62

Goodpasture Syndrome and the Diffuse Alveolar Hemorrhage Syndrome

Stephen M. Bonsib

Diffuse alveolar hemorrhage (DAH) can be one of the most dramatic manifestations of pulmonary disease, prompting an immediate medical consultation.[1–6] DAH may develop within the context of several pulmonary diseases, as part of a systemic disorder, or as a complication of therapy.[1–6] Regardless of the cause, patients with DAH present the triad of hemoptysis, anemia, and alveolar-filling densities on chest x-ray films.[1,2,4] The source of bleeding in DAH is usually widespread, originating from the microvasculature of the lung with erythrocytes and fibrin pouring into alveolar spaces.

In patients with DAH syndrome and extrapulmonary disease, the systemic manifestations provide important clues to the diagnosis and influence the clinical workup (Table 62-1). The extrapulmonary components, particularly the severity of renal involvement, significantly affect the patient's prognosis, regardless of the underlying cause.[7,8]

CLASSIFICATION

The etiologic diversity within DAH syndromes became apparent in 1973 with the identification of two immunologic mechanisms in these patients. Wilson and Dixon identified the antiglomerular basement membrane antibody (AGBM) in a subgroup of patients with DAH and rapidly progressive glomerulonephritis (RPGN), now known as Goodpasture syndrome (GPS), and several groups identified immune complexes associated with DAH and proliferative glomerulonephritis.[9,10] The appreciation that diverse pathogenic mechanisms may mediate DAH prompted Thomas and Irwin in 1975 to divide DAH into three categories: GPS, immune complex–associated DAH, and idiopathic pulmonary hemosiderosis (IPH).[10]

In the 1980s, additional categories of DAH were recognized: systemic vasculitis, idiopathic crescentic glomerulonephritis, and exposure to exogenous agents that expanded the classification.[2,4] With the discovery of a serologic marker for necrotizing vasculitis, antineutrophil cytoplasmic antibody (ANCA), an immunopathologically oriented schema has been formulated (see Table 62-1). The causes identified in two large series of patients with DAH are listed in Table 62-2.[2,3]

ETIOLOGY

Because immunologic factors appear responsible for or contribute to the parenchymal injury in the first three categories, the serologic assessment of patients suspected of having a DAH syndrome should become the cornerstone of clinical evaluation. The crucial serologic tests are for AGBM and ANCA. Before a discussion of the causes of DAH, the roles of AGBM and ANCA autoantibodies and necrotizing alveolitis, which is responsible for the alveolar bleeding in many DAH syndromes, are reviewed.

Antiglomerular Basement Membrane Antibody

The inaugural report on DAH syndrome was Goodpasture's description in 1919 of two patients who developed a fatal syndrome of alveolar hemorrhage and RPGN after the 1918 influenza epidemic.[11] Forty years later, Stanton and Tange coined the eponym "Goodpasture syndrome" for this pulmonary and renal syndrome.[12] However, pulmonary and renal disease may be encountered in a variety of clinical contexts: AGBM disease, systemic vasculitis,

TABLE 62-1
Diffuse Alveolar Hemorrhage Syndromes

Syndrome	Necrotizing Alveolitis	Erythrocyte and Iron	Other Changes	Direct Immunofluorescence Reaction in Lung	Serology	Systemic Disease	Therapy
AGBM-associated Goodpasture syndrome	+*	+	NS†	Lin IgG	AGBM	Kidney	IS, PE
ANCA-associated vasculitis							
Wegener granulomatosis	+	+	GRAN	–	ANCA	Systemic	IS
Micro PA	+	+	NS	–	ANCA	Systemic	IS
Idio CrGN	+	+	NS	–	ANCA	Kidney	IS
IC-associated DAH							
SLE/MCTD	+	+	NS	Gran IgG	ANA, C_3	Systemic	IS
RA	+	+	NS	Gran IgG	RF	Systemic	IS
HSP	+	+	NS	Gran IgG	–	Skin, gastrointestinal	IS
Cryoglob	–	+	NS	Cryoglob	C_4	Systemic	PE, IS
GNS	–	+	NS	Gran IgG	–	Kidney	IS
Exogenous agent	+	+	NS	–	–	Variable	Remove agent
Idiopathic pulmonary hemosiderosis	–	+	NS	–	–	–	?

** +, indicates presence in some, not necessarily all patients.*
† Nonspecific changes include fibrosis and type 2 pneumocyte hyperplasia.
AGBM, antiglomerular-associated basement membrane; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; C_3, complement 3; C_4, complement 4; CrGN, crescentic glomerulonephritis; Cryoglob, cryoglobulin; DAH, diffuse alveolar hemorrhage; GNS, glomerulonephritis; Gran, granular; HSP, Henoch-Schönlein purpura; IC, immunocomplex; IS, immunosuppressive drugs; Lin, linear; NS, nonspecific changes; PE, plasma exchange; RA, rheumatoid arthritis; RF, rheumatoid factor; SLE/MCTD, systemic lupus erythematosus/mixed connective tissue disease.

immune complex diseases, and spurious causes (*i.e.*, renal and lung diseases with different causes).[1–3,13,14]

During the 1960s, GPS evolved from the nonspecific clinical syndrome of alveolar hemorrhage and RPGN to a specific immunopathologic entity. In 1964, Scheer and Grossman demonstrated a linear deposition of IgG along the glomerular capillary loop basement membranes (Color Fig. 62-1*A*).[15] In 1965, Sturgill and Westervelt demonstrated a similar linear reaction along the alveolar septal basement membranes (Color Fig. 62-1*B*) by direct immunofluorescence (DIF).[16] The pathogenicity of the antibody responsible for these linear reactions was demonstrated in 1967 by Lerner and colleagues by eluting the antibody from kidneys and producing disease in monkeys by passive transfer of the antibody.[17] The specific molecular target of the AGBM antibody resides in the NC1 domain of the α3 chain of type IV collagen.[18] This antibody can be measured in serum.

The diagnosis of GPS requires demonstration of the appropriate linear DIF reactions in lung or kidney, documentation of the antibody in serum or preferably both.[19] However, cautious interpretation of AGBM serology is necessary, because AGBM antibody is detectable in several clinical contexts other than GPS (Display 62-1).[20–24]

TABLE 62-2
Causes of Diffuse Alveolar Hemorrhage Syndromes

Cause	Number of Patients: LEATHERMAN ET AL[2]	Number of Patients: TRAVIS ET AL[3]
Goodpasture syndrome	10	4
Wegener granulomatosis	3	11
Systemic vasculitis	6	3
Idiopathic rapidly progressive glomerulonephritis*	5	2
Connective tissue diseases	1	4
Idiopathic or unclassified†		9
Other	1	1
Total	26	34

** Most are Antineutrophil cytoplasmic antibody–positive and often classified as microscopic polyarteritis.*
† Includes idiopathic pulmonary hemosiderosis.

