PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE **176,** 226–237 (1984)

MINIREVIEW

Autoimmune Diseases of the Kidney (41864)

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Autoimmune diseases are due to a breakdown of the tolerant state to autologous constituents. Some autoimmune diseases, including kidney diseases, can occur spontaneously in man. Our present understanding of the pathogenesis of human autoimmune diseases, however, is based mainly on the results of studies of diseases induced in laboratory animals by appropriate immunization. These diseases usually involve strong immunization such as incorporation of autologous tissue in "adjuvants," like Freund's adjuvant, or immunization of animals with a similar tissue from a different species that shares cross-reactive antigens.

Autoimmune reactions can be manifested by the production of autoantibodies and/or of autoreactive T cells. Thus, tissue damage may result from the reaction of antibodies with antigens present in the kidney, from tissue deposition of circulating immune complexes, and from cellular immune processes (1, 2). These mechanisms of hypersensitivity are not mutually exclusive. It is only for didactic reasons that we arbitrarily classify the various autoimmune renal diseases as if they were induced by a single pathogenic mechanism (Table I). In this review two groups of animal models of nephritis will be described. In the first group kidney lesions are induced by autoantibodies reacting with structural kidney antigens such as those of basement membranes or those present on the surface of cells. In immunofluorescence microscopy the immune reactants may be found along basement membranes in either a linear (e.g., in anti-basement membrane nephritis) or a granular pattern (e.g., in Heymann glomerulonephritis). In the second group the nephropathies are conceivably the result of deposition in the kidney of circulating autologous immune complexes. The immune complexes accumulate in a granular pattern.[1] Where possible, we will present evidence that similar diseases occur in man. Because insufficient solid data are available, a separate discussion of the role of autoreactive T cells in the development of kidney diseases is not included in this review.

I. Injury Resulting from the Interaction of Autoantibodies with Structural Antigens of the Kidney. *1. Glomerulonephritis Mediated by Antibodies to Glomerular Basement Membrane (GBM). a. Animal models. i. Glomerulonephritis resulting from immunization with GBM antigens.* Steblay and his associates have shown that sheep immunized with either heterologous (human) or homologous GBM in complete Freund's adjuvant develop GBM antibodies and a rapidly progressive, crescentic glomerulonephritis (3). Some of the antibodies are clearly autoantibodies because they react with autologous GBM. Study by direct immunofluorescence microscopy shows characteristic linear deposits of sheep IgG along the GBM. C3 may be bound to GBM in a similar pattern. Antibodies eluted from diseased kidneys react *in vitro* with sheep and human GBM, as well as with alveolar basement membranes (ABM) (4). The antibodies eluted from kidneys of sheep with Steblay's glomerulonephritis react with structural components localized mainly in the lamina rara interna of the GBM. This reaction is completely inhibited by prior absorption of the antibodies with collagenase-digested human GBM. Furthermore, the antibodies eluted from kidneys of nephritic sheep inhibit the

[1] The term "immune complex nephritis" has been traditionally used to encompass all those nephropathies in which granular immune deposits are found irrespective of whether these deposits are formed locally or from circulating immune complexes. Therefore, this term will only seldom be used in this review.

0037-9727/84 $1.50

TABLE I. KIDNEY DISEASES WITH AN AUTOIMMUNE PATHOGENESIS

I. *Injury resulting from the interaction of autoantibodies with structural antigens of the kidney*
  1. Glomerulonephritis mediated by antibodies to glomerular basement membrane (GBM)
    a. Animal models
      i. Glomerulonephritis resulting from immunization with GBM antigens
      ii. Glomerulonephritis induced by mercuric chloride
      iii. Spontaneous glomerulonephritis
    b. Human glomerulonephritis
  2. Glomerulonephritis mediated by antibodies to glomerular epithelial antigens
    a. Animal models
      i. Heymann glomerulonephritis
    b. Human glomerulonephritis (?)
  3. Tubulo-interstitial nephritis mediated by antibodies to tubular basement membrane (TBM)
    a. Animal models
      i. Tubulo-interstitial nephritis resulting from immunization with TBM antigens
      ii. Anti-TBM antibodies following kidney transplantation
    b. Human tubulo-interstitial nephritis
  4. Tubular injury mediated by antibodies to tubular epithelial antigens
    a. Animal models
    b. Tubular injury in man (?)

II. *Injury presumably resulting from deposition in the kidney of circulating autologous immune complexes*
  1. Glomerulonephritis
    a. Animal models
      i. Glomerulonephritis induced by graft-versus-host or host-versus-graft reactions
      ii. Glomerulonephritis induced by thyroglobulin or sperm antigens
      iii. Glomerulonephritis induced by antigens of basement membranes and of the collagen matrix
      iv. Glomerulonephritis in mice with spontaneous lupus-like syndrome
    b. Human diseases
      i. Systemic lupus erythematosus nephritis
      ii. Other types of glomerulonephritis
  2. Tubulo-interstitial nephritis
    a. Animal models
    b. Human diseases

reaction of Goodpasture's antibodies (see Sect. I1b) with human GBM, suggesting that common antigenic determinants of the GBM react with Steblay's and Goodpasture's antibodies (5). Steblay's glomerulonephritis can be passively transferred with antibody to sheep, which develop a glomerulonephritis identical to that of the donor animal (4). Sheep passively or actively immunized do not develop autoimmune hemorrhagic pneumonitis despite the presence in the circulation of elevated levels of antibodies capable of reacting with sheep ABM *in vitro*. It is conceivable that, in addition to antibodies, other factors increasing the permeability of the alveolar capillary wall may be required for the development of lung injury (6). In the sheep model the precise role of the mediators of the inflammatory reaction is not well established. The exudative lesions are characterized by accumulation of bloodborne macrophages which contribute to the formation of crescents (2).

