Pulmonary Renal Syndromes
II. Etiology and Pathogenesis

JOHN A. RANKIN, M.D., AND RICHARD A. MATTHAY, M.D.

Pulmonary Section, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

Received February 16, 1982

Numerous systemic diseases share immunopathogenic mechanisms. This article reviews the proposed etiologies and immunopathogenic mechanisms of a group of diseases which share pulmonary and renal abnormalities. Specifically, we discuss the following diseases: Goodpasture's syndrome, systemic lupus erythematosus, progressive systemic sclerosis, Wegener's granulomatosis, lymphomatoid granulomatosis, and Churg-Strauss syndrome.

INTRODUCTION

This article reviews the proposed etiologies and immunopathogenic mechanisms of a group of systemic diseases which share pulmonary and renal abnormalities. Emphasis will be placed on the immunopathogenesis of (1) Goodpasture's syndrome; (2) two connective tissue (collagen vascular) diseases, systemic lupus erythematosus and progressive systemic sclerosis (scleroderma); and (3) three granulomatous vasculidities, Wegener's granulomatosis, lymphomatoid granulomatosis, and Churg-Strauss syndrome. The clinical and chest radiographic manifestations of these diseases have been reviewed recently in this journal [1]. It is our purpose here primarily to review the immunologic mechanisms currently thought to be operating in these diseases.

GOODPASTURE'S SYNDROME

Goodpasture's syndrome is characterized by pulmonary hemorrhage often with hemoptysis, diffuse alveolar filling on the chest radiograph, anemia, and glomerulonephritis [1–14]. It is generally felt that the pathologic changes observed in this disease are an example of a cytotoxic antibody-mediated (type II) reaction (Table 1) because the disease appears to be due to an autoantibody which cross-reacts with both glomerular and alveolar basement membranes [1,4,7,15]. In order to understand the immunopathologic mechanisms which operate in this disease a few general comments about autoimmune anti-glomerular basement membrane disease are appropriate.

Immunologic tolerance refers to the inability of an individual to mount either a cell-mediated or humoral immune response to a molecule or antigen to which it would otherwise respond [16]. Normally, our own tissue antigens are protected from immunologic attack by this tolerance. Our immune system has been programmed
| TABLE I  |
|----------|
| Hypersensitivity Reactions |

**Type I. (Immediate hypersensitivity)**
- **Antigen**
  - Cell-bound
  - Reaginic antibody (IgE)
  - IgG
- **Mast cells release**
  - Chemical mediators (Histamine, SRSa etc.)
- **Anaphylaxis**
  - Smooth muscle contraction and bronchospasm
  - Mucus stimulation
  - Influx of eosinophils (Chemotactic stimuli)

**Type II. (Cytotoxic)**
- **Auto-antibody**
  - (IgG, IgM)
- **Cell-bound antigen**
  - (?) Antibody-mediated cytotoxicity

**Type III. (Arthus)**
- **Antigen**
  - Antibody complex
- **Activation**
  - Macrophages
- **Chemotactic factors**
  - (C5a and of macrophage origin)
- **Toxic O₂ radicals**
- **Proteolytic enzymes**
- **Collagenase**
- **Fibroblasts**
- **Altered Collagen synthesis**
- **PMN**
- **Eosinophils**
- **Lymphocytes**
- **Alveolitis**
- **Interstitial inflammation**
  - **Fibrosis**

**Type IV. (Delayed hypersensitivity)**
- **Antigen**
  - Mononuclear cell activation
- **Lymphokine secretions**
- **Macrophage activation and altered mobility**
- **Epithelioid cell differentiation**
  - **Granuloma**
during fetal life to recognize our own antigens as self, thereby circumventing immunologically mediated destruction. Occasionally this tolerance falters, leading to autoimmune diseases which appear to be mediated primarily by immunologic responses directed against our own tissues. An ever-increasing number of diseases are being found to be autoimmune in character. Of the renal diseases in this category, Goodpasture's syndrome is an example.

Immunologically induced glomerulonephritis can be precipitated by either of two major antibody-associated mechanisms which are divided on the basis of the physical state of the involved antigen: tissue-fixed or soluble [17]. For the purposes of this discussion we will be concerned only with anti-glomerular basement membrane (anti-GBM) disease which is the prototype of anti-tissue fixed antigen disease. Several recent and excellent reviews of this subject exist and are recommended highly [15,17,18].

Studies in Animals

In the 1930s, Masugi developed an animal model of nephrotoxic serum nephritis [16]. Since that time several important observations of particular relevance to anti-GBM disease have been made. In 1962, Steblay [19] immunized sheep with either heterologous or homologous GBM in complete Freund's adjuvant. These animals developed severe and progressive glomerulonephritis. Monkeys similarly immunized likewise developed this disease. When the glomeruli of these animals were examined, IgG and complement were observed in a linear pattern along the glomerular basement membrane [20]. This suggested that glomerular lesions might result from the formation of antibody directed against host glomerular basement membrane. Lerner and Dixon verified the autoimmune character of these glomerular lesions by transferring this disease to normal sheep using immunoglobulin from the serum of the afflicted sheep [21].

It is now appreciated that experimentally induced anti-GBM glomerulonephritis can assume either of two forms [17]. To produce the first type, anti-GBM antibody is harvested from animals immunized with GBM and injected into normal animals. When large amounts of antibody are injected, the animal develops an acute glomerulonephritis due to fixation of anti-GBM antibody to glomerular basement membrane. If only small amounts of anti-GBM antibody are injected, fixation of antibody to glomerular basement membrane occurs but does so in amounts insufficient to elicit glomerulonephritis. Glomerulonephritis will eventually develop when the animal produces antibody directed against anti-GBM antibody.

The second type of experimentally induced anti-GBM glomerulonephritis occurs in some animals immunized with glomerular basement membrane in adjuvant [17]. In this case the anti-GBM antibody which develops cross-reacts with the animals' own glomerular basement membrane and produces glomerulonephritis.

