of T cell function linked to the major histocompatibility complex.

7) There is evidence and conjecture that CMI may be involved in the pathogenesis of idiopathic nephrotic syndrome. This syndrome, which occurs predominantly in young children, has not been associated with any of the hallmark of a humoral (i.e. antibody-mediated) immune process. However, a number of curious observations suggest participation of some cellular mechanism:

(1) Recurrence or exacerbations are associated frequently with infections.
(2) Prompt response to steroid therapy occurs in over 95% of the patients.
(3) Alkylation agents such as nitrogen mustard and cytoxan also lead to remission of the syndrome. In addition, a short course of cytoxan has been shown to effect a prolonged remission in patients with frequent relapses.
(4) The disorder may be association with Hodgkin’s disease. In addition, a similar syndrome has also been observed in acquired immunodeficiency syndrome\(^ {70}\), and following the treatment of mycosis fungoides with interferon\(^ {72}\). We have also observed it after autologous bone marrow transplantation for leukemia.

(5) Patients who are steroid-resistant and develop progressive sclerosis with renal failure necessitating transplantation, may develop recurrence of the disease in 20–30% of the instances.

A number of immunologic studies have been carried out on the lymphoid cells from these patients, but no clear-cut consistent findings have been described which bear directly on altered glomerular permeability (reviewed in\(^ {72}\)). Some of the described immune abnormalities appear to be a consequence of the hyperlipidemia or are present in other forms of the nephrotic syndrome. Beale et al.\(^ {70}\) have recently demonstrated increased Ig synthesis by mononuclear cells from patients with this syndrome suggesting that these cells may be “turned on”. In addition, a slight increase in glomerular lymphoid-monocytic cells has been observed in some patients with this syndrome—especially if mesangial proliferation is present\(^ {72}\).

Non-Antibody Dependent Complement Activation

There is some suggestive evidence that non-antibody dependent complement activation may play a role in some renal disease. Prior studies have suggested this possibility primarily in diseases in which there is a dominant presence of complement components with minimal amounts of Ig (e.g. dense deposit disease and some instances of acute glomerulonephritis). Recent studies have demonstrated the presence of the membrane attack complex (MAC) of complement in the kidney in progressive renal disease of varied etiology—
usually in extracellular matrices. The mechanism and significance of these observations await further study and clarification.

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References


Physiological role of lateral interspaces and tight junctions in the renal tubule

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Isosmotic transporting epithelia. It is generally accepted that epithelia can be divided into two extreme categories. One includes epithelia with high transmural electrical resistances (in the order of k.Ω. cm² of epithelium) like frog skin, amphibian, reptile and mammalian urinary bladder. These are designated as tight epithelia (60). If both sides of these tissue are bathed with identical Ringer solution of the same osmolality these epithelia will effect net transport of salt from the apical side of their cells to their basal side. Water is also transported in the same direction but at a rate that is comparatively smaller than that of salt. As a consequence these epithelia always transport a hyperosmotic solution, that is, a solution with an osmolality higher than that bathing the basal side, even in the presence of ADH or in the presence of a solution with a low pH bathing their apical side (two conditions in which the water permeability of the epithelia increases considerably 14, 27a). In these epithelia there seems to be no conceptual difficulty in explaining solute-solvent coupling since an osmotic force located somewhere in the epithelium, secondary to the accumulation of transported salt will be more than sufficient to account for the observed water flow.

On the other extreme are the so called leaky