Anti-GBM glomerulonephritis can be induced by both xeno- and allo-immunization of rats, rabbits, mice, guinea pigs, and monkeys (2). The urine of normal rabbits contains GBM antigens that, when used for immunization of rabbits, induce anti-GBM glomerulonephritis. In guinea pigs complement activation does not seem important for the development of proteinuria. Mice immunized with human GBM develop a conspicuous expansion of the lamina rara externa and large "spikes." The eluates from kidneys of nephritic mice contain all IgG subclasses but only IgG_1 binds to normal mouse GBM. This finding was interpreted as indicating that *in vivo* fixation to the GBM of IgG subclasses other than IgG_1 results from synthesis of antibodies to abnormal GBM components generated as a consequence of the initial injury induced by GBM antibodies of the IgG_1 subclass (7).

ii. Glomerulonephritis induced by mercuric chloride ($HgCl_2$). New Zealand rabbits

injected intramuscularly with $HgCl_2$ develop a biphasic, systemic disease first characterized by autoantibodies reactive to basement membranes and collagen matrix and, then, by antigen–antibody complexes containing the same kind of antibodies (8). A similar biphasic disease occurs in Brown-Norway rats (9, 10). In these animals the autoimmune response depends upon two or three genes, one of which is H-1 linked (11). Other studies have shown that $HgCl_2$ induces a polyclonal B-cell activation (12) and, possibly, a loss of T-cell suppression function (13). In the rat a proliferative and exudative glomerulonephritis can be observed 10 to 15 days after the beginning of administration of $HgCl_2$. In the rabbit this initial inflammatory injury was not described. In a later stage of $HgCl_2$ injection both rabbits and rats develop a systemic immune complex disease, including membranous glomerulonephritis (Sect. II1a.iii), presumably as a consequence of tissue deposition of circulating immune complexes (10, 14).

iii. Spontaneous glomerulonephritis. A glomerulonephritis induced by antibodies to GBM was described in the horse (15).

b. Human glomerulonephritis. Lerner *et al.* (16) have shown that human renal disease may infrequently (1.5–2% of the nephritic population) result from autoantibodies directed against constituents of the GBM. Anti-GBM glomerulonephritis is usually characterized by extensive crescent formation and rapid deterioration of renal function. Because of antigenic similarities among GBM, TBM, and ABM, anti-GBM glomerulonephritis may be associated with tubulo-interstitial nephritis and/or with hemorrhagic pneumonitis. A number of clinical syndromes can result. "Anti-renal basement membrane nephritis" is characterized by the presence of antibodies to GBM and TBM. In "Goodpasture's disease" or "anti-GBM glomerulonephritis with hemorrhagic pneumonitis" antibodies binding to GBM and ABM are found. The antigens responsible for the immune response occurring in Goodpasture's disease and in some cases of isolated rapidly progressive glomerulonephritis are contained in the noncollagenous fractions of the GBM (2) and, especially, in their most cationic 25- and 45-kDa components (17). One of the antigenic sites is located on a polypeptide with a molecular weight of 26,000 (18). Immunocytochemical studies have shown that these antigenic components are restricted to the lamina rara interna of the GBM (19).

The basic pathogenetic mechanism responsible for anti-GBM glomerulonephritis or Goodpasture's disease is, at least partially, known. The demonstration that anti-GBM antibodies are responsible for the development of the disease is based on the following evidence: first, linear deposits of IgG, frequently but not always associated with C3, are present along the basement membranes; second, antibodies to GBM can be detected in the circulation, especially after bilateral nephrectomy; third, the immunoglobulins eluted from diseased kidneys contain antibodies, that, upon intravenous injection into monkeys, bind in a linear pattern to the GBM and induce a proliferative and exudative glomerulonephritis and proteinuria; and, fourth, anti-GBM glomerulonephritis may recur in a renal graft if transplantation is performed when antibodies are still present in the circulation of the recipient (2, 20).

The demonstration of linear deposits of IgG in ABM of patients with Goodpasture's disease together with the observation that anti-ABM antibodies cross-react with GBM suggests that the immunological mechanisms inducing injury in the lung and in the kidney are identical. Although etiologic factors are not known, three hypotheses may be considered. First, exogenous antigens, cross-reacting with GBM and ABM, could initiate autoantibody formation. Second, endogenous GBM or ABM, secreted in increased amounts or altered in composition, could be the immunogenic stimulus. Third, an abnormality of the immune response, involving polyclonal B-cell activation and other alterations of stimulatory or inhibitory signals, may predispose individuals carrying the HLA-DRW2 allotype to develop basement membrane antibodies. The chief difference between experimental and human anti-GBM glomerulonephritis is the absence of lung hemorrhage in laboratory animals. The observation that in patients with anti-GBM nephritis lung disease may be absent despite the presence in the circulation of antibodies cross-reacting *in vitro* with ABM

and the demonstration that the titer of circulating antibodies does not correlate with the severity of lung involvement in patients with Goodpasture's disease suggest that, besides antibodies, additional factors are needed for lung disease to occur (6, 21).

2. Glomerulonephritis Mediated by Antibodies to Glomerular Epithelial Antigens. a. Animal models. i. Heymann glomerulonephritis. Heymann and his associates (22) described the development of nephrotic syndrome in rats immunized with homogenates of homologous kidney in Freund's adjuvant. The massive proteinuria is caused by glomerular lesions characteristic of membranous nephropathy. The disease is associated with the formation of autoantibodies reactive with antigens present on the cells of proximal tubules (a cellular fraction called F × 1A) (23) and also expressed on glomerular visceral epithelial cells. More recently the antigen has been characterized as a glycoprotein (gp 330) concentrated mainly in the "coated pits" of the plasma membrane of the apical part of the proximal tubule cells, and in the plasma membrane of glomerular visceral epithelial cells, and of other absorptive epithelia (24).

An immune complex disease similar to active Heymann nephritis develops in rats soon after passive transfer of homologous F × 1A antibodies (25). A comparable membranous nephropathy can also be induced by passive transfer of heterologous F × 1A antibody (26). Since perfusion of isolated rat kidney with heterologous antibody to F × 1A is followed by formation of granular immune deposits along the epithelial side of GBM, it is conceivable that the granular immune deposits of IgG found along GBM arise by the reaction of the perfusing antibodies with the gp 300 antigen present in glomeruli (27, 28). Whether *in situ* formation of immune complexes plays an exclusive role in the pathogenesis of active Heymann nephritis remains a matter of debate.

The development of Heymann nephritis is genetically controlled. Five different inbred rat strains, representing three haplotypes of the major histocompatibility locus H-1, were studied. It was found that Lewis, AS (H-1), and Lewis × BDV (H-1d) were highly susceptible to disease stimulation, whereas Brown-Norway and Lewis × Brown-Norway were resistant or only slightly susceptible. These findings indicate that the expression of the disease is linked to genes of the major histocompatibility complex (29).

b. Human glomerulonephritis (?). Tubular antigens, similar to those responsible for Heymann glomerulonephritis, were tentatively identified in Japan in a few patients with membranous glomerulonephritis. Outside Japan, these observations were not confirmed (2), with the exception of one patient with glomerulonephritis and tubulo-interstitial nephritis that appeared to have analogies with Heymann nephritis (30). It is conceivable, however, that in patients with idiopathic membranous nephropathy autoantibodies have reacted *in situ* with structural glomerular capillary wall components other than the Heymann antigen.