The renal injury in these two forms of experimentally induced anti-GBM glomerulonephritis appears to be tied closely to the ability of these antibodies to fix complement [17]. Activation of the complement systems results in neutrophil chemotaxis to the glomeruli where lysosomal enzymes are released and participate in renal injury. The crucial role of this cell was demonstrated when it was observed that neutrophil-depleted animals suffered less glomerular injury [17,22,23]. Recently, research has shown that the macrophage also may play a pivotal role in some forms of glomerulonephritis. In this study, macrophages were shown to be present in large numbers within the glomeruli of rabbits with experimentally induced glomerulone-
phritis. Depletion of circulating macrophages prevented the accumulation of these cells in glomeruli and largely prevented the development of glomerulonephritis [24]. The fact that not all anti-GBM glomerulonephritis is associated with observable deposits of complement suggests that complement may not be necessary in all forms of this disease [17].

Studies in Humans

The availability of this animal model has aided our ability to understand many of the observations made in humans with Goodpasture’s syndrome. This disease appears to be due to an autoantibody which cross-reacts with both glomerular and alveolar basement membranes. Several pieces of evidence, in addition to the animal data mentioned previously, support this view. First, linear deposits of immunoglobulin are found along the glomerular [25] (Fig. 1) and alveolar basement membranes [26,27] (Fig. 2) in many of these patients. Most often the immunoglobulin is of the IgG class, although recently a patient with the clinical manifestations of Goodpasture’s syndrome was found to have IgA deposits on both alveolar and glomerular basement membranes [28]. Second, circulating anti-glomerular basement membrane antibodies are found in the sera of most patients with Goodpasture’s syndrome [29]. Third, immunoglobulin eluted from the lung tissue of a patient with Goodpasture’s syndrome was shown to cross-react with glomerular basement membrane [30]. Fourth, plasmaphoresis has been shown both to lower the circulating levels of anti-GBM antibodies and concomitantly to result in clinical improvement [31,32]. Plasmaphoresis removes circulating anti-glomerular basement membrane antibodies before they are able to bind in the kidney. The addition of cyclophosphamide therapy, which may decrease antibody production, also may have a beneficial effect [32]. Fifth, the disease has recurrent in a renal allograft in a form similar to that present in the patient’s own kidneys [33].

Theories of Pathogenesis

What triggers the onset of anti-GBM antibody formation remains an enigma. Two theories regarding possible pathogenic mechanisms share widespread interest at this time. The first theory suggests that antigenic determinants on glomerular basement membrane tissue stimulate cytotoxic antibody formation. Glomerular base-

FIG. 1. Goodpasture’s syndrome—renal tissue (post-mortem) revealing the classic linear immunofluorescent staining for IgG anti-glomerular basement membrane antibody. (Photograph courtesy of Dr. M. Kashkarian, Dept. of Pathology, Yale University School of Medicine.)
ment membrane antigenic material has been found in the urine of normal humans [34] and animals [35,36]. When reinjected into the animal, immune disease results [36]. These data suggest that glomerular basement membrane normally is capable of stimulating an immune response but does not, possibly because it is anatomically sequestered from contact with circulating immune cells and because it is eliminated in the urine where it avoids contact with the systemic immune system. These same authors have suggested that the initiating event in Goodpasture's may be an abnormality which permits the reabsorption of this antigenic material. In this regard the association of viral infection [37–39] and hydrocarbon inhalation [40,41] with Goodpasture's syndrome is intriguing. Infection or exposure to hydrocarbons might cause basement membrane antigens that are anatomically sequestered but potentially immunogenic to be exposed to the immune system [6,7].

The second theory suggests that infectious agents may share antigenic determinants with basement membrane. In this case infection with these organisms would elicit the production of antibody which would cross-react with basement membrane. Wilson et al. [37] have suggested influenza A2 virus antigen might operate by this mechanism. Additionally, experimental evidence suggests that streptococci possess shared antigenic determinants [42]. However, there is currently little substantial evidence to support this mechanism in human disease [33].

There is little doubt that anti-GBM antibodies participate in the renal manifestations of this disorder. However, while the evidence is highly suggestive, proof is lacking that cross-reactivity of these antibodies with alveolar basement membrane causes the pulmonary component of this syndrome. It is somewhat distressing that circulating antibodies against alveolar basement membrane have not been described [33]. Moreover, no model of pulmonary disease due to damage by anti-GBM antibody exists [33]. Therefore, the possibility that cross-reactivity between anti-GBM antibody and alveolar basement membrane is the mechanism for lung disease remains only an assumption, albeit a reasonable one.

While the data stressing an association between hydrocarbon inhalation and Goodpasture's is convincing, the low incidence of this disorder despite the large numbers of people exposed to hydrocarbons is puzzling. It is possible that exposure to fumes or infection may elicit disease only in genetically susceptible persons. The occurrence of Goodpasture's syndrome in twins [43] and the recently observed
association between HLA-DRW2 and Goodpasture's syndrome [44] strongly argue for the importance of hereditary factors in this disease.

In summary, data obtained from animal studies and observations made on humans with Goodpasture's syndrome argue convincingly for a central pathogenic role for an anti-GBM antibody which cross-reacts with alveolar basement membrane. Polymorphonuclear leukocytes, macrophages, and complement appear also to be important in the development of alveolar and glomerular lesions. However, the etiology and precise mechanisms of injury remain unknown.

**SYSTEMIC LUPUS ERYTHEMATOSUS**

Systemic lupus erythematosus (SLE) is a multisystem disease associated with autoimmune antibodies and circulating immune complexes. It is considered by some to be a prototype of immune complex (type III) disease (Table 1) [45-47]. Renal involvement is more common in these patients than is pulmonary disease. A great deal of our understanding of this disease comes from studies of the renal pathology. In the past few years, however, a more active search for immunologic abnormalities in this disease has provided us with a greater understanding of the immunopathology of the lung lesions.

Immune-complex-mediated disease is caused by the formation of antigen-antibody complexes which fix complement and produce inflammatory injury [15,48]. Several human diseases have been attributed to injurious effects mediated by these complexes. Specifically, complexes activate both cellular and humoral immune responses which participate in tissue injury.