Antineutrophil Cytoplasmic Antibody

ANCA comprises a family of autoantibodies having specificity for several proteases located in the primary granules of neutrophils and lysosomal granules of monocytes.[25,26] ANCA antibodies can be separated into two broad groups based on their indirect im-

DISPLAY 62-1. CONDITIONS ASSOCIATED WITH ANTIGLOMERULAR BASEMENT MEMBRANE ANTIBODY

Goodpasture syndrome (*i.e.*, pulmonary and renal disease)
Associated pulmonary disease (*i.e.*, no kidney disease)
Antiglomerular basement membrane disease (*i.e.*, no lung disease)
Coexistent antiglomerular basement membrane– and antineutrophil cytoplasmic antibody–associated disease
Renal transplantation in Alport syndrome

munofluorescence staining pattern of ethanol-fixed neutrophils: a cytoplasmic pattern (C-ANCA) and a perinuclear pattern (P-ANCA; Color Fig. 62-2). Most C-ANCA specificity is directed against proteinase 3, and most P-ANCA activity is directed against myeloperoxidase. However, the specificity of 5% of these antibodies has not been determined.[25,26] Serum from most patients with active Wegener granulomatosis contains C-ANCA, and serum from patients with microscopic polyarteritis (MPA) and idiopathic crescentic glomerulonephritis contains P-ANCA. Patients with any form of vasculitis may have either antibody (Display 62-2).

The principal significance of a positive test is that it indicates an ANCA-associated disease. Its pattern or enzyme specificity does not form the basis for further subclassification. A positive test indicates a potentially serious systemic disease or a variant limited to the kidney (*i.e.*, idiopathic crescentic glomerulonephritis), corroborates the pathologist's histologic diagnosis of vasculitis, and assists in resolving the differential diagnosis of a DAH syndrome (see Table 62-1). It also provides the clinician with a serologic marker that can reflect a response to therapy with a declining titer and predict a clinical relapse with a rising titer. The vasculitides and their frequency of a positive test are listed in Display 62-2.

DISPLAY 62-2. ANTINEUTROPHIL CYTOPLASMIC ANTIBODY SEROLOGY IN SYSTEMIC VASCULITIS

ANCA-Positive (%)

Wegener granulomatosis (90%)
Microscopic polyarteritis (90%)
Idiopathic crescentic glomerulonephritis (90%)
Kawasaki disease (90%)
Churg-Strauss syndrome (50%)
Classic polyarteritis nodosa (50%)
Goodpasture syndrome (<50%)

ANCA-negative (0%)

Temporal arteritis
Takayasu arteritis
Schönlein-Henoch purpura
Connective tissue diseases
Cryoglobulinemia
Acute rheumatic fever
Hypersensitivity angiitis

ANCA, antineutrophil cytoplasmic antibody.

Necrotizing Alveolitis

Necrotizing alveolitis (*i.e.*, acute capillaritis, neutrophilic capillaritis) is characterized histologically by an intense neutrophil infiltrate decorating widened and edematous alveolar septa (Fig. 62-1*A*). It is accompanied by fibrin thrombi within alveolar septal capillaries, erythrocytes and nuclear debris within septal walls, and copious intraalveolar erythrocytes and fibrin.[3,27] The preferential location of neutrophils along the septa rather than within alveolar spaces differentiates necrotizing alveolitis from the more common suppurative pneumonias. Although septal necrosis may not be apparent by hematoxylin and eosin staining, the Jones methenamine silver stain (Fig. 62-1*B*) graphically reveals multifocal alteration of septal architecture and disruption of its integrity, permitting brisk capillary bleeding directly into the alveolar spaces.[14]

Necrotizing alveolitis is the most frequently identified inflammatory lesion responsible for widespread intraalveolar bleed-

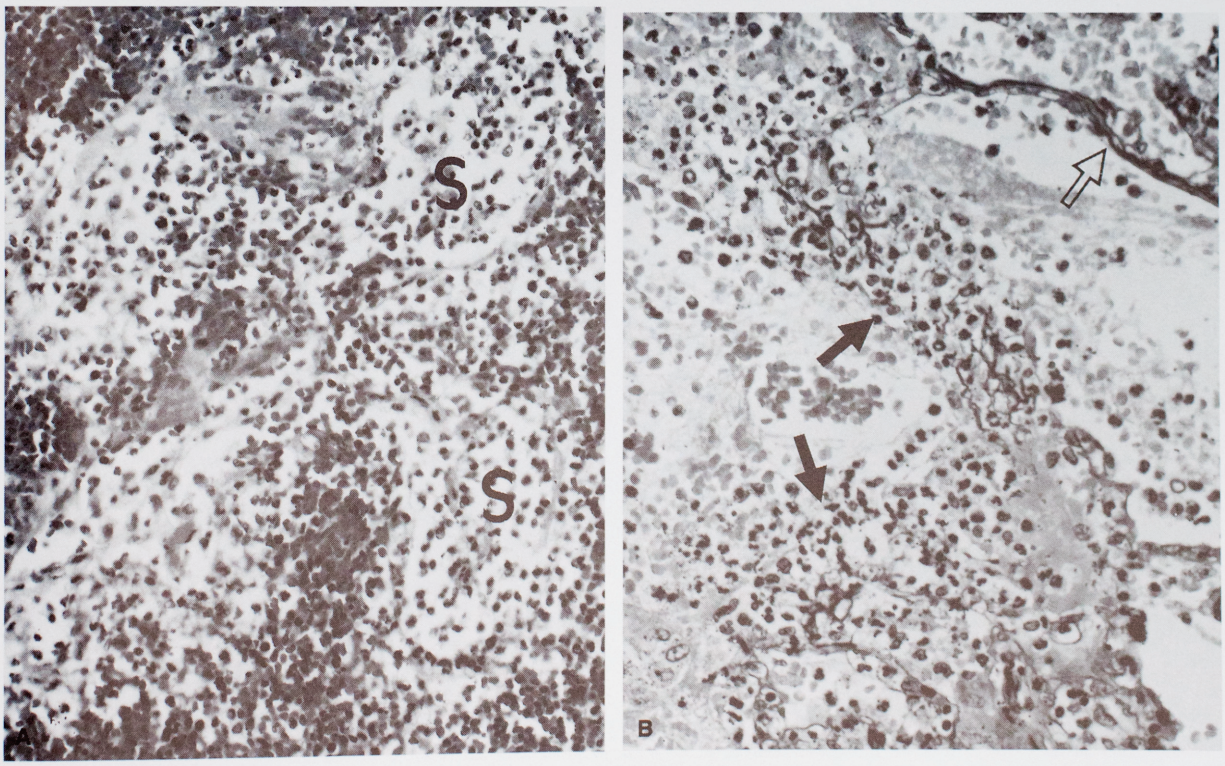

FIGURE 62-1. Autopsy lung showed diffuse necrotizing alveolitis in a fulminant case of microscopic polyarteritis. (**A**) Notice the septal (S) neutrophils and edema. (H & E stain; low magnification.) (**B**) Septal disruption (*arrows*) is also revealed. (Jones methenamine silver stain; low magnification.)