3. Tubulo-interstitial Nephritis Mediated by Antibodies to Tubular Basement Membrane (TBM). a. Animal models. i. Tubulo-interstitial nephritis resulting from immunization with TBM antigens. The first laboratory model of tubulo-interstitial nephritis induced by antibody reactive with TBM was described by Steblay and Rudofsky in guinea pigs immunized with rabbit TBM (31). The animals develop a severe renal disease as well as autoantibodies that react with the guinea pig's own TBM to form continuous linear deposits of IgG, detectable by direct immunofluorescence tests, along the basement membrane of proximal tubules. C3 is also bound to TBM in the same pattern. The kidneys of immunized guinea pigs become swollen and petechiae are visible at the surface. Examination by light and electron microscopy reveals interstitial mononuclear cell infiltrates and formation of giant cells which surround and destroy the tubules. The glomeruli exhibit little or no pathologic changes despite the presence of weak IgG deposits along GBM. Absorption studies with renal eluates reveal that TBM shares antigens with GBM, although some TBM determinants are distinct from those of GBM. Guinea pigs of strain 13 develop tubulo-interstitial nephritis with conditions of immunization that usually do not generate a comparable disease in strain 2. The increased susceptibility to develop anti-TBM antibody

appears to be inherited as a single dominant or codominant trait, linked to the major histocompatibility complex (32). With larger immunizing doses of TBM antigens, strain 2 animals develop tubulo-interstitial nephritis indistinguishable from that seen in strain 13 and outbred Hartley guinea pigs, although longer time is required for the full expression of severe disease in strain 2. The disease can be transferred to animals of the same species with serum or renal eluates or with autoantibodies of the IgG_1 or IgG_2 isotype. If transferred by IgG_1 or by IgG_2 autoantibodies, the recipient guinea pigs generate antibodies of the isotype that had not been transferred and higher titers than expected of the isotype that had been transferred (33). This "autoimmune amplification," similar to that described in autoimmune hemolytic anemia, could have importance in the self-perpetuation of the disease.

Anti-TBM tubulo-interstitial nephritis can be induced in guinea pigs genetically deficient in C4. Passive transfer of tubulo-interstitial nephritis by serum can be inhibited by depletion of complement, using cobra venom factor, or by depletion of leukocytes with irradiation. Furthermore, an inhibition of the autoimmune anti-TBM response and the ensuing disease is achieved by injection of heterologous antibodies to the anti-TBM antibodies. This inhibition may be caused by idiotype suppression (34). The disease cannot be transferred by sensitized lymphocytes.

Another model of anti-TBM tubulo-interstitial nephritis was described in Brown-Norway and Lewis × Brown-Norway rats immunized with Sprague–Dawley rat kidney homogenate in complete Freund's adjuvant and pertussis vaccine (35). The evidence supporting a primary pathogenetic role for anti-TBM autoantibodies in this model consists of: first, presence of linear deposits of rat IgG and C3 along TBM; second, presence of anti-TBM antibodies in the serum and in renal eluates of immunized rats; and third, transfer of the disease to normal rats with serum or renal eluates of nephritic rats. The histopathology of the tubulo-interstitial nephritis observed in rats is similar to that seen in guinea pigs. However, several weeks after the onset of tubulo-interstitial nephritis, Heymann nephritis may also appear, with characteristic granular deposits of IgG and C3 along glomerular capillary walls.

Anti-TBM tubulo-interstitial nephritis in Brown-Norway or Lewis × Brown-Norway F_1 hybrid rats has been produced by immunization with bovine TBM (36). The analysis of the various antibodies generated in this animal model shows that only the antibodies reactive with autologous collagenase solubilized TBM are deposited in the kidneys of nephritic rats and play a major role in the development of inflammatory injury. Studies of cross-absorption indicate that these antibodies are induced by an immune response to bovine TBM antigens cross-reactive with the TBM of BN rats (37).

ii. Anti-TBM antibodies following kidney transplantation. Anti-TBM antibodies may be generated by renal allograft implantation [for review see Ref. (38)]. In one study, however, the anti-TBM response was shown not to be autoimmune in nature. Lewis rats receiving Lewis × Brown-Norway F_1 hybrid kidneys develop anti-TBM antibodies which bind to kidneys of the donor, but not of the recipient, strain. In contrast, Brown-Norway rats receiving Lewis × Brown-Norway F_1 hybrid kidneys do not make anti-TBM antibodies. The observations indicate that the antibody response is generated by a TBM alloantigen introduced by transplantation (39).

Renal alloantibody formation was studied in Lewis rats immunized with DA rat kidney homogenates or receiving DA renal allografts. Using a ^{125}I anti-IgG binding assay with kidney homogenate as target tissue, it was found that the alloantigen is present in the TBM of proximal convoluted tubules and in Bowman's capsule, that the locus coding for this alloantigen is not linked to the major histocompatibility complex, and that the immune response to the TBM alloantigen does not induce detectable graft damage (40).

b. Human tubulo-interstitial nephritis. There is convincing evidence that anti-TBM disease occurs in man, although it is rare. Anti-TBM tubulo-interstitial nephritis is well documented in association with anti-GBM glomerulonephritis (2, 17, 38). The presence of anti-TBM antibodies is indicated by linear deposits of IgG, and occasionally of C3, along TBM. As the eluates of renal tissue contain

antibodies which react with GBM, TBM, and ABM, the autoantibodies appear to be directed against antigenic determinants shared by these three structures. In order to evaluate the pathogenic role of anti-TBM antibodies, a comparative immunopathologic study was performed in three groups of patients: one with anti-GBM glomerulonephritis, another with anti-GBM and anti-TBM nephritis, and still another with nephritides not associated with autoantibodies to renal basement membranes. The results showed that tubulo-interstitial nephritis is most frequent and severe when anti-TBM autoantibodies are detectable. It was concluded that autoantibodies to TBM contribute to the development of tubulo-interstitial lesions (41).