Immune complexes are formed when antigen and antibody combine. As described in the section on Goodpasture's syndrome, the antigen can be tissue-fixed (type II reaction, Table 1). As might be expected, injury induced by immune complexes formed with tissue-fixed antigen is generally confined to the anatomic location of the fixed antigen. In contrast, antigen can also be non-tissue-fixed, i.e., freely circulating. In this case (type III reaction, Table 1), immune complexes induce injury in any organ which traps these complexes. However, it should be mentioned that recent observations challenge the widely held theory that passive entrapment of circulating immune complexes by the kidney is responsible for the glomerulonephritis in SLE and other diseases [49]. The alternative hypothesis proposed by Couser [49] suggests that freely circulating antigen is trapped in glomeruli where antibody then reacts with antigen to form immune complexes which induce glomerulonephritis. This mechanism differs from the anti-tissue fixed disease, Goodpasture's syndrome, in that the antigen, while being tissue-fixed, is not renal tissue itself. Which of these two mechanisms predominates in causing tissue injury remains to be determined.

Of particular importance in the immunopathogenesis of disease due to circulating immune complexes is the size of the immune complex [15,18]. Large complexes, which form when either antigen or antibody are present in extreme excess, do not cause disease, as the former remain in the circulation and the latter precipitate and are quickly cleared by the reticuloendothelial system [18]. Very small complexes remain soluble and probably fix complement in insufficient quantities to initiate pathogenic mechanisms [18]. Complexes of intermediate size form in moderate antigen excess, and trigger the cascade of events which culminate in tissue injury [15,18]. These complexes are small enough to remain soluble, yet large enough to activate the complement system and to be trapped in vessel walls. The amount and affinity of antibody produced in response to antigen challenge is clearly important.
Variability between individuals in this response may be determined genetically in part and may account for part of the reason some individuals develop immune complex disease and others do not [18].

Once immune complexes of the appropriate size are formed, a cascade of events is initiated which leads to tissue injury and clinical disease (Fig. 3). The precise chronological order of these events remains to be proven. While it is most likely many events occur simultaneously, experimental animal data suggest that an increase in the permeability of blood vessels is an early event [15,18]. The changes in permeability appear to be mediated by vasoactive amines released when immune complexes interact with basophils or platelets [15,18]. Activation of the complement system by these complexes results in neutrophil chemotaxis to the sites of complex deposition. Here the neutrophils release lysosomal enzymes; such as neutral proteases, elastase, and collagenase, and other mediators of inflammation, such as prostaglandins [5,50]. The importance of neutrophils in immune-complex-mediated tissue injury is underscored by the observation that neutrophil- and complement-depleted animals do not develop arteritis [17]. The end result of these events is an intense inflammatory reaction located in the arterial walls of multiple organs.

It should be emphasized that both heterologous and autologous antigens may possibly be involved. Much of the experimental data discussed above is derived from experiments using heterologous antigen. Autologous tissue may become antigenic if

1) Circulating soluble immune complexes in antigen excess
2) Increased vascular permeability via platelet derived vasoactive amines and lge mediated reactions.
3) Trapping of immune complexes along basement membrane of vessel wall and activation of complement components.
4) Complement derived chemotactic factors (C5a, C5a, C567) cause accumulation of PMNs.
5) PMNs release lysosomal enzymes (collagenase, elastase)
6) Damage and necrosis of vessel wall, thrombosis, occlusion, hemorrhage.

FIG. 3. Circulating immune complexes of intermediate size form. Vascular permeability is altered by vasoactive amines released from platelets or basophils which interact with these immune complexes. The complexes are trapped in vessel walls and activate complement which causes polymorphonuclear chemotaxis and accumulation at the site of injury. PMN cells release lysosomal enzymes and mediators of inflammation which ultimately result in an intense inflammatory reaction in affected vessels. (Reproduced from Fauci et al. [108] with permission of the publisher.)
altered by either infectious or toxic agents. Tissue perceived as “non-self” elicits the production of antibody that complexes with it [17].

Although the most common cause of pulmonary infiltrates in patients with SLE is infection [51], many patients develop infiltrates without an apparent infectious etiology [3,51–69]. Pulmonary function abnormalities can be detected in a majority of patients without clinical or radiographic evidence of lung disease [70].

The evidence for involvement of immune complex mechanisms in the non-infectious pulmonary manifestations of SLE is persuasive. First, both immunoglobulin and complement have been found in the lungs of some patients with SLE [71–75]. Second, the pathogenic appearance of these findings suggest the lesions are analogous to those seen in the glomeruli [46]. Third, interstitial lung disease has been elicited in animals following the production of circulating immune complexes [76]. Fourth, in two recently reported patients with lupus pneumonitis immune complexes composed of DNA, anti-DNA antibody, and complement have been found in the interstitium of alveolar walls and alveolar capillary walls [77]. Fifth, cellular analysis of material obtained from the lungs of patients by bronchoalveolar lavage reveals that an increased number of neutrophils are present [78]. Sixth, immune complexes have been detected in alveolar macrophages in some patients with the lung disease associated with connective tissue disorders [79]. Alveolar macrophages can be stimulated by immune complexes to release chemotactic factors that attract neutrophils to the lung [80–83]. This latter finding is consistent with the hypothesis that chemotactic factors recruit these cells to the lung where they participate in lung injury. In this manner, the alveolar macrophage might be intimately involved in the inflammatory reaction.

PROGRESSIVE SYSTEMIC SCLEROSIS (SCLERODERMA)

Progressive systemic sclerosis (PSS) is a disease of unknown etiology which is characterized by widespread vascular lesions and major alterations in connective tissue [1,79]. Because of these characteristic changes, PSS is included under the heading of connective tissue (collagen vascular) diseases. However, unlike SLE, the evidence is much less convincing that immune complexes have an important pathogenic role in PSS.

The reported frequency of lung involvement in this disease varies to some extent with the method of detection. However, either clinical or chest radiographic abnormalities appear in most patients sometime during the course of their disease and some degree of pulmonary interstitial fibrosis is almost always found at postmortem examination [79,84–95]. Pulmonary vascular resistance is elevated in many patients [96], but only one-half of these patients demonstrate clinical or chest radiographic signs of right ventricular hypertrophy. It is of considerable interest that there appears to be little correlation between the degree of pulmonary fibrosis and the severity of the pulmonary vascular lesions [79,96].

