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Pulmonary Renal Syndromes
II. Etiology and Pathogenesis

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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

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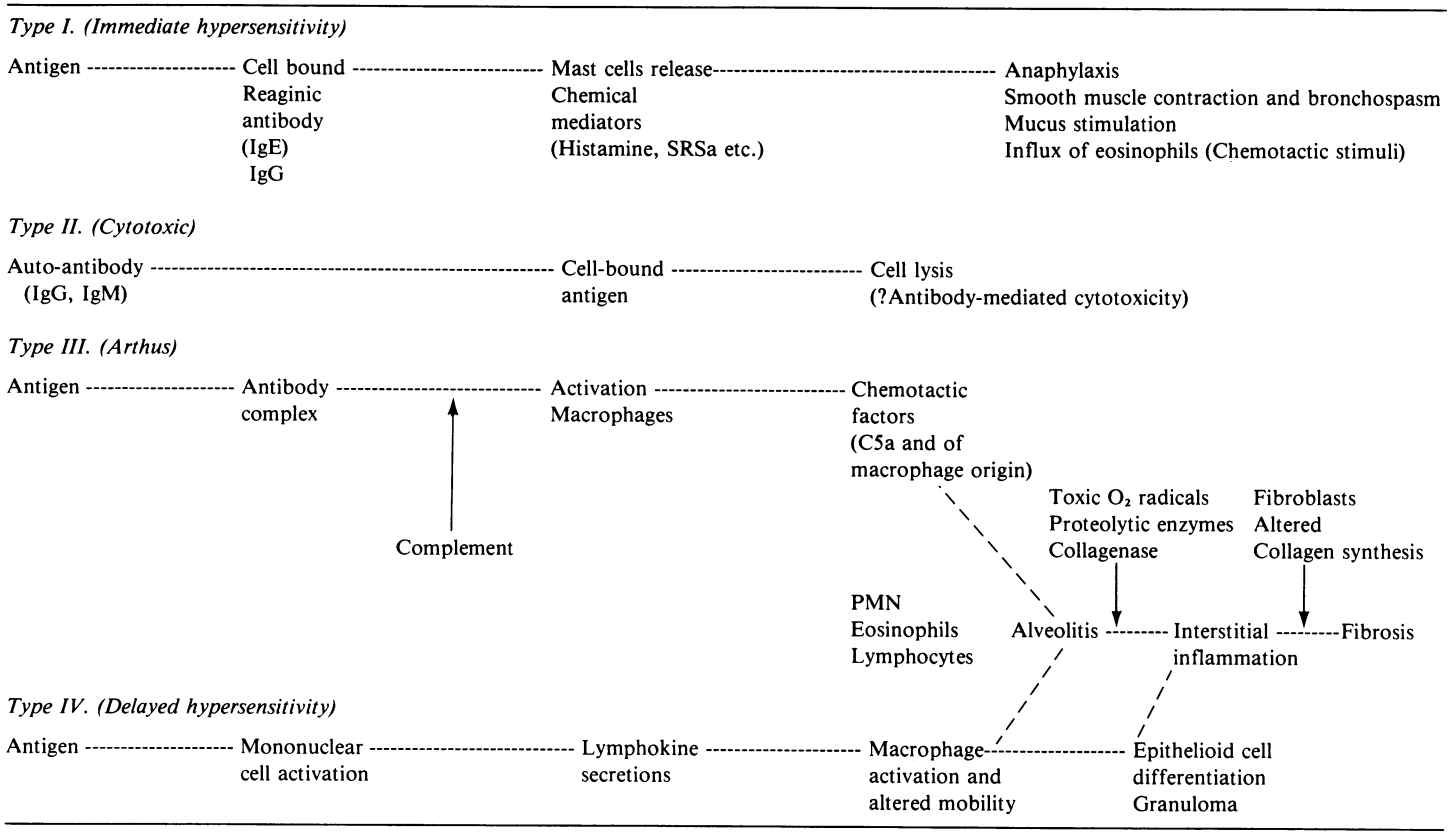
TABLE 1
Hypersensitivity Reactions



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 fixing 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 recurred 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-

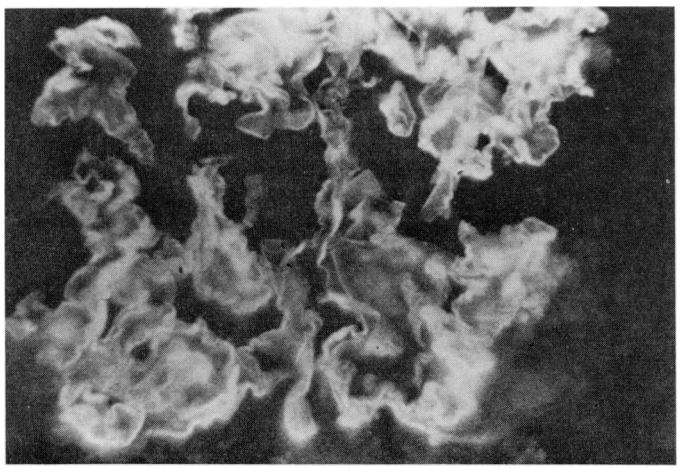


FIG. 1. Goodpasture's syndrome—renal tissue (post-mortem) revealing the classic linear immunofluorescent staining for IgG anti-glomerular basement membrane antibody. (Photograph courtesy of Dr. M. Kashkarian, Dept. of Pathology, Yale University School of Medicine.)