DISPLAY 62-3. DISEASES ASSOCIATED WITH NECROTIZING ALVEOLITIS

Goodpasture syndrome
Wegener granulomatosis
Microscopic polyarteritis
Connective tissue diseases
Schönlein-Henoch purpura
Cryoglobulinemia
Iatrogenic disorders
Toxic injury

ing in patients with immunopathologic and toxic forms of DAH.[3,27] Necrotizing alveolitis was originally recognized in the 1930s and 1940s in fatal cases of acute rheumatic fever, systemic hypersensitivity angiitis of an iatrogenic and experimental nature, and in the original reports of the microscopic form of polyarteritis nodosa and pulmonary-renal syndromes.[28–30] One of the patients described by Goodpasture in his original 1919 report may have developed this lesion.[11] Necrotizing alveolitis has been observed in a variety of DAH syndromes, and it should elicit the differential diagnosis of the disorders listed in Display 62-3.

DIFFUSE ALVEOLAR HEMORRHAGE SYNDROMES

Goodpasture Syndrome

GPS is a pulmonary renal syndrome that preferentially affects young males.[9,20,31] Two thirds of patients with AGBM have GPS, one third have only renal disease, and fewer than 2% of patients have only pulmonary disease.[20] Some source of preexisting lung injury appears necessary for GPS to develop in the presence of AGBM antibody.[32] The most common injurious agent appears to be tobacco smoke, although hydrocarbons, oxygen toxicity, and viral infections have also been implicated.[32–34]

Most patients present with respiratory symptoms and are then found to have renal disease.[9,20,31] The renal component or pulmonary component can predominate in a patient without involvement of the other organ or before involvement of the other organ. The pattern or severity does not correlate with the AGBM antibody titer.[9,20,31] A significant fraction of patients also are positive for ANCA and may have systemic disease consistent with vasculitis.[8,26] The pulmonary manifestations range from an asymptomatic infiltrate seen on chest x-ray films to cough and dyspnea with blood-tinged sputum to overt hemoptysis with respiratory insufficiency.[4,9,20,31] Similarly, the renal disease may range from mild hematuria and proteinuria with normal renal function to RPGN with renal failure and erythrocyte casts in the urine.[9,20,31]

Grossly, the lungs are diffusely hemorrhagic, beefy red, and heavy, often weighing as much as 1 to 2 kg each. The principal microscopic finding in the lung is DAH. Intact red blood cells fill alveolar spaces and are accompanied by fibrin and variable numbers of hemosiderin-laden macrophages (Fig. 62-2). The alveolar septa are widened by edema and hemorrhage, and in the acute stage, they may show necrotizing alveolitis.[3,35] This condition may be accompanied by septal fibrosis or rarely by hyalin membranes.[35] DIF examination of the lung reveals a linear reaction with IgG along septal and capillary basement membranes (see Color Fig. 62-1*B*), often accompanied by a similar reaction for complement.[3,16,35,36]

Although necrotizing alveolitis has been described in GPS, particularly in the series of Travis and Lombard, some investigators have not observed an inflammatory component or observed a

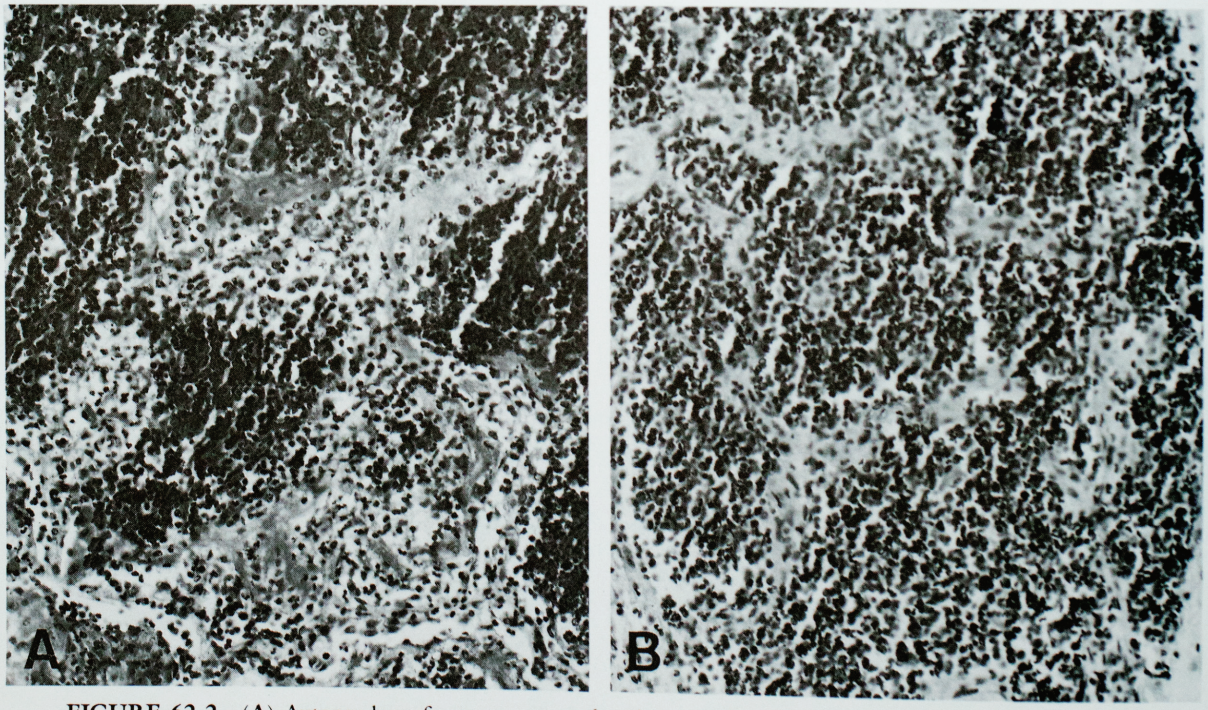

FIGURE 62-2. (**A**) Autopsy lung from an untreated patient with Goodpasture syndrome shows necrotizing alveolitis. (**B**) No inflammation is seen in a treated patient. (H & E stains; low magnifications.)

solely mononuclear cell component in serologically confirmed cases of GPS.[3,20,35,36] Several factors may contribute to the various observations described in the literature. The histologic findings can be influenced by the size of specimen, severity of the process, and any prior immunosuppressive therapy. Capillaritis may be seen focally, and blood may spread into alveoli not affected by the capillaritis.[3,27] A small biopsy specimen, especially if transbronchial, may show alveolar hemorrhage without necrotizing alveolitis. The clinical manifestations of alveolar hemorrhage and the histologic finding of capillaritis subside 1 to 2 weeks after effective therapy.[3,5,36]

The characteristic histologic renal lesion in GPS is a necrotizing and crescentic glomerulonephritis (Fig. 62-3). Affected glomeruli shows lysis of the mesangial matrix and capillary loop basement membrane, with fibrin deposition and crescent formation.[13–15,20,31] The glomerular tuft not involved by the necrosis appears normal. The necrotizing process varies in the percentage of glomeruli affected (0%–100%), size of lesion (*i.e.*, segmental *versus* global), and stage (*i.e.*, cellular *versus* organizing crescent). In most patients, the majority of glomeruli are affected by large circumferential crescents. However, a patient rarely may have normal renal function without a necrotizing lesion despite immunofluorescent and serologic demonstration of the antibody.[37]

The diagnostic finding of GPS in the kidney is demonstration of a linear reaction along the glomerular capillary loop basement membranes for IgG and occasionally also for C3 (see Color Fig. 62-1*A*). The linear pattern is delicate and ribbonlike.[13–15,20,35,36] A similar finding may involve the Bowman capsule and tubular basement membranes. Cases of linear IgA and linear λ light chain reactions have also been reported.[38,39] Ultrastructural findings are nonspecific.[20,40] There is the anticipated basement membrane lysis, fibrin, and cellular response, but the nephrotoxic antibody and complement do not form a visible deposit as in immune complex–mediated disease.

