CHAPTER 18

Idiopathic Interstitial Fibrosis

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Fibrosis is a nonspecific reaction to injury typically occurring in association with or after a significant inflammatory process. In the case of a myocardial infarct, for example, the region of ischemic necrosis is eventually replaced by a dense fibrous scar. In skin, regions of surgical incision or traumatic laceration undergo fibrosis as part of the normal healing process. Similarly, the lung is an organ in which fibrotic reactions occur. In some instances, such as pulmonary infarcts, fibrosis may be part of a normal healing process and the mechanism of fibrosis is relatively well understood. In other conditions, such as asbestosis, the etiology is apparent but the mechanism of fibrosis is poorly understood. In myocardial infarcts and wound healing, fibrosis serves a useful purpose. When it occurs in the interstitium of peripheral lung tissue, it has a deleterious effect, interfering with normal physiologic functions such as blood flow and gas diffusion.

Interstitial lung disease refers to a condition in which the predominant tissue abnormality is in the alveolar septa, in contrast to intrabronchial and intraalveolar locations. More than 100 known causes of interstitial lung disease are recognized, and most are associated with some degree of interstitial fibrosis.[1–3] In approximately two-thirds of cases, the cause is unknown and the morphogenesis is poorly understood.[4] This unknown group of interstitial lung diseases has a prevalence in the United States of 5–10 cases/100,000 population and results in 10,000 admissions to hospitals each year.[4] Some cases of interstitial lung disease are acute,[5,5a,6] and may be caused by viral or mycoplasma infections,[7] but most have an insidious onset over months to years, have no obvious cause, and result in diffuse interstitial pulmonary fibrosis. In this chapter, the features of idiopathic pulmonary fibrosis are discussed.

History and Nosology

The recognition of diffuse interstitial pulmonary fibrosis as a distinct entity can be traced to the publications of Louis Hamman and Arnold Rich.[8,9] Between 1931 and 1935, they encountered four patients aged 21, 37, 47, and 68 years who developed a rapidly progressive pulmonary illness and died between 20 days and 3 months after admission to hospital. At autopsy, the lungs were described as being firm and consolidated, and showed the following similar microscopic changes: (1) inflammatory infiltrates, which were mostly interstitial and contained few polymorphonuclear leukocytes; (2) alveolar lining cell hypertrophy and hyperplasia; (3) necrosis of alveolar and bronchiolar epithelium; (4) formation of hyaline membranes that lined alveoli; (5) marked edema and fibrin deposits in alveolar walls; (6) extensive diffuse and progressive interstitial proliferation of fibrous tissue throughout all lobes of both lungs, associated with focal organization of intraalveolar exudate; (7) the presence of eosinophils in the interstitial tissue in three of four cases; and (8) the absence of stainable bacteria in the tissue. The changes they described are similar to those described in acute alveolar damage[5] and those seen in the lungs of patients dying from adult respiratory distress syndrome.[10] The acuteness of the clinical syndrome, and some of the pathologic changes such as hyaline membranes and necrosis of epithelium, are not characteristically seen in most cases of idiopathic pulmonary fibrosis.

In the 1960s, Liebow and Carrington[11] began a study of interstitial lung disease that resulted in the histologic typing of these diseases into five distinct groups: (1) usual interstitial pneumonitis (UIP); (2) usual interstitial pneumonitis with bronchiolitis obliterans (BIP); (3)

D. H. Dail et al. (eds.), *Pulmonary Pathology*

desquamative interstitial pneumonitis (DIP); (4) lymphocytic interstitial pneumonitis (LIP); and (5) giant cell interstitial pneumonitis (GIP). Usual interstitial pneumonitis was described as a lesion with histologic features that extended from acute diffuse alveolar damage with hyaline membrane formation to interstitial fibrosis and predominantly chronic inflammation. Usual interstitial pneumonitis with bronchiolitis obliterans was characterized as having features of usual interstitial pneumonitis with superimposed damage to bronchioles and organizing exudate in the lumens of bronchioles. Desquamative interstitial pneumonitis was initially described in 1965[12] as a relatively uniform lesion characterized by accumulation of large mononuclear cells in alveolar spaces, prominent lymphoid follicles and lack of necrosis, exudation and hyaline membrane formation, and minimal interstitial fibrosis. Lymphocytic interstitial pneumonitis was characterized histologically as showing an interstitial infiltrate of mature lymphocytes and plasma cells without germinal center formation, lymph node involvement, or nodular parenchymal masses of lymphocytes.[13] Giant cell interstitial pneumonitis was described as a rare lesion characterized by the accumulation of bizarre giant cells in alveolar spaces.