Anti-TBM antibodies have been detected in the sera and in TBM of a few patients with severe acute tubulo-interstitial nephritis apparently not associated with concomitant factors (2, 38). Attempts to transfer the disease to BN rats or to other mammals by iv injections of serum antibodies have been unsuccessful and only minimal binding of human IgG to TBM was found, suggesting that the antigen is not readily available to circulating IgG (personal observations). Anti-TBM antibodies may occur in recipients of renal allografts (2, 38). In some of these patients the antibodies react with the TBM of both the graft and the native kidneys and, therefore, behave as autoantibodies. In other patients, however, the antibodies react only with the TBM of the grafted kidney, suggesting that they may have been generated by an alloimmune response to a foreign TBM antigen present in the graft but not in the recipient. Anti-TBM antibodies have also been described in association with immune complex glomerulonephritis and in some patients with tubulo-interstitial nephritis associated with administration of methicillin.

4. Tubular Injury Mediated by Antibodies to Tubular Epithelial Antigens. a. Animal models. In rats with Heymann nephritis autoantibodies bind *in vivo* to antigens of the apical part of the cells of the proximal tubules during the first week of proteinuria. Antibodies with similar reactivity are found in the urine. Concomitantly, an extensive loss of microvilli together with degeneration and proliferation of epithelial cells of proximal tubules are observed. The results of indirect immunofluorescence tests using Heymann antibodies on kidneys of rats with Heymann nephritis confirm the loss of antigens from the tubules. In rats with Heymann nephritis of long duration, which have little or no circulating antibodies and persistent proteinuria, a partial recovery of tubular epithelia is seen. Direct evidence of the cytotoxic action of these autoantibodies on proximal tubule cells has been obtained from passive transfer experiments (42).

Tamm–Horsfall protein is an antigen present in the plasma membrane of the cells of the thick ascending limb of Henle's loop (43). When rats are immunized with Tamm–Horsfall protein, they develop granular immune deposits, containing this antigen, immunoglobulin, and complement, at the base of the epithelium of the thick ascending limb. Infiltration of leukocytes is observed around these segments of the nephron. These lesions are induced by *in situ* formation of immune complexes that originate from a reaction between plasma membrane antigens and circulating antibodies (44).

b. Tubular injury in man (?). Granular deposits of immunoglobulin along the TBM of proximal convoluted tubules have been described in one patient with membranous glomerulonephritis that appeared to be analogous to Heymann nephritis (30). If, however, a tubular injury comparable to Heymann nephritis occurs in man, its frequency is very rare. Antibodies reacting with the apical part of the cells of proximal convoluted tubules have been detected in the sera of patients with renal allografts (45). Proof that these antibodies contribute to the development of tubular damage is still lacking.

Antibodies to Tamm–Horsfall protein are frequently detected in the sera of patients with urinary tract obstruction, infection, and vesicoureteral reflux. In some patients with tubulo-interstitial nephritis deposits of Tamm–Horsfall protein are found sequestered in the renal interstitium where they should have the potential for eliciting inflammatory and immunologic responses (46, 47). However, a precise correlation between Tamm–Horsfall antibodies, abnormal interstitial deposits, and

tubulo-interstitial nephritis has not been established.

II. Injury Presumably Resulting from Deposition in the Kidney of Circulating Autologous Immune Complexes. *1. Glomerulonephritis. a. Animal models. i. Glomerulonephritis induced by graft-versus-host or host-versus-graft reactions.* One of the most common pathologic events in F_1 mice with chronic graft-versus-host reaction (GVHR) is membranous glomerulonephritis (48). The disease has all the characteristic immunopathologic features of immune complex injury. In the initial experiments it was assumed that the nephritogenic antibodies were anti-H-2 alloantibodies produced by donor B cells (49). Later, however, it became evident that autoreactive B cells normally exist and can be triggered by a number of mechanisms, including GVHR. It was found that F_1 mice with GVHR develop a disease resembling murine lupus with host-derived autoantibodies against erythrocytes, and nuclear antigens. The underlying mechanism of the autoimmune response in GVHR is thought to consist of an abnormal cooperation between alloreactive helper T cells of the donor and the normally existing (auto)reactive B cells of the recipient (50).

A similar membranous glomerulonephritis occurs in mice perinatally inoculated with related F_1 hybrid spleen cells (51). The model of host-versus-graft reaction is characterized by a rapid fatal evolution with severe depletion of T lymphocytes in lymphoid organs, influx of polymorphonuclear leukocytes, early activation of the B-cell system with hypergammaglobulinemia and immune complex disease, disseminated intravascular coagulation, hepatic necrosis, and intestinal hemorrhage. The disease does not appear to be related to any special H-2 incompatibility between host and F_1 donor. Other studies of host-versus-graft reaction induced by perinatal injection of semi-allogeneic F_1 hybrid spleen cells show that mice develop a lupus-like autoimmune disease characterized by hypergammaglobulinemia, autoantibodies, especially rheumatoid factor-like and anti-single-stranded DNA antibodies, systemic immune complex injury, and transplantation tolerance, as assessed by the inability of the recipient's spleen cells to generate cytolytic responses to donor alloantigens (52). The antinuclear antibodies bear allotypes specific of the F_1 donor as well as the parental host, indicating that the autoantibodies are of both donor and host origin. The mechanisms that stimulate autoreactive B cells are not firmly established but could involve a stimulus from T helper cells, a T-cell-independent polyclonal B-cell activation, or an impairment of the function of suppressor T cells.

ii. Glomerulonephritis induced by thyroglobulin or sperm antigens. Autologous thyroglobulin or sperm acrosomal antigens may induce a mild immune complex glomerulonephritis. Rabbits immunized with thyroglobulin develop glomerular lesions when the amount of thyroglobulin available for immune complex formation is artificially increased (53). Likewise, granular deposits of immune complexes are found in glomeruli of some vasectomized rabbits with persistent high concentrations of circulating anti-sperm antibodies. As immunoglobulins eluted from the kidneys of these rabbits bind to acrosomes, it is possible that the glomerular lesions result from a local deposition of circulating antigen–antibody complexes (54).