Evidence suggesting a role for immune complexes in PSS is less persuasive than for SLE. Salerni [86] detected only small amounts of immunoglobulin G and complement C1q component in the pulmonary arteries of three patients. Small deposits have also been described in the interlobar arteries of the kidney in PSS [97–99]. About 50 percent of patients do have hypergammaglobulinemia and approximately 50 to 60 percent demonstrate antinuclear antibodies [100]. While the response to corticosteroids is dramatic in SLE, however, therapy with corticosteroids has not proven effective in PSS [101,102].
Additionally, pathologic examination of involved arteries reveals the predominant lesion to be intimal proliferation and/or thickening, with fibrosis and narrowing of the vascular lumen. An arteritis is seen only occasionally in acute forms of the disease [103]. It currently appears more likely, as some postulate, that a failure of vasoregulatory mechanisms may be the initiating event and that the autoimmune findings in PSS are epiphenomena [104].

While evidence presently is scanty for a humoral mechanism in the pathogenesis of this disease, more recent studies suggest cell-mediated immunity may have an important role. Dermal cellular infiltrates in PSS consist mostly of T lymphocytes [105]. These cells appear to be sensitized to skin extracts taken from patients with PSS. Others have shown that normal human peripheral blood mononuclear cells, when stimulated with phytohemagglutinin, produce a lymphokine which increases collagen accumulation in human embryonic lung fibroblast cultures [106]. Fibroblasts isolated from patients with PSS and cultured in vitro demonstrate increases in collagen accumulation over controls [107]. The fact that this effect persists for many generations suggests that the mechanisms governing growth reside within the cell, but does not rule out an important role for cell-mediated immunity. Lastly, some patients with PSS develop Sjögren’s syndrome which is associated, in part, with a T-cell-mediated reaction [108]. All these factors taken together are highly suggestive that cell-mediated immunity is involved in PSS.

WEGENER’S GRANULOMATOSIS

This disease has a distinctive clinico-pathologic triad of necrotizing granulomatous vasculitis of the upper and lower respiratory tracts, glomerulonephritis, and variable degrees of disseminated small vessel vasculitis [1]. The etiology of this disease is unknown and the immunologic components have not been well defined. Several observations suggest both immune complex (type III) and cell-mediated (type IV) mechanisms may be involved (Table 1). First, serologic testing has revealed the presence of rheumatoid factor in many of these patients [109-112]. Antinuclear antibody is also seen occasionally [111]. Second, and more convincing, is the observation that circulating immune complexes [111] can be found in some patients with active disease. The failure of others to find immune complexes may be explained by the observation that immune reactants are often undetectable in vessel walls 24 to 48 hours after their injection into animals [109,113]. Third, in some patients, renal electron microscopic and immunofluorescence findings are consistent with immune complex disease [114]. In other cases, granular immunofluorescent deposits have been seen [115-118]. However, others have shown that many cases lack these hallmarks of immune-complex-mediated disease [119].

The evidence for involvement of cell-mediated immune mechanisms is equally suggestive. Favoring a role for cell-mediated immunity is the presence of a characteristic necrotizing granulomatous vasculitis [15]. These lesions represent a collection of lymphocytes, histiocytes, plasma cells, and Langhans’ type giant cells. Small arteries and veins are similarly involved. Granulomas similar to those seen in sarcoidosis are uncommon but are occasionally seen [120]. Langhans’ type giant cells are likely formed from the coalescence and fusion of macrophages [121,122]. The presence of these cells along with a granulomatous inflammatory reaction suggests type IV reactivity [121,123]. Furthermore, defects in delayed hypersensitivity reactions [124] and impaired lymphocyte-blast transformation have been demonstrated [125]. Accordingly, the suspicion that hypersensitivity mechanisms may be
involved [121,126] persists [123]. As suggested by Fauci et al. [109], it is possible that circulating antigen triggers sensitized lymphocytes to release lymphokines which initiate a granulomatous reaction with granuloma and giant cell formation (Fig. 4). Alternatively, immune complexes may be phagocytosed by macrophages, resulting in activation of this cell and initiating granuloma formation [109] (Fig. 4).

In summary, perturbations in both humoral and cell-mediated immunity appear to be present. It remains unclear whether the immune system has primary importance in the pathogenesis of this disease.

LYMPHOMATOID GRANULOMATOSIS

Lymphomatoid granulomatosis is a disease grouped, along with Wegener's granulomatosis, under the heading of granulomatous vasculitis [1]. While in certain cases it is difficult to distinguish this entity from Wegener's granulomatosis, important pathological differences exist which suggest different immunopathological mechanisms may be operating. First, the characteristic pathology of this disease is an angiotrophic and angiodestructive infiltration of tissues by atypical lymphomatoid and plasmacytoid cells [127]. Second, in this disease the "granulomatosis" consists of necrotic foci, occasionally involving areas infiltrated with these atypical cells, but also occasionally involving lung tissue not extensively infiltrated and in continuity with necrotic vessels [127]. Third, small noncaseating sarcoid-like granulomas were found in only one of the first 40 cases reported [127]. Fourth, Langhans' type giant cells are also conspicuously absent [127–129]. Fifth, these findings are in contrast to the pathologic findings in Wegener's granulomatosis [112] previously described. Sixth, the renal disease is not a glomerulonephritis as seen in

![FIG. 4. Immune complex and cell-mediated immune mechanisms of granulomatous vasculitis. (Adapted from Fauci et al. [108] with permission of the publisher.) Antigen interacts with lymphocytes, causing the release of lymphokines which recruit and activate macrophages. The activated macrophage may also result from interaction with immune complexes. Activated macrophages may ultimately evolve into granulomas. In addition, this cell complement and polymorphonuclear cells (PMN) induce a vascular inflammatory reaction.](image-url)
Wegener's [112]. Seventh, Liebow et al., in their original description of this entity, stressed that there is no clear evidence of an autoimmune state [127]. Eighth, antinuclear antibodies have been reported as negative [112,127,130], and only rarely has a patient had a positive rheumatoid factor [127].

Others have speculated that an acquired abnormality of the lymphocyte may be involved, based on the absence of delayed hypersensitivity to skin test antigens, including dinitrochloro-benzene, and the response of the lung lesions to corticosteroids [130]. Liebow et al. [127] were impressed by the lack of obvious evidence of autoimmune phenomena and suggested that a viral agent may be the cause.