The term idiopathic fibrosing alveolitis was suggested by Scadding[14] on the advice of Alfred Fishman[15] to refer to the gamut of histopathologic changes ranging from the acute disease described by Hamman and Rich to more frequently observed diffuse interstitial pulmonary fibrosis with inflammation. A similar name, chronic diffuse idiopathic fibrosing alveolitis, was offered by Gough.[16] Scadding and Hinson[17] suggested that the histologic patterns of desquamative interstitial pneumonitis and usual interstitial pneumonitis represented the early and late stages of a single disorder and that there was not a sharp clinical or pathologic distinction between these forms of "interstitial pneumonia." They also proposed the terms "mural fibrosing alveolitis" to be equivalent to usual interstitial pneumonitis and "desquamative fibrosing alveolitis" to be equal to desquamative interstitial pneumonitis.

In the few years following the publication by Hamman and Rich in 1944, several reports described a chronic form of "interstitial" lung disease.[18–22] It soon became apparent that this chronic form was more frequent than acute disease, and several review articles describing its clinical, pathologic, and physiologic features were published in the late 1950s and early 1960s.[23–25] Livingstone et al.[25] presented clinical, radiologic, and pathologic information on 45 patients and thoroughly reviewed the relevant literature to 1964. Scadding[26] subsequently reviewed some of the controversies concerning pulmonary fibrosis, including a discussion of problems inherent in using the term "interstitial." Despite Scadding's valid reasons for not using this descriptive but perhaps imprecise designation, it is ingrained in the medical literature and (in the United States) is used more than any other term to describe this disease. Even Scadding, in an article published in 1960,[27] used interstitial in referring to pulmonary fibrosis. Various names are currently used to describe a chronic disease of unknown cause whose predominant pathologic features are alveolar septal fibrosis and chronic inflammation; these are listed in Table 18–1.

Table 18–1. Terms used for chronic fibrosis

Idiopathic interstitial pulmonary fibrosis
Idiopathic fibrosing alveolitis
Usual interstitial pneumonitis
Diffuse interstitial pulmonary fibrosis
Diffuse alveolar fibrosis of the lungs
Idiopathic pulmonary fibrosis
Idiopathic fibrosing alveolitis (mural type)
Chronic Hamman–Rich syndrome
Hamman–Rich syndrome
Cryptogenic fibrosing alveolitis

Etiology

The designation *idiopathic* indicates an unknown cause. In approximately 10–20% of cases, interstitial fibrosis is associated with a systemic disease, most notably a collagen vascular disease such as rheumatoid arthritis, polymyositis-dermatomyositis, systemic lupus erythematosus, Sjögren's syndrome, scleroderma, or mixed connective tissue disease. Most of the pertinent references concerning pulmonary involvement in the collagen vascular diseases until 1979 are listed in the review by Hunninghake and Fauci[28] (see Chapter 17). Additional reports of pulmonary disease in these conditions have appeared since 1979.[29–43] Pulmonary fibrosis has also been reported in association with various liver disorders.[44–46]

Several reports have described interstitial pulmonary fibrosis in families, thus suggesting the importance of genetic factors.[47–52] This author has seen two such examples of familial pulmonary fibrosis, one involving three brothers and the other two sisters, which suggest that familial occurrence may be more common than reported. Also, the possible association of pulmonary fibrosis with specific HLA types would suggest a genetic predisposition of the disease,[53–56] although the validity of this association remains uncertain.[57]

Cigarette smoking is a potentially significant factor that is infrequently mentioned in discussions concerning pulmonary fibrosis. In 1963, Auerbach[58,59] showed

that cigarette smoking can cause interstitial fibrosis, resulting in an abnormal chest radiograph. The potential fibrogenic effect of cigarette smoking was recently commented on by Weiss[60] in the context of its association with asbestos in causing pulmonary fibrosis. It is of interest that Carrington et al.,[61] in their comparison of usual interstitial pneumonitis and desquamative interstitial pneumonitis, stated that 90% of patients diagnosed as having desquamative interstitial pneumonitis and 71% with usual interstitial pneumonitis had a cigarette smoking history of greater than 10 pack-years.