iii. Glomerulonephritis induced by antigens of basement membranes and of the collagen matrix. If administered in large amounts, compounds containing mercury are nephrotoxic and cause tubular lesions. When injected in small doses into rabbits or Brown-Norway rats, however, $HgCl_2$ induces a membranous glomerulonephritis (55). As mentioned in Section IIa.ii the autoimmune response is first characterized by formation of antibodies reactive with rabbit or rat basement membranes and collagen matrix and, later, by circulating antigen–antibody complexes, containing the same kind of autoantibodies detected during the first stage of disease (8–10, 14). Studies performed with the aid of syngeneic kidney transplantation have shown that the renal lesions are due to an alteration of the immune response rather than to direct renal injury. Furthermore, these studies have demonstrated that the membranous glomerulonephritis occurs only when antigen–antibody complexes are detectable in the circulation. This finding is consistent with the in-

terpretation that in the $HgCl_2$ model the granular immune deposits seen in the subepithelial part of the GBM are not, or not exclusively, formed *in situ* (56).

iv. Glomerulonephritis in mice with spontaneous lupus-like syndrome. Mice with lupus-like syndrome provide a useful model for the study of a generalized autoimmune disease that includes a glomerulonephritis characterized by granular deposits of antigen–antibody complexes, containing native (57) and single-stranded (58) DNA. The possibility that part of these immune deposits may be formed *in situ* is a matter of debate (59). The most studied strains are NZB, NZB/NZW F_1, MRL, and the BXSB mice. All these animals develop hypergammaglobulinemia, anti-DNA and other antinuclear antibodies, anti-retroviral gp 70 antibodies, circulating immune complexes, and glomerulonephritis, the most common cause of death (60). The features of the disease, however, are different from strain to strain and concern the amounts and specificities of the autoantibodies, the rapidity of progress of nephritis, the influence of sex on the severity of the disease, and the extent and nature of lymphoid hyperplasia (60). NZB/NZW F_1 females, BXSB males, and MRL/Mp-*lpr/lpr* develop immunopathological abnormalities a few weeks after birth and significant mortality within the first 6 months of life. MRL/Mp-*lpr/lpr* also have necrotizing polyarteritis and a rheumatoid arthritis-like disease associated with rheumatoid factors in the serum, anti-Sm antibodies, and frequently monoclonal γ-globulins of the IgG_1 and IgG_{2a} varieties. In contrast, in NZB, BXSB females, and MRL/Mp the disease occurs in the second year of life. In (NZB $\times$ BXSB)F_1 the incidence of coronary vascular disease and myocardial infarction is as high as 75% (61). In all mouse strains the development of overt systemic disease is associated with enhanced production of polyclonal autoantibodies and a switch from IgM to IgG antibody production, with subsequent formation of pathogenic antigen–antibody complexes (61).

Studies of appropriate bone marrow, spleen, or fetal liver cell chimeras show that the autoimmune disease is not induced by abnormal autoantigens but rather by abnormalities of the lymphoid-precursor cells, related to the genetic background (61). The autosomal recessive *lpr* (lymphoproliferation) gene in MRL-*lpr/lpr* mice, a Y-chromosome-linked gene in BXSB males, and females hormones in NZB/NZW F_1 are responsible for the early development and for the particular severity of the disease. The abnormality of the lymphoid-precursor cells is mainly expressed by a B-cell hyperactivity manifested by increased numbers of IgG-containing and/or Ig-secreting cells, increased numbers of cells which spontaneously form antibodies to incidental antigens, such as haptens, and increased numbers of colony-forming B cells. The cause of B-cell hyperactivity has not been definitively established. It could be due to an intrinsic B-cell defect, abnormal levels of suppressor or helper T cells, or abnormalities in the way B cells respond to accessory signals from suppressor or helper T cells (61). The data presently available argue against any consistent alteration related to suppressor T cells as the responsible factor. In contrast, they support the interpretation that an abnormal response to, and/or production of, T-cell-derived B-cell activating factors may have a central role in the pathogenesis of the autoimmune disease (62). B cells from BXSB and NZB/NZW strains, once triggered by the usual signals, give abnormally high responses. In contrast, B cells from MRL-*lpr/lpr* respond normally but are exposed to an increased help provided by T cells. This helper function, which is not antigen specific, is induced by a soluble B-cell differentiation factor promoting a switch from IgM to IgG antibody production with predominant secretion of IgG_2 antibodies, the primary subclass of IgG involved in autoantibody and immune complex formation in mice with lupus-like disease (62).

b. Human diseases. i. Systemic lupus erythematosus (SLE) nephritis. The best example of autoimmune immune complex glomerulonephritis in man is nephritis in SLE. In that disease, nuclear antigens including native (63) and denatured DNA (64) (presumably of endogenous nature), antinuclear antibodies, and complement components, including the membrane attack complex (65), are found in glomeruli. Additional antigen–antibody systems, such as IgG–anti-IgG complexes may also be important in the pathogenesis of the disease (66). A wide spectrum of histologic lesions is found in glomeruli and

in tubulo-interstitial structures. There is evidence that the type and severity of glomerular lesions may depend on the quantity and quality of the antibodies. As for possible analogies between the features of human and murine lupus, the disease manifestation in NZ mice parallels that in humans in the sex distribution and the immunopathological aspects of the disease. The BXSB males could be the counterpart of a recently described lupus that affects primarily fathers and sons. In contrast, the disease in MRL-*lpr/lpr* has no apparent human counterpart (61, 62).

ii. Other types of glomerulonephritis. Immune deposits have been identified in the glomeruli of patients with thyroiditis and glomerulonephritis (67, 68). Anti-thyroglobulin antibodies are usually present in great excess in the circulation during thyroiditis. Therefore, nephritogenic immune complexes in equivalence or in slight antigen excess are seldom found. Therapeutic manipulation, such as radioiodine therapy or irradiation, may either increase the amount of antigen available in the circulation or decrease the antibody concentration, leading to formation of nephritogenic immune complexes.

IgG–anti-IgG complexes, of rheumatoid factor type, have been considered as possible nephritogenic agents in several glomerulonephritides including SLE (66), post-streptococcal glomerulonephritis (69), and essential cryoglobulinemia (70). It is unknown whether an antigen, besides IgG, is present in these immune complexes. Other complexes present in glomerular immune deposits might be formed by specific IgG antigenic determinants (idiotypes) and by anti-idiotype antibodies (71, 72).

During the course of GVHR induced by bone marrow allotransplantation, some patients develop autoantibodies and immune complex glomerulonephritis (73). It is conceivable that the pathogenesis of this renal injury is similar to that occurring in non-autoimmune strains of mice undergoing experimentally induced GVHR (see Sect. II1a.i). Nephrotic syndrome, possibly due to immune complex glomerulonephritis, has been observed in children successfully treated with fetal liver transplantation for severe combined immunodeficiency (74). In these patients the possibility of an unusual chronic form of GVHR, induced by the transplantation of healthy stem cells, cannot be excluded.