Diffuse Alveolar Hemorrhage in Systemic Vasculitis

DAH occurs principally in two forms of systemic vasculitis, Wegener granulomatosis and MPA, and in idiopathic (*i.e.*, pauci-immune) crescentic glomerulonephritis.[1–6,41–43] Affected patients have overlapping clinical features, such as multisystem disease with a frequent pulmonary-renal presentation. Their renal disease is histologically identical to GPS, although a medium-sized vessel arteritis may also occur. The patients have an absence or paucity of antibody or immune complexes detectable in biopsy material, and 90% of patients have detectable ANCA antibody, usually C-ANCA in Wegener granulomatosis and P-ANCA in MPA and idiopathic crescentic glomerulonephritis.[25,26]

Wegener granulomatosis is granulomatous disease with a vasculitic component that classically produces a triad of upper and lower respiratory tract and renal disease.[43] Some clinical variants have protracted mucocutaneous lesions (*e.g.*, pathergic granulomatosis), and there are limited forms confined to the lung, sinopulmonary tracts, or kidney (*e.g.*, ELK variants proposed by DeRemee) or affecting two or these sites in any combination.[44–46] Mild pulmonary hemorrhage is common in Wegener granulomatosis, but DAH is uncommon, occurring in 5% of patients.[42] The development of DAH produces a fulminant clinical syndrome with a significant risk of death (see Chap. 68).[42,47–49]

DAH is more common in MPA than in Wegener granulomatosis and may be one of the most common causes of DAH.[41,50–53] The term "microscopic polyarteritis" was coined by Davson and colleagues for a group of autopsied patients in which systemic necrotizing vasculitis was identified on histologic sections without the grossly visible aneurysms typical of classic polyarteritis nodosa.[50] Unlike classic polyarteritis nodosa, patients with MPA typically lack hypertension and commonly have pulmonary involvement.[50–54] The vasculitis affects small to medium-sized ves-

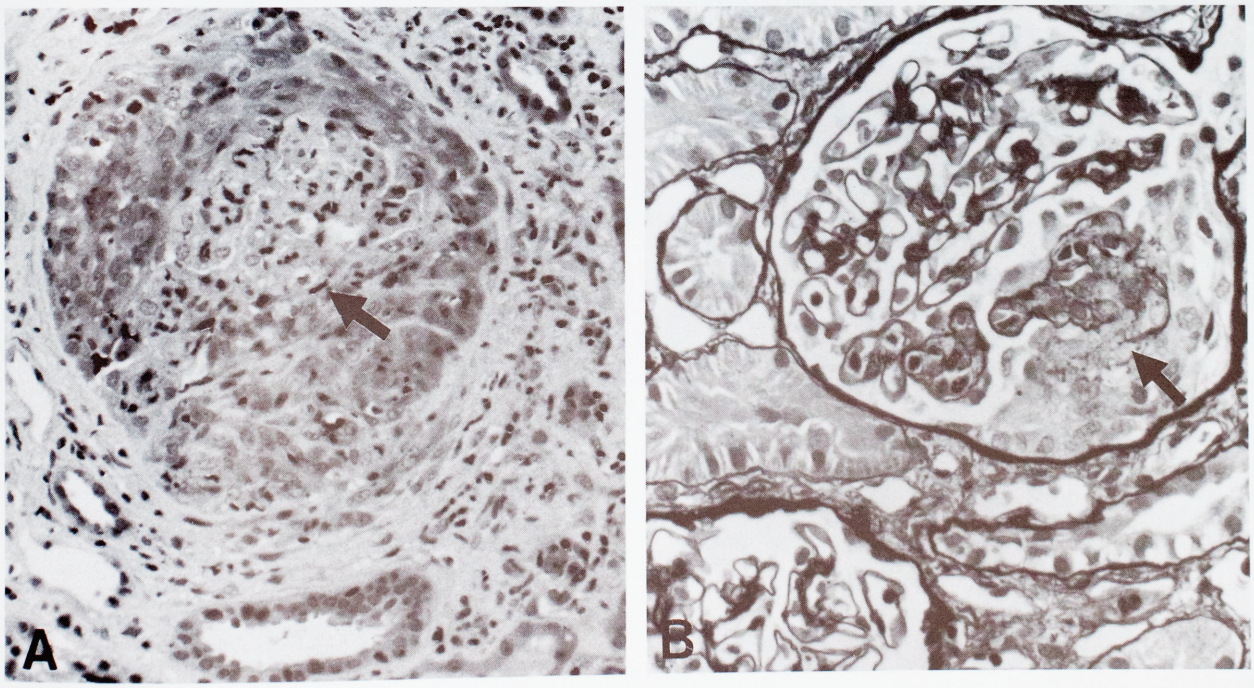

FIGURE 62-3. (**A**) Kidney specimens from two patients with Goodpasture syndrome showed a circumferential crescent (*arrow*) glomerulus. (H & E stain; low magnification.) (**B**) A segmental crescent with capillary loop disruption (*arrow*) is also seen. (Periodic acid-Schiff stain; low magnification.)

sels without a predilection for vessel branch points. The lesions are acute and of similar age without the chronic lesions often seen in classic polyarteritis nodosa. Although any organ may be involved in MPA, the skin, kidneys, and lungs are most commonly affected. Some investigators include patients with idiopathic crescentic glomerulonephritis (*i.e.*, RPGN due to an immune complex, negative crescentic glomerulonephritis) within the category MPA as a renal-limited form. The fequency of clinical symptoms consistent with vasculitis such as hemoptysis and a positive result for ANCA testing validates their position.[51,52]

When DAH develops in patients with MPA or Wegener granulomatosis, necrotizing alveolitis is usually the responsible lesion.[3,27,42] In MPA, necrotizing alveolitis may be a widespread phenomena with patients at risk for death (see Fig. 62-1), or focal with lesser degrees of pulmonary hemorrhage (Fig. 62-4). Pulmonary arteritis is not observed. The diagnosis of Wegener granulomatosis in the context of necrotizing alveolitis with DAH requires identification of the granulomatous component or vasculitis involving larger vessels.[42–49] These lesions may not be easily located in fulminant cases of DAH in Wegener granulomatosis, because giant cells or microscopic necrotic granulomas may occur focally (Fig. 62-5). They should be identified in the lung or some other biopsy specimen before rendering a diagnosis of Wegener granulomatosis.[3,42,43]

Immune Complex Diseases Associated With Vasculitis

DAH has been reported as an infrequent complication of a variety of immune complex-associated diseases.[1–3,55,56,64] These disorders are heterogenous and present with systemic multiorgan involvement or predominately with lung and renal disease.