The pathologic changes seen in acute interstitial pneumonitis are characteristically those seen in patients with adult respiratory distress syndrome. Thus there are several causes, including shock, oxygen toxicity, radiation, and infection.[62] Some cases of acute interstitial pneumonitis may have no obvious cause.[5] Viral pneumonitis typically produces acute changes, but may rapidly lead to a chronic condition with pathologic changes indistinguishable from idiopathic pulmonary fibrosis.[63–65] Verganon et al.[66] recently identified antibodies with titers greater than 1 : 160 to various Epstein-Barr virus antigens in bronchoalveolar lavage fluid from 10 of 13 patients with cryptogenic fibrosing alveolitis. In contrast, none of 12 patients with other types of interstitial lung disease (6 with extrinsic allergic alveolitis, 3 with drug-induced disease, 2 with collagen vascular disease, 1 with asbestosis) had IgG antibodies against Epstein-Barr virus antigens in lavage fluid. These findings suggested that Epstein-Barr virus may play a role in causing idiopathic fibrosing alveolitis.

Immunopathogenesis

The pathogenesis of idiopathic pulmonary fibrosis is poorly understood, although much basic information exists concerning such cells as neutrophils, pulmonary alveolar macrophages, lymphocytes, and pulmonary epthelial cells, cell products such as fibronectin and lymphokines, and collagen production, all of which are thought to be important in the development of pulmonary fibrosis. The normal number, the turnover rates, and the alveolar surface area covered by normal lung cells are listed in Table 18–2.[67–70] (Also see Chapter 2.)

In pulmonary fibrosis, the number and character of these cells are markedly altered. Pulmonary alveolar macrophages are bone marrow derived, but a population of immature cells exists in the interstitium of the lung that may give rise to a normal number of alveolar macrophages in the absence of bone marrow precursors.[71] The interaction between alveolar macrophages, neutrophils, and lymphocytes appears important in the pathogenesis and morphogenesis of pulmonary fibrosis. Alveolar macrophages produce a chemotactic factor that induces migration of polymorphonuclear leukocytes into the lung and another factor that stimulates bone marrow production of granulocytes and monocytes.[72–74] The observed increase in neutrophils in lavage fluid from patients with idiopathic fibrosis may be caused by these factors. In addition, alveolar macrophages produce fibronectin, a 440-kilodalton glycoprotein that recruits fibroblasts to regions of inflammation and causes the attachment of fibroblasts to collagenous matrix.[75,76] Fibronectin is increased in bronchoalveolar lavage fluid from patients with pulmonary fibrosis.

Alveolar macrophages from patients with interstitial fibrosis also release an 18,000-dalton molecular weight growth factor, termed alveolar macrophage growth factor, that causes proliferation of fetal fibroblasts in cell culture.[77] This factor is not produced by alveolar macrophages from normal persons; it is distinct from other growth factors such as insulin-like growth factor, appears to exert its effect by stimulating target cells to synthesize DNA, and acts in concert with fibronectin. The synthesis and release of this factor is stimulated by activated T lymphocytes and immune complexes. Immune complexes have been demonstrated by direct immunofluorescence in the lung tissue from patients with pulmonary fibrosis.[78] Most of the factors produced by alveolar macrophages are done so by "activated macrophages." The demonstration of DR or Ia antigen

Table 18–2. Normal lung cells

Cell type	*Total alveolar cells (%)*	*Alveolar surface area covered (%)*	*Average turnover rate (days)*
Type I pneumocyte	8–10	90	7–35
Type II pneumocyte	12–16	10	7–35
Endothelial cell	30–40	NA[a]	77
Interstitial cell	30–36	NA	?
Macrophages	2–10	NA	21(?)