In summary, adequate numbers of cases have not been studied with the aim of delineating immunologic perturbations to permit a conclusion about a potential pathogenetic role for the immune system in this disease. Clearly, this is a fruitful area for future investigations.

ALLERGIC ANGIIITIS AND GRANULOMATOSIS
(CHURG-STRAUSS SYNDROME)

Churg and Strauss first described this syndrome in 1951 [131]. It is a disease which in some ways strongly resembles classic polyarteritis nodosa (PAN) but also has several distinguishing features: association with an allergic diathesis, prominent lung involvement manifested by eosinophilic infiltrates, and the presence of vascular and extravascular granulomas [15,131–133]. Complete data on the immunological aberrations in this disease are lacking. The rarity of the disease contributes to our limited insight into its immunopathogenesis.

Much of the evidence supporting a role for immune mechanisms in this disease has been extrapolated from the apparently closely related disease, PAN. An association, in some cases, between the classic form of PAN and hepatitis B antigenemia is now well established [112,134]. Moreover, additional studies suggest that immune complexes of hepatitis B antigen and antibody may be playing an important role in the pathogenesis of PAN [135]. Because Churg-Strauss syndrome possesses some of the pathologic abnormalities seen in PAN, it is reasonable to speculate that similar immunologic mechanisms of tissue injury may be involved. First, several patients have been found to possess positive rheumatoid factor [133]. Most of these titers were low, but two patients had titers >1:2,560. Second, one patient has been described with immunofluorescent evidence for immunoglobulin and complement in the pulmonary vascular lesions [136].

The fact that this disease occurs primarily in patients with an allergic background or asthma or both may also be etiologically significant [131]. The presence of eosinophilia and serum elevations of IgE [133] in some of these patients suggests that an immediate hypersensitivity (type I) reaction may be involved [15] (Table 1). In this regard, it is of interest that in one series asthma was present for a mean of eight years prior to the detection of vasculitis [133]. It remains unclear whether these findings are an early manifestation of the disease or somehow predispose to its development.

The characteristic pathologic changes in this syndrome include necrotizing extravascular granulomas and necrotizing vasculitis of small arteries and veins [131,133]. Giant cells of the Langhans' type are also present frequently [131]. Similar giant cells are seen in some cases of Wegener's granulomatosis, as previously discussed, and they suggest that cell-mediated immune mechanisms also may be involved [121,123].
In summary, it must be emphasized that the above observations really are only tantalizing clues to the immunologic mechanisms that may be involved. The current sophistication of our ability to survey many components of the immune system will, we hope, soon be used to improve our understanding of the pathogenesis of this disease.