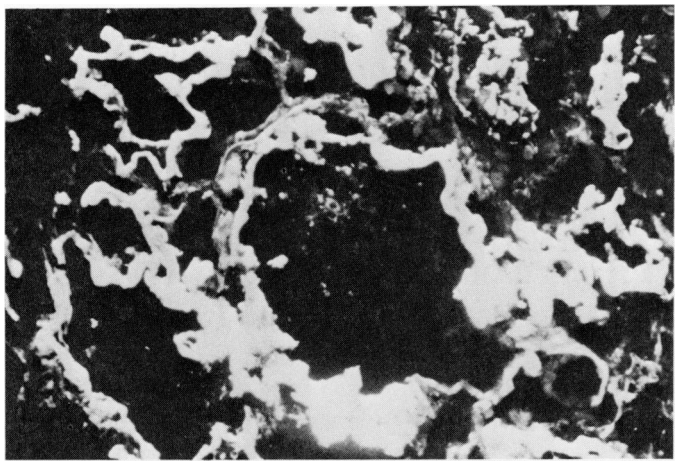


FIG. 2. Goodpasture's syndrome—lung tissue (post-mortem) demonstrating positive immunofluorescence for linear deposits of IgG antibody on alveolar basement membrane. (Photograph courtesy of Dr. M. Kashkarian, Dept. of Pathology, Yale University School of Medicine.)

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 remian 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

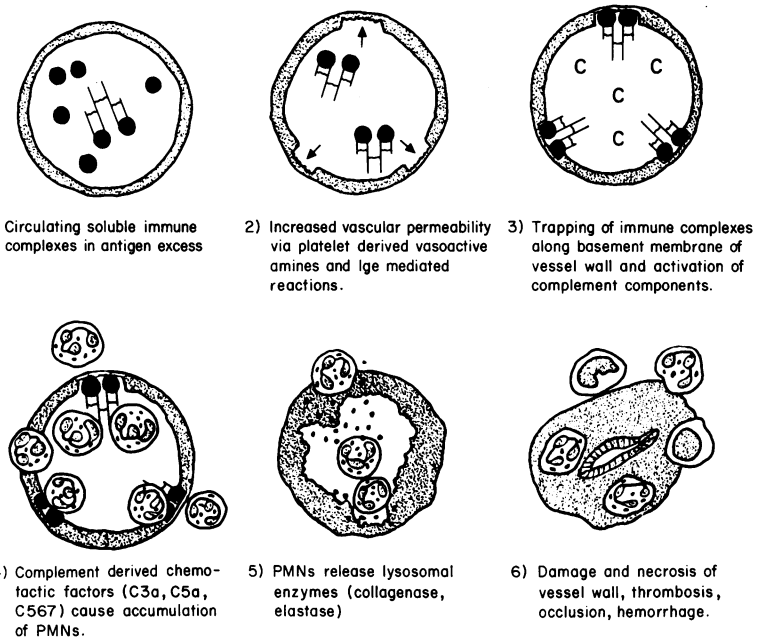


FIG. 3. Circulating immune complexes of intermediate size form. Vascular permeability is altered by vasoactive amines released from platelets or basophils which interact with these immune complexes. The complexes are trapped in vessel walls and activate complement which causes polymorphonuclear chemotaxis 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 C_{1q} component in the pulmonary arteries of three patients. Small deposits have also been described in the interlobular 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 phytohemaglutinin, 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

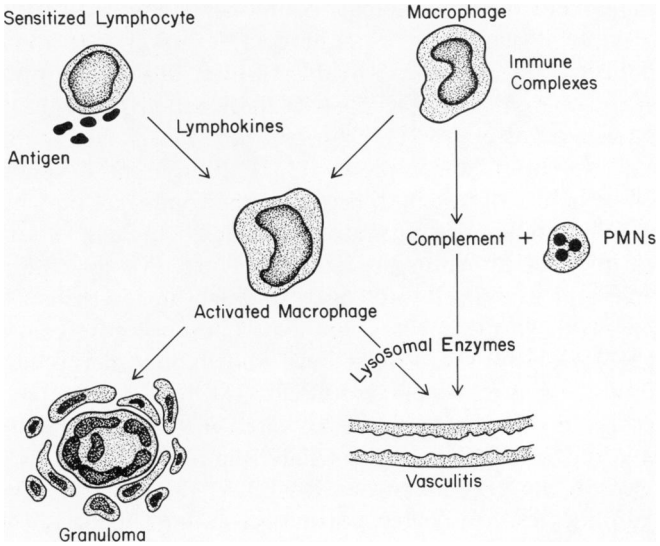


FIG. 4. Immune complex and cell-mediated immune mechanisms of granulomatous vasculitis. (Adapted from Fauci et al. [108] with permission of the publisher.) Antigen interacts with lymphocytes, causing the release of lymphokines which recruit and activate macrophages. The activated macrophage may also 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.

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 ANGIITIS 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 aberrancies 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.

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