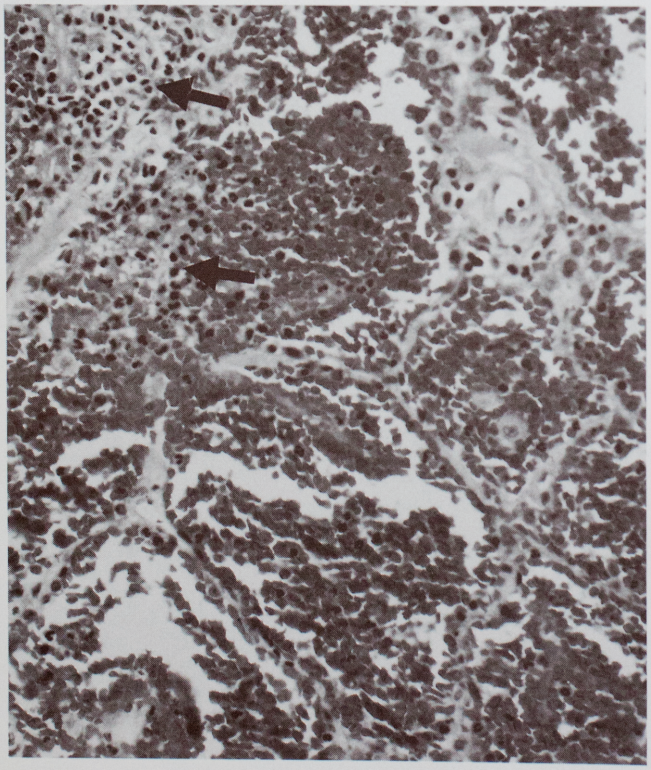

FIGURE 62-4. Focal necrotizing alveolitis (*arrows*) was found by an open lung biopsy in a patient with microscopic polyarteritis. (H & E stain; low magnification.)

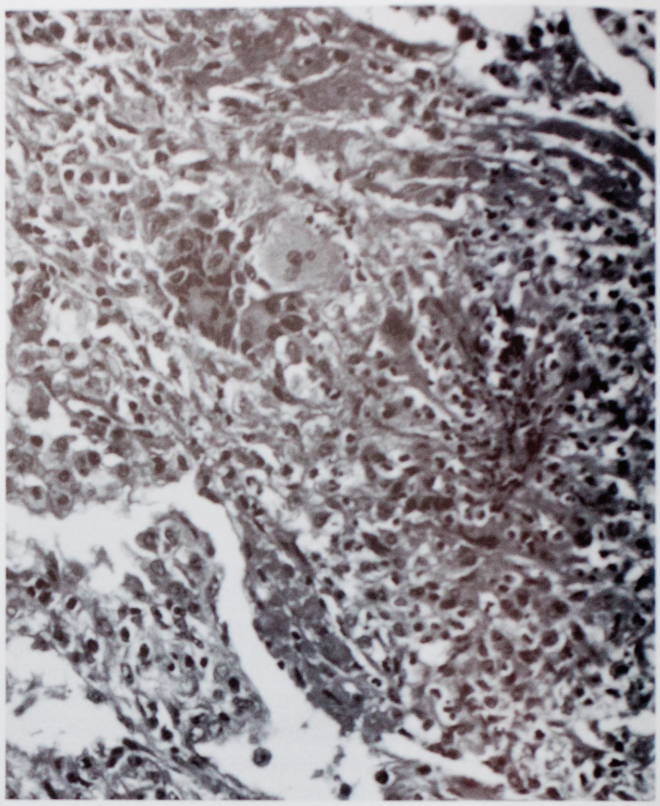

FIGURE 62-5. An example of Wegener granulomatosis with alveolar hemorrhage shows a septal necrotizing granuloma. (H & E stain; low magnification.)

Although the histologic changes encountered in the lung have not been reported in every case, necrotizing alveolitis, indistinguishable from that encountered in GPS, Wegener granulomatosis, or MPA, has been described (Fig. 62-6). The immune complexes have been demonstrable by DIF in the lung in categories composed of IgG-C3 complexes, IgA, or cryoglobulin de-

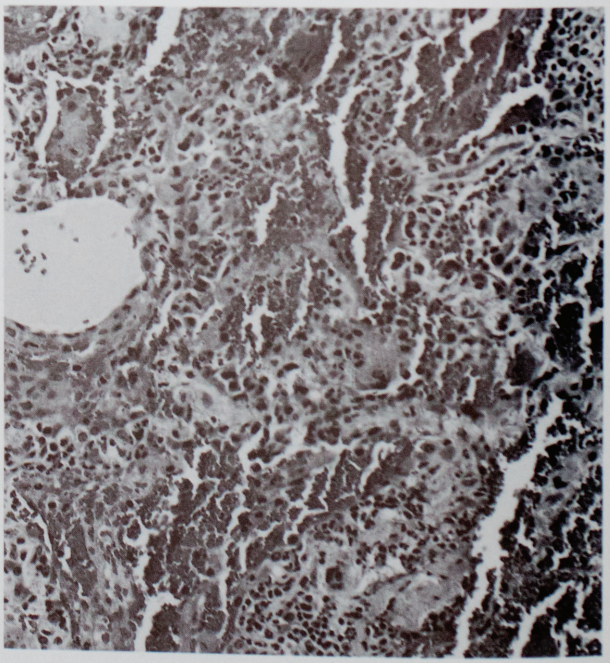

FIGURE 62-6. Alveolar hemorrhage in systemic lupus with a mixed neutrophilic and lymphocyte alveolitis. (H & E stain; low magnification.)