REFERENCES

1. Matthay RA, Bromberg SI, Putman CE: Pulmonary renal syndromes—A Review. Yale J Biol Med 53:497–523, 1980
2. Benoit FL, Rulon DB, Their GB, et al: Goodpasture's syndrome. Am J Med 37:424–444, 1964
3. Hunninghake GW, Fauci AS: Pulmonary involvement in the collagen vascular diseases. Am Rev Respir Dis 119:471–503, 1979
4. Teague CA, Doak PB, Simpson IJ, et al: Goodpasture's syndrome: an analysis of 29 cases. Kidney Int 13:492–504, 1978
5. Schwartz EE, Teplick JG, Onesti G, et al: Pulmonary hemorrhage in renal disease: Goodpasture's syndrome and other causes. Radiology 122:36–39, 1977
6. Goodpasture EW: The significance of certain pulmonary lesions in relation to the etiology of influenza. Am J Med Sci 158:863–870, 1919
7. Wilson CB, Dixon FJ: Antiglomerular basement membrane antibody induced glomerulonephritis. Kidney Int 3:74–89, 1973
8. Fauci AS, Wolf SM: Wegener's granulomatosis and related diseases. In Disease-A-Month Vol 23, No 7. Edited by HF Dowling. Chicago, Year Book Medical Publishers, Inc, 1977, pp 1–36
9. Lerner RA, 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
10. Poskitt TR: Immunologic and electron microscopic studies in Goodpasture's syndrome. Am J Med 49:250–257, 1970
11. Wilson DB, Dixon FJ: Diagnosis of immunopathologic renal disease (editorial). Kidney Int 5: 390–401, 1974
12. McPhaul JJ Jr, Dixon FJ: The presence of antiglomerular basement membrane antibodies in peripheral blood. J Immunol 103:1168–1175, 1969
13. Matthew TH, Hobbs JB, Kalowski S, et al: Goodpasture's syndrome normal renal diagnostic findings. Ann Intern Med 82:215–218, 1975
14. Lockwood CM, Boulton-Jones JM, Lowenthal RM, et al: Recovery from Goodpasture's syndrome after immunosuppressive treatment and plasmaphoresis. Br Med J 2:252–254, 1975
15. Schatz M, Patterson R, Fink J: Immunologic lung disease. N Engl J Med 300:1310–1320, 1979
16. Benacerraf B, Unanue ER: Textbook of Immunology. Baltimore, MD, Williams and Wilkins Co, 1979, pp 166–246
17. Wilson CB, Neale J, Holdsworth JR, et al: Renal Diseases. In Basic and Clinical Immunology. Edited by HH Fudenberg, DP Sites, JL Caldwell, JV Wells. Los Altos, Lange Medical Publications, 1980, pp 568–579
18. Merrill JP: Glomerulonephritis. N Engl J Med 290:257–266, 313–319, 374–380, 1974
19. 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
20. Steblay RW: Glomerulonephritis induced in monkeys by injections of heterologous glomerular basement membrane and Freund's adjuvant. Nature (London) 197:1173–1176, 1963
21. Lerner RA, Dixon FJ: Transfer of ovine experimental allergic glomerulonephritis (EAG) with serum. J Exp Med 124:431–442, 1966
22. Cochrane CG, Unanue ER, Dixon FJ: A role of polymorphonuclear leukocytes and complement in nephrototoxic nephritis. J Exp Med 122:99–117, 1965
23. Naish PF, Thomson NM, Simpson IJ, et al: The role of polymorphonuclear leukocytes in the autologous phase of nephrototoxic nephritis. Clin Exp Immunol 22:102–111, 1975
24. Holdsworth SR, Neale TJ, Wilson CB: Abrogation of macrophage-dependent injury in experi-mental glomerulonephritis in the rabbit. J Clin Invest 68:686–698, 1981
25. McPhaul JJ Jr, Mullins JD: Glomerulonephritis mediated by antibody to glomerular basement membrane: immunological, clinical and histopathological characteristics. J Clin Invest 57:351–361, 1976
26. Beechler CR, Enquist RW, Hunt KK, et al: Immunofluorescence of transbronchial biopsies in Goodpasture's Syndrome. Am Rev Respir Dis 121:869–872, 1980
27. Abboud RT, Chase WH, Ballon HS, et al: Goodpasture's Syndrome: Diagnosis by transbronchial biopsy. Ann Intern Med 89:635–638, 1978
28. Border WA, Boheler RW, Hathena D, et al: IgA anti-basement membrane nephritis with pulmonary hemorrhage. Ann Intern Med 91:21–25, 1979
29. Mahieu P, Lambert PH, Miescher PA: Detection of antiglomerular basement membrane antibodies by a radioimmunological technique: clinical application in human nephropathies. J Clin Invest 54:128–137, 1974
30. Koffler D, Sandson J, Carr R: Immunologic studies concerning the pulmonary lesions in Goodpasture's Syndrome. Am J Path 54:293–305, 1969
31. Lockwood CM, Boulton-Jones JM, Wilson CB: Plasmaphoresis: the role of this new technique in the recovery of a patient with Goodpasture's Syndrome and severe renal failure. Sixth International Congress on Nephrology, Florence, 1975
32. Rosenblatt SG, Knight W, Bannaran GA, et al: Treatment of Goodpasture's Syndrome with plasmaphoresis: A Case Report and Review of the Literature. Am J Med 66:689–696, 1979
33. Case 17-1976. N Engl J Med 294:944–951, 1976
34. McPhaul JJ Jr, Dixon FJ: Immunoreactive basement membrane in normal human urine and serum. J Exp Med 130:1395–1409, 1969
35. Willoughby WF, Dixon FJ: Experimental hemorrhagic pneumonitis produced by heterologous anti-lung antibody. J Immunol 104:28–37, 1970
36. Lerner RA, Dixon FJ: The induction of acute glomerulonephritis in rabbits with soluble antigens isolated from normal homologous and autologous urine. J Immunol 100:1277–1287, 1968
37. Wilson CB, Smith RC: Goodpasture's syndrome associated with influenza A2 virus infection. Ann Intern Med 76:91–94, 1972
38. Pasternack E, Linder E, Kuhlback B: Glomerulonephritis with initial pulmonary hemorrhage. Acta Med Scand 177:601–605, 1965
39. Goodpasture EW: The significance of certain pulmonary lesions in relation to the etiology of influenza. Am J Med Sci 158:863–870, 1919
40. Beirne GJ: Goodpasture's syndrome and exposure to solvents. JAMA 222:1555, 1972
41. Beirne GJ, Brennan JJ: Glomerulonephritis associated with exposure to hydrocarbons: mediated by antibodies to glomerular basement membranes. Arch Environ Health 25:365–369, 1972
42. Markowitz AS, Lange CF Jr: Streptococcal related glomerulonephritis. I. Isolation, immunchemistry and comparative chemistry of soluble fractions from type 12 nephritogenic streptococci and human glomeruli. J Immunol 92:565–575, 1964
43. D'Apice AFJ, Kincaid-Smith P, Becker GJ: Goodpasture's syndrome in identical twins. Ann Intern Med 88:61–62, 1978
44. Rees AJ, Peters DK, Comston DAS, et al: Strong association between HLA-DRW2 and antibody-mediated Goodpasture's syndrome. Lancet 1:966–968, 1974