2. Tubulo-interstitial Nephritis. a. Animal models. The first description of autologous immune complex tubulo-interstitial nephritis was in rabbits injected with preparations of homologous renal tissue (75) or given repeated renal allografts (76). The rabbits develop granular deposits of IgG and C3 along TBM of proximal tubules, interstitial fibrosis, tubular cell damage, and thickening or splitting of TBM. Mild and focal interstitial infiltration of mononuclear cells is present. Some rabbits have glucosuria and aminoaciduria. The immunoglobulins eluted from diseased kidneys react with the deposits present along TBM in the diseased kidneys and with the cytoplasm of the epithelial cells of proximal tubules of normal rabbits. It seems, therefore, that the immune deposits along TBM result from the reaction of circulating autoantibodies with autologous antigens as they move out of tubular cells (77). A similar mechanism may be responsible for the immune deposits observed at the epithelial side of the basement membrane of proximal tubules of rats with active Heymann nephritis.

b. Human diseases. Granular deposits of IgG and C3 along TBM, usually associated with tubulo-interstitial nephritis, are found in 50–60% of patients with proliferative SLE glomerulonephritis. The deposits have been shown to react with fluorescein-conjugated antibody to thymidine and cytidine, indicating that DNA is a constituent of the immune deposits (78, 79).

Aside from those found in SLE nephritis, extraglomerular immune deposits in the kidney are rare in patients with glomerulonephritis. Patients with renal allografts may occasionally develop granular deposits of IgG and C3 along TBM, similar to those described in rabbits receiving multiple renal allografts (80). It is unknown, however, if these tubular immune deposits result from *in situ* formation of autologous immune complexes.

This study was sponsored by Grant AI-10334 of the National Institute of Allergy and Infectious Diseases, U.S. Public Health Service.

1. Dixon FJ. The pathogenesis of glomerulonephritis. Amer J Med **44**:493, 1968.

2. Wilson CW, Dixon FJ. The renal response to immunological injury. In: Brenner BM, Rector FC, eds. The Kidney. Philadelphia, Saunders pp1234–1350, 1981.
3. Steblay RW. Glomerulonephritis induced in sheep by injections of heterologous glomerular basement membrane and Freund's complete adjuvant. J Exp Med **116**:253–272, 1962.
4. Steblay RW. Anti-glomerular basement membrane glomerulonephritis. Amer J Pathol **96**:875–878, 1979.
5. Jeraj K, Michael AF, Fish AJ. Immunologic similarities between Goodpasture's and Steblay's antibodies. Clin Immunol Immunopathol **23**:408–413, 1982.
6. Jennings L, Roholt O, Pressman D, Blau M, Andres G, Brentjens J. Experimental anti-alveolar basement membrane antibody-mediated pneumonitis. I. The role of increased permeability of the alveolar capillary wall induced by oxygen. J Immunol **127**:129–134, 1981.
7. Bolton WK, Benton FR, Sturgill BC. Autoimmune glomerulotubular nephropathy in mice. Clin Exp Immunol. **33**:463–473, 1978.
8. Roman-Franco AA, Turiello M, Albini B, Ossi E, Andres G. Anti-basement membrane antibody (A-BM Ab) and immune complexes (IC) in rabbits injected with mercuric chloride ($HgCl_2$). Kidney Int **10**:549, 1976.
9. Sapin C, Druet E, Druet P. Induction of anti-glomerular basement membrane antibodies in the Brown-Norway rat by mercuric chloride. Clin Exp Immunol **28**:173–179, 1977.
10. Druet P, Druet E, Potdevin F, Sapin C. Immune type glomerulonephritis induced by $HgCl_2$ in the Brown Norway rat. Ann Immunol (Inst Pasteur) **129C**:777, 1978.
11. Druet E, Sapin C, Gunther E, Feingold N, Druet P. Mercuric chloride-induced anti-glomerular basement membrane antibodies. Eur J Immunol **7**:348–351, 1977.
12. Hirsch F, Couderc J, Sapin C, Fournie G, Druet P. Polyclonal effect of $HgCl_2$ in the rat, its possible role in an experimental autoimmune disease. Eur J Immunol **12**:620–625, 1982.
13. Weening JJ, Hoedemaeker J, Bakker WW. Immunoregulation and anti-nuclear antibodies in mercury-induced glomerulopathy in the rat. Clin Exp Immunol **45**:64–71, 1981.
14. Roman-Franco AA, Turiello M, Albini B, Ossi E, Milgrom F, Andres GA. Anti-basement membrane antibodies and antigen–antibody complexes in rabbits injected with mercuric chloride. Clin Immunol Immunopathol **9**:464–481, 1978.
15. Banks KL, Henson JB. Immunologically-mediated glomerulonephritis of horses. II. Antiglomerular basement membrane antibody and other mechanisms in spontaneous disease. Lab Invest **26**:708–715, 1972.
16. Lerner R, Glassock RJ, Dixon FJ. The role of anti-glomerular basement membrane antibody in the pathogenesis of human glomerulonephritis. J Exp Med **126**:989–1004, 1967.
17. Yoshioka K, Kleppel M, Price RG, Michael AF, Fish AJ. Characterization of Goodpasture (GP) antigen(s) by high resolution two-dimensional electrophoresis. Amer Soc Nephrol p84A, 1983 (abstr).
18. Wieslander J. Glomerular Basement Membrane Antigens and Goodpasture's Syndrome. Thesis, University of Lund, 1983.
19. Sisson S, Dysart NK, Fish AJ, Vernier RL. Localization of the Goodpasture antigen by immunoelectron microscopy. Clin Immunol Immunopathol **23**:414–429, 1982.
20. Wilson CB, Dixon FJ. Anti-glomerular basement membrane antibody-induced glomerulonephritis. Kidney Int **3**:74–89, 1973.
21. Wilson CB, Dixon FJ. Renal injury from immune reactions involving antigens in or of the kidney. In: Brenner BM, Stein JH, eds. Immunologic Mechanisms of Renal Disease, Contemporary Issues in Nephrology. New York, Churchill Livingstone, Vol 3:p35, 1979.
22. Heymann W, Hackel DB, Harwood S, Wilson SGF, Hunter JLP. Production of nephrotic syndrome in rat by Freund's adjuvant and rat kidney suspension. Proc Soc Exp Biol Med **100**:660–664, 1959.
23. Edgington TS, Glassock RJ, Dixon FJ. Autologous immune complex nephritis induced with renal tubular antigens. I. Identification and isolation of the pathogenetic antigen. J Exp Med **127**:555–572, 1968.
24. Kerjaschki D, Sacktor B, Reiss U, Farquhar MG. Microdomains of distinctive glycoprotein composition in the kidney proximal tubule brush border. J Cell Biol **97**:178a, 1983 (abstr).
25. Sugisaki T, Klassen J, Andres GA, Milgrom F, McCluskey RT. Passive transfer of Heymann nephritis with serum. Kidney Int **3**:66–73, 1973.
26. Barabas AZ, Lannigan R. Induction of autologous immune complex glomerulonephritis in the rat by intravenous injection of heterologous anti-rat kidney tubular antibody. I. Production of chronic progressive immune complex glomerulonephritis. Brit J Exp Pathol **55**:47–55, 1974.
27. Van Damme BJC, Fleuren GJ, Bakker WW, Vernier RL, Hoedemaeker PhJ. Experimental glomerulonephritis in the rat induced by antibodies directed against tubular antigens. Lab Invest **38**:502–509, 1978.
28. Couser WG, Steinmuller DR, Stilmant MM, Salant DJ, Lowenstein LM. Experimental glomerulonephritis in the isolated perfused rat kidney. J Clin Invest **62**:1275–1287, 1978.
29. Stenglein B, Thoenes GH, Günther E. Genetic control of susceptibility to autologous immune complex glomerulonephritis in inbred rat strains. Clin Exp Immunol **33**:88–94, 1978.
30. Douglas MFS, Rabideau D, Schwartz MM, Lewis EJ.