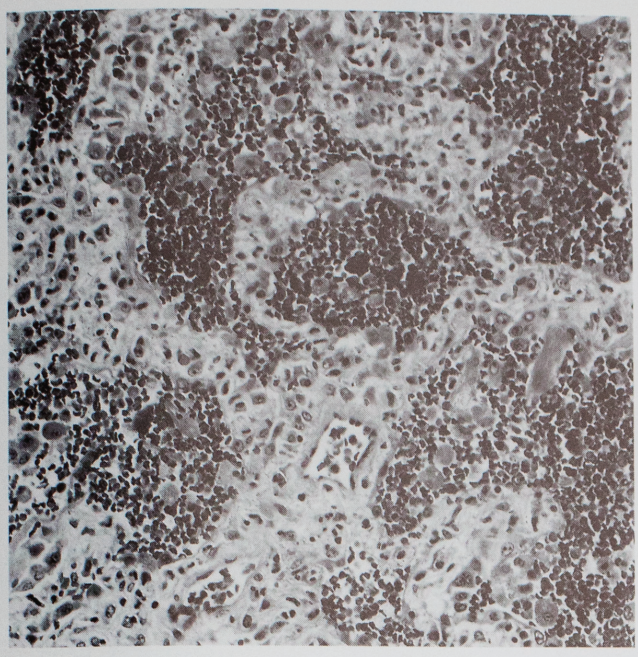

FIGURE 62-7. In this example of severe intraalveolar hemorrhage caused by toxic inhalation of solvents, there is widening of alveolar septa by edema, mononuclear cells, lymphocytes, and neutrophils; type II pneumocyte hyperplasia also is evident. (H & E stain; low magnification.)

posits, depending on the underlying disorder.[55,58–63] The role of immune complexes in mediating tissue damage is not clear, because inflammation is not a uniform feature. The serologic profile and nature of the systemic involvement must clarify the diagnostic possibilities. Although the underlying condition may be known before the onset of alveolar hemorrhage, in some patients, particularly those with lupus erythematosus, alveolar hemorrhage may be the initial manifestation of the systemic disease.[57]

Diffuse Alveolar Hemorrhage as a Result of Exogenous Agents

DAH may develop as a rare iatrogenic complication or result from inhalation of toxic substances.[2,65–69] Identification of toxic causes may be more difficult, requiring careful attention to occupational histories and possible illicit drug use.

Biopsies have revealed a necrotizing basis for DAH in some patients.[66,67] Nonspecific changes of acute lymphocytic pneumonitis, intraalveolar hemorrhage, and reactive interstitial changes have been reported for the remainder (Fig. 62-7).

Idiopathic Pulmonary Hemosiderosis

IPH is characterized by recurrent, often severe pulmonary hemorrhages, predominantly occurring in young children or adolescents. A similar syndrome occurring in adults is typically milder.[1,2,70,71] Patients present with cough and hemoptysis, alveolar or reticulonodular infiltrates seen on chest x-ray films, and iron-deficiency anemia, which is often disproportionately severe compared with the magnitude of the hemoptysis.[1,2] The hemorrhage is episodic and occasionally life threatening. Familial cases have been reported, and several other diseases occasionally coexist (*e.g.*, IgA nephropathy, celiac disease, dermatitis herpetiformis).[2] The histologic picture in the lungs (Fig. 62-8) varies from severe intraalveolar hemorrhage with intact erythrocytes to dense aggregates of hemosiderin-laden macrophages with mild septal fibrosis.[70,74] Because IPH is a diagnosis of exclusion, a prerequisite for

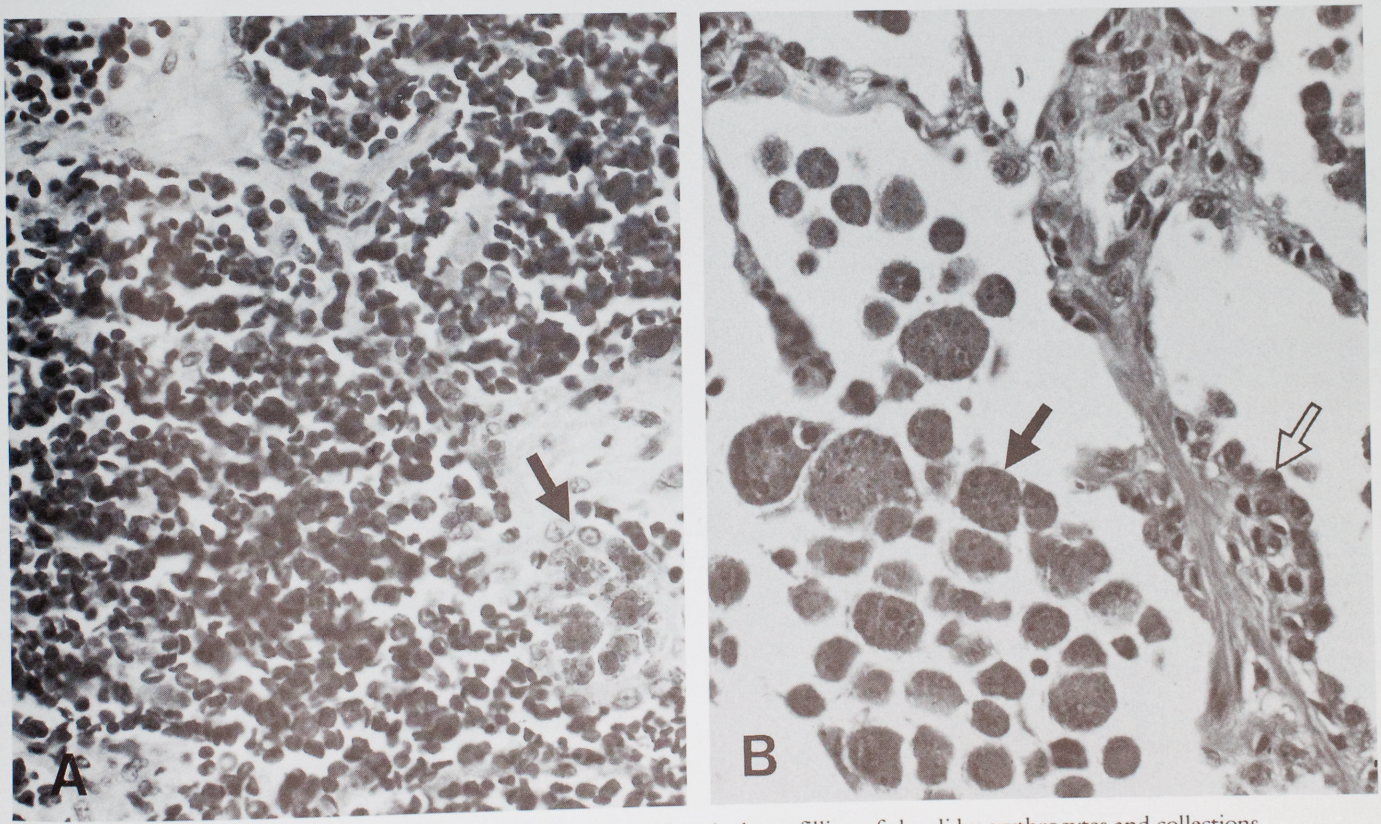

FIGURE 62-8. (**A**) Idiopathic pulmonary hemosiderosis shows filling of alveoli by erythrocytes and collections of hemosiderin-laden macrophages (*arrow*). (H & E stain; intermediate magnification.) (**B**) A later-stage specimen shows hemosiderin-laden macrophages in the alveolar space (*solid arrow*). There is already some interstitial fibrosis and hyperplasia of the alveolar lining cells (*open arrow*). (H & E stain; high magnification.)

the diagnosis is the absence of inflammation and necrosis and no evidence of systemic disease, iatrogenic cause, infection, or cardiovascular disease. Some patients initially diagnosed as having IPH were subsequently shown to have Wegener granulomatosis or GPS.[75,76] The results of DIF studies must be negative, and circulating autoantibodies (*i.e.*, AGBM, ANCA) must not be detectable to make this diagnosis.