45. Cochrane CG, Koffler D: Immune complex disease in experimental animals and man. Adv Immunol 16:185–264, 1973
46. Schwartz MM, Roberts JL, Eagen JH, et al: Immune-complex-mediated pulmonary disease. N Engl J Med 301:724, 1979
47. Koffler D, Agnello V, Thoburn R: Systemic Lupus Erythematosus: prototype of immune complex nephritis in man. J Exp Med 134: Suppl:169–171, 1971
48. Wiggins RC, Cochrane CG: Immune-complex-mediated biological effects. N Engl J Med 304:518–580, 1981
49. Couser WG: What are circulating immune complexes doing in glomerulonephritis? N Engl J Med 1230–1232, 1981
50. Weissmann G, Smolen JE, Korchak HM: Release of inflammatory mediators from stimulated neutrophils. N Engl J Med 303:27–34, 1980
51. Matthay RA, Schwartz MI, Petty TL, et al: Pulmonary manifestations of systemic lupus erythematosus: review of twelve cases of acute lupus pneumonitis. Medicine 54:397–409, 1975
52. Inoue T, Kanayama Y, Ohe A, et al: Immunologic pathologic studies of pneumonitis in systemic lupus erythematosus. Ann Intern Med 91:30–33, 1979
53. Clark RA, Kimball HR, Decker JL: Neutrophil chemotaxis in systemic lupus erythematosus. Ann Rheum Dis 33:167–172, 1974
54. Staples PJ, Gering DN, Decker JL, et al: Incidence of infection in systemic lupus erythematosus. Arthritis Rheum 17:1–20, 1970
55. Matthay RA, Hudson LD, Petty TL: Acute lupus erythematosus: Response to azathioprine therapy. Chest 63:117–120, 1973
56. Levin DC: Proper interpretation of pulmonary roentgen changes in systemic lupus erythematosus. Am J Roentgenol Ther Nucl Med 111:510–517, 1971
57. Matthay RA, Petty TL: Treatment of acute lupus pneumonitis with azathioprine. Chest 66:219–220, 1974
58. Israel HC: The pulmonary manifestations of disseminated lupus erythematosus. Am J Med Sci 226:387–392, 1953
59. Hoffbrand BI, Beck ER: Unexplained dyspnea and shrinking lungs in systemic lupus erythematosus. Br Med J 12:1273–1276, 1965
60. Harvey AM, Shulman LE, Tumulty PA, et al: Systemic lupus erythematosus: Review of the literature and clinical analysis of 138 cases. Medicine 33:291–437, 1954
61. Gould DM, Daves MC: Roentgenologic findings in systemic lupus erythematosus. An analysis of 100 cases. J Chron Dis 2:136–146, 1955
62. Estes D, Christian CL: The natural history of systemic lupus erythematosus by prospective analysis. Medicine 50:85–95, 1971
63. Ellman P, Cudkowicz L: Pulmonary manifestations of diffuse collagen diseases. Thorax 9:46–57, 1954
64. Eisenberg H, Dubois EL, Sherwin RP, et al: Diffuse interstitial disease in systemic lupus erythematosus. Ann Intern Med 79:37–45, 1973
65. Dubois EL: The clinical picture of systemic lupus erythematosus. In Lupus Erythematosus: A review of the current status of discoid and systemic lupus erythematosus and their variants. 2nd ed. Los Angeles, University of Southern California Press, 1974, p 380
66. Dubois EL, Tuffanelli DL: Clinical manifestations of systemic lupus erythematosus. JAMA 190:104–109, 1964
67. Divertie MB: Systemic lupus erythematosus. Med Clin North Am 49:1016–1030, 1964
68. Alarcon-Segovia D, Alarcon DG: Pleuropulmonary manifestations of systemic lupus erythematosus. Dis Chest 39:7–17, 1961
69. Wohlgelernter D, Loke J, Matthay RA, et al: Systemic and discoid lupus erythematosus: analysis of pulmonary function. Yale J Biol Med 51:157–164, 1978
70. Huang CT, Hennigar GR, Lyons HA: Pulmonary dysfunction in systemic lupus erythematosus. N Engl J Med 272:28–293, 1965
71. Eagen JW, Memoli VA, Roberts JL, et al: Pulmonary hemorrhage in systemic lupus erythematosus. Medicine 57:545–547, 1974
72. Turner-Warwick M: Immunological aspects of systemic diseases of the lung. Proc R Soc Med 67:541–547, 1974
73. Yeo PPB, Sinniah R: Lupus cor pulmonale with electron microscope and immunofluorescent antibody studies. Ann Rheum Dis 34:457–460, 1975
74. Brentjens J, Ossi E, Albini B: Disseminated immune deposits in lupus erythematosus. Arthritis Rheum 20:962–968, 1977
75. Eisenberg H, Simmons DH, Barnett EV: Diffuse pulmonary interstitial disease: An immunohistologic study. Chest 75:Suppl 262–264, 1979
76. Brentjens JR, O'Connell DW, Pawlowski IB, et al: Experimental immune complex disease of the lung. J Exp Med 140:105–125, 1974
77. Inoue T, Kanayama Y, Ohe A, et al: Immunopathologic studies of pneumonitis in systemic lupus erythematosus. Ann Intern Med 91:30–34, 1979
78. Weinberger SE, Kelman JA, Elson NA, et al: Bronchoalveolar lavage in interstitial lung disease. Ann Intern Med 89:459–466, 1978
79. Hunninghake G, Fauci A: Pulmonary involvement in the collagen vascular diseases. Am Rev Respir Dis 119:471–503, 1979
80. Hunninghake GW, Gallin JI, Fauci AS: Immunological reactivity of the lung: The in vivo and in vitro release of a neutrophil chemotactic factor by alveolar macrophages. Am Rev Respir Dis 15:117, 1978
81. Kazmierski JA, Gallin JI, Reynolds HY: Mechanism for the inflammatory response in primate lungs: Demonstration and partial characterization of an alveolar macrophage chemotactic factor with preferential activity for polymorphonuclear leukocytes. J Clin Invest 59:273, 1977
82. Gadek J, Hunninghake GW, Zimmerman RL, et al: Regulation of release of alveolar macrophage derived neutrophil chemotactic factor. Am Rev Respir Dis 121:723–733, 1980
83. Gadek JE, Hunninghake GW, Lawley TA, et al: Role of immune complexes in amplifying the alveolitis of idiopathic pulmonary fibrosis. Clin Res (Abstr) 26:446A, 1978
84. Cannon PJ: Medical management of renal scleroderma. N Engl J Med 299:886-887, 1978
85. Wilson RJ, Rodnan GP, Robin EP: An early pulmonary physiologic abnormality in progressive systemic sclerosis (diffuse scleroderma). Am J Med 36:361, 1964
86. Salerni R, Rodnan GP, Leon DF, et al: Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (scleroderma). Ann Intern Med 86:394-397, 1977
87. Sackner MA, Akgun N, Kimbel P, et al: The pathophysiology of scleroderma involving the heart and respiratory system. Ann Intern Med 60:611, 1964
88. D'Angelo WA, Fries JF, Masi AT, et al: Pathologic observations in systemic sclerosis (scleroderma): A study of fifty-eight autopsy cases and fifty-eight matched controls. Am J Med 46:428, 1969