Evidence of autologous immune-complex nephritis. N Engl J Med **305**:1326–1329, 1981.

31. Steblay RW, Rudofsky U. Renal tubular disease and autoantibodies against tubular basement membrane induced in guinea pigs. J Immunol **107**:589–594, 1971.
32. Hyman LR, Colvin RB, Steinberg AD. Immunopathogenesis of autoimmune tubulo-interstitial nephritis. I. Demonstration of different susceptibility in strain II and strain XIII guinea pigs. J Immunol **116**:327–335, 1976.
33. Hall CL, Colvin RB, Carey K, McCluskey RT. Passive transfer of autoimmune disease with isologous IgG_1 and IgG_2 antibodies to the tubular basement membrane in strain XIII guinea pigs. J Exp Med **146**:1246–1260, 1977.
34. Brown AC, Carey K, Colvin RB. Inhibition of autoimmune tubulointerstitial nephritis in guinea pigs by heterologous antisera containing anti-idiotype antibodies. J Immunol **123**:2102–2107, 1979.
35. Sugisaki T, Klassen J, Milgrom F, Andres GA, McCluskey RT. Immunologic study of an autoimmune tubular and interstitial renal disease in Brown Norway rats. Lab Invest **28**:658–671, 1973.
36. Lehman DH, Wilson CB, Dixon FJ. Interstitial nephritis in rats immunized with heterologous tubular basement membrane. Kidney Int **5**:187–195, 1974.
37. Zanetti M, Wilson CB. Analysis of anti-tubular basement membrane (TBM) antibodies (Ab) in Brown Norway (BN) rats. Kidney Int **21**:208, 1982 (abstr).
38. Andres GA, McCluskey RT. Tubular and interstitial renal disease due to immunologic mechanisms. Kidney Int **7**:271–289, 1975.
39. Lehman DH, Lee S, Wilson CB, Dixon FJ. Induction of antitubular basement membrane antibodies in rats by renal transplantation. Transplantation **17**:429–455, 1974.
40. Hart DNJ, Fabre JW. Kidney-specific alloantigen system in the rat. Characterization and role in transplantation. J Exp Med **151**:651–666, 1980.
41. Andres G, Brentjens J, Kohli R, Anthone R, Anthone S, Baliah T, Montes M, Mookerjee BK, Prezyna A, Sepulveda M, Venuto R, Elwood C. Histology of human tubulo-interstitial nephritis associated with antibodies to renal basement membranes. Kidney Int **13**:480–491, 1978.
42. Noble B, Mendrick DL, Brentjens JR, Andres G. Antibody mediated injury in proximal tubules in the rat kidney induced by passive transfer of homologous anti-brush border serum. Clin Immunol Immunopathol **19**:289–301, 1981.
43. Hoyer JR, Sisson SP, Vernier RL. Tamm–Horsfall glycoprotein. Ultrastructural immunoperoxidase localization in rat kidney. Lab Invest **41**:168–171, 1979.
44. Hoyer JR. Tubulointerstitial immune complex nephritis in rats immunized with Tamm–Horsfall protein. Kidney Int **17**:284–292, 1980.
45. Paul LC, Stuffers-Heiman M, van Es LA, de Graeff J. Antibodies directed against brush border antigens of proximal convoluted tubules in renal allograft recipients. Clin Immunol Immunopathol **14**:238–243, 1979.
46. Zager RA, Cotran RS, Hoyer JR. Pathologic localization of Tamm–Horsfall protein in interstitial deposits in renal disease. Lab Invest **38**:52–57, 1978.
47. Resnick JS, Sisson S, Vernier RL. Tamm–Horsfall protein. Abnormal localization in renal disease. Lab Invest **38**:550–555, 1978.
48. Lewis RM, Armstrong MYK, André-Schwartz J, Muftuoglu A, Beldotti L, Schwartz RS. Chronic allogeneic disease. I. Development of glomerulonephritis. J Exp Med **128**:653–680, 1968.
49. Kano K, Beldotti L, Milgrom F, Schwartz RS. Glomerulonephritis in the graft-vs-host reaction: Serologic demonstration of anti-host antibodies. J Immunol **112**:410–412, 1974.
50. Rolink AG, Gleichmann H, Gleichmann E. Diseases caused by reactions of T lymphocytes to incompatible structures of the major hystocompatibility complex. J Immunol **130**:209–215, 1983.
51. Hard RC, Moncure CW, Still WJS. Renal lesions with organized deposits and lipid as part of the host versus graft syndrome in parent/F_1 mouse chimeras. Lab Invest **28**:468–476, 1973.
52. Goldman M, Feng H-M, Engers H, Hochman A, Louis J, Lambert P-H. Autoimmunity and immune complex disease after neonatal induction of transplantation tolerance in mice. J Immunol **131**:251–258, 1983.
53. Weigle WO, Nakamura RM. Perpetuation of autoimmune thyroiditis and production of secondary renal lesions following periodic injections of aqueous preparations of altered thyroglobulin. Clin Exp Immunol **4**:645–657, 1969.
54. Bigazzi PL, Kosuda L, Hsu KC, Andres GA. Immune complex orchitis in vasectomized rabbits. J Exp Med **143**:382–404, 1976.
55. Bariety J, Druet P, Laliberte F, Sapin C. Glomerulonephritis with γ and B_1c globulin deposits induced in rats by mercuric chloride. Amer J Pathol **65**:293–302, 1971.
56. Houssin D, Druet E, Hinglais N, Verroust P, Grossetete J, Bariety J, Druet P. Glomerular and vascular IgG deposits in $HgCl_2$ nephritis: Role of circulating antibodies and of immune complexes. Clin Immunol Immunopathol **29**:167–180, 1983.
57. Lambert P-H, Dixon FJ. Pathogenesis of the glomerulonephritis of NZB/W mice. J Exp Med **127**: 507–522, 1968.
58. Seegal BC, Accinni L, Andres GA, Beiser SM, Christian CL, Erlanger BF, Hsu KC. Immunologic studies of autoimmune disease in NZB/NZW F_1 mice. I. Binding of fluorescein-labeled antinucleoside antibodies in lesions of lupus-like nephritis. J Exp Med **130**:203–216, 1969.
59. Izui S, Lambert P-H, Miescher PA. In vitro dem-