Although the pathogenesis and cellular basis of the hemorrhage in IPH is undefined, it is thought to originate from alveolar tissue, because autopsies fail to reveal a more proximal bleeding site in bronchi or trachea.[70] Careful ultrastructural studies have not revealed septal capillary disruptions, although nonspecific changes in septal capillary basement membranes and iron deposition on septal elastic fibers support the septal capillary bleeding postulate (see Chap. 11).[72–74]

Patients with DAH have a serious disorder that may have a variety of causes. Unfortunately, several relatively common conditions may mimic a DAH syndrome because of the low specificity of histologic, clinical, and radiologic findings. These disorders include infection, neoplasms, cardiac disease, pulmonary embolism, uremia, and disseminated intravascular coagulation. Clinical information supplemented by selective serologic data is essential for the diagnosis of these diseases.

REFERENCES

1. Bradley JD. The pulmonary hemorrhage syndromes. Clin Chest Med 1982;3:593.
2. Leatherman JW, Davies SF, Hoidal JR. Alveolar hemorrhage syndrome: diffuse microvascular lung hemorrhage in immune and idiopathic disorders. Medicine (Baltimore) 1984;63:343.
3. Travis WD, Colby TV, Lombard C, et al. A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. Am J Surg Pathol 1990;14:1112.
4. Albelda SM, Gefter WB, Epstein DM, et al. Diffuse pulmonary hemorrhage: a review and classification. Radiology 1985;154:289.
5. Leatherman JW, Sibley RK, Davies SF. Diffuse intrapulmonary hemorrhage and glomerulonephritis unrelated to antiglomerular basement membrane antibody. Am J Med 1982;72:401.
6. Boyce NW, Holdsworth SR. Pulmonary manifestations of the clinical syndrome of acute glomerulonephritis and lung hemorrhage. Am J Kidney Dis 1986;8:31.
7. Weiss MA, Crissman JD. Segmental necrotizing glomerulonephritis: diagnostic, prognostic, and therapeutic significance. Am J Kidney Dis 1985;6:199.
8. Andrassey K, Kuster S, Waldherr R, et al. Rapidly progressive glomerulonephritis: analysis of prevalence and clinical course. Nephron 1991;59:206.
9. Wilson CB, Dixon FJ. Anti-glomerular basement membrane antibody-induced glomerulonephritis. Kidney Int 1973;3:74.
10. Thomas III HM, Irwin RS. Classification of diffuse intrapulmonary hemorrhage. Chest 1975;68:483.
11. Goodpasture EW. The significance of certain pulmonary lesions in relation to etiology of influenza. Am J Med Sci 1919;158:863.
12. Stanton MC, Tange JD. Goodpasture's syndrome (pulmonary hemorrhage associated with glomerulonephritis). Aust Ann Med 1958; 132:132.
13. Salant DJ. Immunopathogenesis of crescentic glomerulonephritis and lung purpura. Kidney Int 1987;32:408.
14. Bonsib SM, Walker WP. Pulmonary-renal syndrome: clinical similarity amidst etiologic diversity. Mod Pathol 1989;2:129.
15. Scheer RL, Grossman MA. Immune aspects of the glomerulonephritis associated with pulmonary hemorrhage. Ann Intern Med 1964; 60:1009.
16. Sturgil BC, Westervelt FB. Immunofluorescence studies in a case of Goodpasture's syndrome. JAMA 1965;194:172.
17. Lerner RA, Glassock RJ, Dixon FJ. The role of antiglomerular basement membrane antibody in the pathogenesis of human glomerulonephritis. J Exp Med 1967;126:989.
18. Hudson BG, Wieslander J, Wisdom BJ Jr, et al. Biology of disease. Goodpasture syndrome: molecular architecture and functions of basement membrane antigen. Lab Invest 1989;61:286.
19. Martinez JS, Kohler PF. Variant "Goodpasture's syndrome"? The need for immunologic criteria in rapidly progressive glomerulonephritis and hemorrhagic pneumonitis. Ann Intern Med 1971;75:67.
20. Heptinstall RH. Antiglomerular basement membrane antibody disease. In: Pathology of the kidney. 4th ed. Boston: Little, Brown, 1992:677.
21. Weber MFA, Andrassy K, Pullig O, et al. Antineutrophil-cytoplasmic antibodies and antiglomerular basement membrane antibodies in Goodpasture's syndrome and in Wegener's granulomatosis. J Am Soc Nephrol 1992;2:1227.
22. McCoy, Johnson HK, Stone WJ, et al. Absence of nephritogenic GBM antigen (S) in some patients with hereditary nephritis. Kidney Int 1982;21:641.
23. Milliner DS, Pierides AM, Holley KE. Renal transplantation in Alport's syndrome. Anti-glomerular basement membrane glomerulonephritis in the allograft. Mayo Clin Proc 1982;57:35.
24. Savige JA, Dowling J, Kincaid-Smith P. Superimposed glomerular immune complexes in anti-glomerular basement membrane disease. Am J Kidney Dis 1989;14:148.
25. Jennette JC, Wilkman AS, Falk RJ. Anti-neutrophil cytoplasmic antibody-associated glomerulonephritis and vasculitis. Am J Pathol 1989;135:360.
26. Goeken JA. Antineutrophil cytoplasmic antibody—a useful serologic marker for vasculitis. J Clin Immunol 1991;11:161.
27. Mark EJ, Ramirez EJ. Pulmonary capillarities and hemorrhage in patients with systemic vasculitis. Arch Pathol Lab Med 1985;109:413.
28. Parkin TW, Rusted IE, Burchell HB, et al. Hemorrhagic and interstitial pneumonitis with nephritis. Am J Med 1955;18:220.
29. Wainwright J, Davson J. The renal appearances in the microscopic form of periarteritis nodosa. J Pathol Bacteriol 1950;62:189.
30. McCaulley WTE, Thomas BJ. Pulmonary hemorrhage and glomerulonephritis. Am J Clin Pathol 1962;38:577.
31. Teague CA, Doak PB, Simpson IJ, et al. Goodpasture's syndrome: an analysis of 29 cases. Kidney Int 1978;13:492.
32. Queluz TH, Pawlowski I, Brunda MJ, et al. Pathogenesis of an experimental model of Goodpasture's hemorrhagic pneumonitis. J Clin Invest 1990;85:1507.
33. Donaghy M, Rees AJ. Cigarette smoking and lung hemorrhage in glomerulonephritis caused by autoantibodies to glomerular basement membrane. Lancet 1983;2:1390.
34. Yamamoto T, Wilson C. Binding of anti-basement membrane antibody to alveolar basement membrane after intratracheal gasoline installation in rabbits. Am J Pathol 19987;126:497.
35. Lombard CM, Colby TV, Elliot CG. Surgical pathology of the lung in anti-glomerular basement membrane antibody-associated Goodpasture's syndrome. Hum Pathol 1989;20:445.
36. Beine GJ, Octaviano GN, Koop WL, et al. Immunohistology of the lung in Goodpasture's syndrome. Ann Intern Med 1968;69:1207.
37. Bailey RR, Simpson IJ, Lynn KL, et al. Goodpasture's syndrome with normal renal function. Clin Nephrol 1981;15:211.
38. Border WA, Baehler RW, Bhathena D, et al. IgA antibasement membrane nephritis with pulmonary hemorrhage. Ann Intern Med 1979; 91:21.
39. Savige JA, Young SO, Bierre AR, et al. Lambda-light-chain-mediated anti-GBM disease. Nephron 1989;52:144.
40. Donald KJ, Edwards RL, McEvoy JDS. Alveolar capillary basement membrane lesions in Goodpasture's syndrome and idiopathic pulmonary hemosiderosis. Am J Med 1978;59:642.
41. Haworth SJ, Savage COS, Carr D, et al. Pulmonary hemorrhage