89. Colp CR, Riker J, Williams MH: Serial changes in scleroderma and idiopathic interstitial lung disease. Arch Intern Med 132:506, 1973
90. Trelle E, Lindstrom C: Pulmonary hypertension in systemic sclerosis. Ann Rheum Dis 30:390, 1971
91. Godfrey S, Bluestone R, Higgs BE: Lung function in response to exercise in systemic sclerosis. Thorax 24:427, 1969
92. Hughes DTD, Lee FL: Lung function in patients with systemic sclerosis. Thorax 18:16, 1963
93. Ritchie B: Pulmonary function in scleroderma. Thorax 19:28, 1964
94. Adhakari PK, Bianchi FA, Boushy SF, et al: Pulmonary function in scleroderma: Its relation to changes in the chest roentgenogram and in the skin in the thorax. Am Rev Respir Dis 86:823, 1962
95. Spain DM, Thomas AG: The pulmonary manifestations of scleroderma: An anatomic-physiologic correlation. Ann Intern Med 32:152, 1950
96. Sackner MA, Akgun N, Kimball P, et al: The pathophysiology of scleroderma involving the heart and respiratory system. Ann Intern Med 60:611-630, 1964
97. McGiven AR, De Boer WGRM, Barnett AJ: Renal immune deposits in scleroderma. Pathology 3:145-150, 1971
98. Scott DG, Rowell MR: Immunohistological studies of the kidney in systemic lupus erythematosus and systemic sclerosis using anti sera to IgG, C3, Fibrin, and human renal glomeruli. Ann Rheum Dis 33:473-481, 1974
99. Gerken MA: Immunohistochemical findings in the renal vascular lesions of progressive systemic sclerosis. Hum Pathol 6:343-347, 1975
100. Winklemann RK: Pathogenesis and staging of scleroderma. Acta Derm Venereol (Stockh) 56:83-92, 1976
101. Colp CR, Riker J, Williams MH: Serial changes in scleroderma and idiopathic interstitial lung disease. Arch Intern Med 132:506-515, 1973
102. Siltzbach LE: Progressive systemic sclerosis with pulmonary involvement. Dis Chest 54:487-488, 1968
103. Robbins SL, Cotran RS: Pathology. Philadelphia, PA, WB Saunders Co, 1979
104. Fries J: The microvascular pathogenesis of scleroderma: A hypothesis. Ann Intern Med 91:788-789, 1979
105. Kondo H, Rabin BS, Rodnan GP: Cutaneous antigen stimulating lymphokine production by lymphocytes of patients with progressive systemic sclerosis (scleroderma). J Clin Invest 58:1388-1394, 1976
106. Johnson RL, Ziff M: Lymphokine stimulation of collagen accumulation. J Clin Invest 58:240-252, 1976
107. Buckingham RB, Prince RK, Rodnan GP: Increased collagen accumulation in dermal fibroblast cultures from patients with progressive systemic sclerosis (scleroderma). J Lab Clin Med 92:5-21, 1978
108. Robbins S, Cotran R: Pathology. Philadelphia, PA, WB Saunders Co, 1979, pp 306-309
109. Fauci AS, Haynes BF, Katz P: The spectrum of vasculitis. Ann Int Med 89:660-676, 1978
110. DeRemee RA, Weiland LH, McDonald TJ: Respiratory vasculitis. Mayo Clin Proc 55:492-498, 1980
111. Howell SB, Epstein WV: Circulating immunoglobulin complexes in Wegener's granulomatosis. Am J Med 60:259-268, 1976
112. Israel HL, Patchefsky AS, Saldana MJ: Wegener's granulomatosis, lymphomatoid granulomatosis, and benign lymphocytic angiitis and granulomatosis of the lung. Ann Intern Med 87:691-699, 1977
113. Cochrane CG, Weigle WO, Dixon FJ: The role of polymorphonuclear leukocytes in the initiation and cessation of the arthus vasculitis. J Exp Med 110:481-494, 1959
114. Wolff SM, Fauci AS, Horn RG, et al: Wegener's granulomatosis. Ann Intern Med 81:513–525, 1974
115. Case Records of the Massachusetts General Hospital (Case 15-1969). N Engl J Med 280:828–834, 1969
116. Case Records of the Massachusetts General Hospital (Case 29-1974). N Engl J Med 291:195–202, 1974
117. Case Records of the Massachusetts General Hospital (Case 24-1979). N Engl J Med 300:1378–1385, 1979
118. Hensley MJ, Feldman MT, Lazarus JM, et al: Diffuse pulmonary hemorrhage and rapidly progressive renal failure. Am J Med 66:894–898, 1979
119. Balow JE, Antonovych T, Fauci AS, et al: The nephritis of Wegener's granulomatosis. Kidney Int 14: (Abstr) 706, 1978
120. Carrington CB, Liebow A: Limited forms of angiitis and granulomatosis of Wegener's type. Am J Med 41:497–527, 1966
121. Robins SL, Cotran RS: Pathology. Philadelphia, PA, WB Saunders Co, 1979, pp 84–86
122. Epstein WL: Granulomatous Hypersensitivity. Prog Allergy 11:36–38, 1967
123. Robins SL, Cotran RS: Pathology. Philadelphia, PA, WB Saunders Co, 1979, pp 316–317
124. Fauci AS, Wolff SM, Johnson JS: Effects of cyclophosphamide upon the immune response in Wegener's granulomatosis. N Engl J Med 285:1493–1496, 1971
125. Niinaka T, Okochi T, Watanaka Y, et al: Lymphocyte functions in Wegener's granulomatosis. J Med 9:491–501, 1978
126. Godman GC, Chung J: Wegener's granulomatosis: pathology and review of the literature. Arch Pathol 58:533–553, 1954
127. Liebow AA, Carrington CRB, Friedman PJ: Lymphomatoid granulomatosis. Hum Pathol 3:457–558, 1972
128. Case Records of the Massachusetts General Hospital (Case 19-1976). N Engl J Med 294:1052–1056, 1976
129. Case Records of the Massachusetts General Hospital (Case 31-1975). N Engl J Med 293:294–298, 1975
130. Bone RC, Verman M, Sobonya RE, et al: Lymphomatoid granulomatosis. Report of a case and review of the literature. Am J Med 65:709–716, 1978
131. Churg J, Strauss L: Allergic granulomatosis, allergic angiitis and periarteritis nodosa. Am J Pathol 27:277–301, 1951
132. Rose GA, Spencer H: Polyarteritis nodosa. Q J Med 26:43–81, 1957
133. Chumley LC, Harrison EG Jr, DeRemee RA: Allergic granulomatosis and angiitis (Churg-Strauss syndrome): report and analysis of 30 cases. Mayo Clin Proc 52:477–484, 1977
134. Sergent JS, Lockshin MD, Christian CL, et al: Vasculitis with hepatitis B antigenemia: long term observations in nine patients. Medicine 55:1–18, 1976
135. Trepo CG, Zuckerman AJ, Bird RC: The role of circulating hepatitis B antigen/antibody immune complexes in the pathogenesis of vascular and hepatic manifestations in polyarteritis nodosa. J Clin Pathol 27:863–868, 1974
136. Paronetto F: Systemic non-supportive necrotizing angiitis. In Textbook of Immunopathology. II. Second Edition. Edited by PA Miescher, HJ Muller-Eberhard. New York, Grune and Stratton, 1976, pp 1013–1024