onstration of a particular affinity of glomerular basement membrane and collagen for DNA: A possible basis for a local formation of DNA–anti-DNA complexes in systemic lupus erythematosus. J Exp Med **144**:428–443, 1976.

60. Andrews BS, Eisenberg RA, Theofilopoulos AN, Izui S, Wilson CB, McConahey PJ, Murphy ED, Roths JB, Dixon FJ. Spontaneous murine lupus-like syndromes: Clinical and immunopathological manifestations in several strains. J Exp Med **148**:1198–1215, 1978.
61. Theofilopoulos AN, Prud'homme GJ, Fieser TM, Dixon FJ. B-Cell hyperactivity in murine lupus. I. Immunological abnormalities in lupus-prone strains and the activation of normal B cells. Immunol Today **4**:287–291, 1983.
62. Theofilopoulos AN, Prud'homme GJ, Fieser TM, Dixon FJ. B-Cell hyperactivity in murine lupus. II. Defects in response to and production of accessory signals in lupus-prone mice. Immunol Today **4**:317–319, 1983.
63. Koffler D, Schur P, Kunkel H. Immunological studies concerning the nephritis of systemic lupus erythematosus. J Exp Med **126**:607–624, 1967.
64. Andres G, Accinni L, Beiser S, Christian C, Cinotti C, Erlanger B, Hsu K, Seegal BC. Localization of fluorescein-labeled antinucleoside antibodies in glomeruli of patients with active systemic lupus erythematosus. J Clin Invest **49**:2106–2118, 1970.
65. Biesecker G, Katz SM, Koffler D. Renal localization of the membrane attack complex in systemic lupus erythematosus nephritis. J Exp Med **154**:1779–1794, 1981.
66. Cochrane CG, Koffler D. Immune complex disease in experimental animals and man. Adv Immunol **16**:185–264, 1973.
67. O'Regan S, Fong JSC, Kaplan BS, de Chadarevian JP, Lapointe N, Drummond KN. Thyroid antigen–antibody nephritis. Clin Immunol Immunopathol **6**:341–346, 1976.
68. Ploth DW, Fitz A, Snetzler D, Seidenfeld J, Wilson CB. Thyroglobulin–antithyroglobulin immune complex glomerulonephritis complicating radioiodine therapy. Clin Immunol Immunopathol **9**:327–334, 1978.
69. McIntosh RM, Griswold WR, Chernack WB, Williams G, Strauss J, Kaufman DB, Koss MN, McIntosh JR, Cohen R, Veill R III. Further studies on the nature, incidence, clinical diagnostic, prognostic, and immunopathologic significance of cryoproteins in renal disease. Q J Med **174**:285–307, 1975.
70. Meltzer M, Franklin EC, Elias K, McCluskey RT, Cooper N. Cryoglobulinemia—A clinical and laboratory study. II. Cryoglobulins with rheumatoid factor activity. Amer J Med **40**:837–856, 1966.
71. Goldman M, Rose LM, Hochmann A, Lambert P-H. Deposition of idiotype–antiidiotype immune complexes in renal glomeruli after polyclonal B cell activation. J Exp Med **155**:1385–1399, 1982.
72. Zanetti M, Wilson CB. Participation of auto-anti-idiotypes in immune complex glomerulonephritis in rabbits. J Immunol **131**:2781–2783, 1983.
73. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE, Hackman R, Tsoi M-S, Storb R, Thomas ED. Chronic graft-versus-host syndrome in man. Amer J Med **69**:204–217, 1980.
74. Keightley RG, Lawton AR, Cooper MD. Successful fetal liver transplantation in a child with severe combined immunodeficiency. Lancet **2**:850–853, 1975.
75. Klassen J, McCluskey RT, Milgrom F. Nonglomerular renal disease produced in rabbits by immunization with homologous kidney. Amer J Pathol **63**:333–350, 1971.
76. Klassen J, Milgrom F. Autoimmune concomitants of renal allografts. Transplant Proc **1**:605–608, 1969.
77. Klassen J, Milgrom F, McCluskey RT. Studies of the antigens involved in an immunologic renal tubular lesion in rabbits. Amer J Pathol **88**:135–141, 1977.
78. Brentjens J, Sepulveda M, Baliah T, Bentzel C, Erlanger B, Elwood C, Montes M, Hsu K, Andres G. Interstitial immune complex nephritis in patients with systemic lupus erythematosus. Kidney Int **7**:342–350, 1975.
79. Lehman DH, Wilson CB, Dixon FJ. Extraglomerular immunoglobulin deposits in human nephritis. Amer J Med **58**:765–786, 1975.
80. Andres GA, Accinni L, Hsu KC, Penn I, Porter KA, Randall JM, Seegal BC, Starzl TE. Human renal transplants III. Immunopathologic studies. Lab Invest **22**:588, 1970.