complicating Wegener's granulomatosis and microscopic polyarteritis. Br Med J 1985;290:1775.
42. Colby TV. Diffuse pulmonary hemorrhage in Wegener's granulomatosis. Semin Respir Med 1989;10:136.
43. Godman GC, Churg J. Wegener's granulomatosis: pathology and review of the literature. Arch Pathol 1851;358:533.
44. Carrington CB, Liebow AA. Limited forms of angiitis and granulomatosis of Wegener's type. Am J Med 1966;49:366.
45. DeRemee RA, McDonald TJ, Harrison EG Jr., Coles DT. Wegener's granulomatosis: anatomic correlates, a proposed classification. Mayo Clin Proc 1976;51:777.
46. Fienberg R. The protracted superficial phenomena in pathergic (Wegener's) granulomatosis. Hum Pathol 1981:12:458.
47. Yoshikawa Y, Watanabe T. Pulmonary lesions in Wegener's granulomatosis: a clinicopathologic study of 22 autopsy cases. Hum Pathol 1986;17:401.
48. Travis WD, Carpenter NA, Lie JT. Diffuse pulmonary hemorrhage: an uncommon manifestation of Wegener's granulomatous. Am J Surg Pathol 1987;11:702.
49. Myers JL, Katzenstein AA. Wegener's granulomatosis presenting with massive pulmonary hemorrhage and capillarities. Am J Surg Pathol 1987;11:895.
50. Davson J, Ball J, Platt R. The kidney in periarteritis nodosa. Q J Med 1948;17:175.
51. Savage COS, Winearls CG, Evans DJ, et al. Microscopic polyarteritis: presentation, pathology and prognosis. Q J Med 1985;56:467.
52. Sierra A, Cameron JS, Runer DR, et al. Vasculitis affecting the kidney: presentation, histopathology and long-term outcome. Q J Med 1984;53:181.
53. Adu D, Howie AJ, Scott DGI, et al. Polyarteritis and the kidney. Q J Med 1987;62:221.
54. Zashin S, Fattor R, Fortin D. Microscopic polyarteritis: a forgotten aetiology of haemoptysis and rapidly progressive glomerulonephritis. Ann Rheum Dis 1990;49:53.
55. Eagen JW, Memoli VA, Roberts J, et al. Pulmonary hemorrhage in systemic lupus erythematosus. Medicine (Baltimore) 1978;57:545.
56. Myers J, Katzenstein AA. Microangiitis in lupus-induced pulmonary hemorrhage. Am J Clin Pathol 1986;85:552.
57. Mintz G, Galindo LF, Fernandez-Diez J, et al. Acute massive pulmonary hemorrhage in systemic lupus erythematous. J Rheumatol 1978;5:39.
58. Kathuria S, Cheifec G. Fatal pulmonary Henoch-Schönlein syndrome. Chest 1982;82:654.
59. Slatopolsky E, Forrest J, Kornfeld, S, et al. Mixed cryoglobulinemia. Clinicopathologic conference. Am J Med 1978;61:95.
60. Zell SC, Duxbury G, Shankel SW. Alveolar hemorrhage associated with a membranoproliferative glomerulonephritis and smooth muscle antibody. Am J Med 1987;82:1073.
61. Naschitz JE, Yeshurun D, Scharg Y, et al. Recurrent massive alveolar hemorrhage, crescentic glomerulonephritis, and necrotizing vasculitis in a patient with rheumatoid arthritis. Arch Intern Med 1989; 149:406.
62. Dehoratious RJ, Abruzzo JL, Williams RC Jr. Immunofluorescent and immunologic studies of rheumatoid lung. Arch Intern Med 1972;129:441.
63. Sanchez-Guerrero J, Cesarman G, Alarcon-Segovia D. Massive pulmonary hemorrhage in mixed connective tissue disease. J Rheumatol 1989;16:1132.
64. Masson RG, Rennke HG, Gottlieb MN. Pulmonary hemorrhage in a patient with fibrillary glomerulonephritis. N Engl J Med 1992;326:36.
65. Herbert FA, Orford R. Pulmonary hemorrhage and edema due to inhalation of resins containing trimetallic anhydride. Chest 1979; 76:546.
66. Averbuch SD, Yungbluth P. Fatal pulmonary hemorrhage due to nitrofurantoin. Arch Intern Med 1980;140:271.
67. Yermakov VM, Hitti IF, Sutton AL. Necrotizing vasculitis associated with diphenylhydantoin. Hum Pathol 1983;13:182.
68. Santolo M, Domingo P, Fontcuberta J, et al. Diffuse pulmonary hemorrhage associated with anticoagulant therapy. Eur J Respir Dis 1986;69:114.
69. Murray RJ, Albin RJ, Merger W, et al. Diffuse alveolar hemorrhage temporally related to cocaine smoking. Chest 1988;93:427.
70. Soergel KH, Sommers SC. The alveolar epithelial lesion of idiopathic pulmonary hemosiderosis. Am Rev Respir Dis 1962;85:540.
71. Matsaniotis N, Karpouzas J, Apostolopoulou E, et al. Idiopathic pulmonary haemosiderosis in children. Arch Dis Child 1968;43:307.
72. Irwin RS, Cottrell TS, Hsu KC, et al. Idiopathic pulmonary hemosiderosis: an electron microscopic and immunofluorescent study. Chest 1974;65:41.
73. Donlan CJ Jr, Srodes CH, Duffy FD. Idiopathic pulmonary hemosiderosis. Electron microscopic, immunofluorescent, and iron kinetic studies. Chest 1975;68:577.
74. Corrin B, Jagusch M, Dwar A, et al. Fine structural changes in idiopathic pulmonary haemosiderosis. J Pathol 1987;153:249.
75. Katz SM, Foster E, Miller AS, et al. Goodpasture's syndrome mimicking idiopathic pulmonary hemosiderosis. Ann Clin Lab Sci 1989; 19:280.
76. O'Donohue WJ Jr. Idiopathic pulmonary hemosiderosis with manifestations of multiple connective tissue and immune disorders. Am Rev Respir Dis 1974;109:473.