[a] NA, not applicable.

on the cell surface of alveolar macrophages indicates they are activated and thus potentially capable of producing these various substances.[79]

Several factors produced by lymphocytes are also thought to be important in the pathogenesis of pulmonary fibrosis. Immune complexes identified in lung tissue and lavage fluid are believed to be derived from immunoglobulin-producing resident B lymphocytes, which are increased in absolute numbers in patients with pulmonary fibrosis.[80] T lymphocytes are also increased in absolute numbers in lung tissue from patients with fibrosing alveolitis, although their exact function in this condition is uncertain.[81] They do not spontaneously release lymphokines and the ratio of helper/inducer to suppressor/cytotoxic T cells is normal.[81] Several studies have shown they may be important in causing fibrosis. In bleomycin-induced pulmonary fibrosis, athymic nude mice deficient in T cells show less cellular infiltration, less fibroblast proliferation, and less collagen deposition than euthymic mice with normal T lymphocytes.[82] Activated human peripheral blood lymphocytes produce a factor that stimulates proliferation of dermal fibroblasts and synthesis of collagen and noncollagenous proteins.[83]

Polymorphonuclear leukocytes and their products may also play a role in interstitial pulmonary fibrosis. Polymorphonuclear leukocytes and neutrophil collagenase are increased in bronchoalveolar lavage fluid from patients with fibrosing alveolitis.[84–86] Neutrophils contain a variety of proteolytic enzymes in their lysosomes, such as elastase and collagenase, which are capable of producing tissue injury. However, in a recent experimental study, beige mice, which have a selective inability to degranulate their neutrophils and consequently do not release hydrolytic enzymes, showed no amelioration of the fibrogenic response to bleomycin.[87] Neutrophils also produce toxic oxygen metabolites such as hydrogen peroxide, which may be more important than proteolytic enzymes in causing tissue injury and subsequent fibrosis in mice.[88]

Another area of uncertainty in idiopathic pulmonary fibrosis is the question of whether there is a definite increase in collagen concentration in the lung or only a variation in the types of collagen. Currently, six polymorphic types of collagen are recognized. In normal lung, types I and III collagen are predominantly in alveolar septa whereas type II collagen is associated with the trachea and bronchi. In normal lung, the ratio of type I to type III collagen in alveolar septa is 2:1, and collagen constitutes about 15% of the dry weight of lung parenchyma. Although the results of one study suggested there was no increase in collagen content in fibrotic lung,[89] another study showed an absolute increase in collagen content and an increase in the ratio of type I to III collagen in cases of idiopathic pulmonary fibrosis.[90] In the latter study, collagen accounted for 25% of the dry weight of lung parenchyma. The discrepancy in these two studies may have resulted from the larger tissue sample used in the latter study. Raghu and colleagues[91] studied lung tissue from patients with pulmonary fibrosis with fluorescein-labeled polyclonal antibodies against human collagens types I, III, IV, and laminin. They found that type III collagen was initially dominant in fibrotic alveolar septa and was replaced by type I collagen as the disease progressed.

A theoretic immunopathogenic mechanism for the development of pulmonary fibrosis, which is proposed by the author, is shown in Fig. 18–1.

The exact mechanism by which fibrosis forms in the peripheral lung tissue is poorly understood. In 1985, Corrin and colleagues[92] studied lung tissue ultrastructurally from 17 patients with cryptogenic fibrosing alveolitis and 8 patients with asbestosis, and found evidence of endothelial cell injury characterized by swelling and reduplicated basal lamina and necrosis of alveolar type I cells with loss of these cells and exposure of the underlying basal lamina. They postulated that the loss of epithelial cells was important in the development of fibrosis, perhaps by loss of epithelial inhibitors of connective tissue proliferation. It is interesting that the ultrastructural changes were the same in the cryptogenic cases of fibrosis and asbestosis.

Basset and co-workers in 1986[93] published a histologic-ultrastructural study regarding the mechanism of fibrosis occurring in a variety of interstitial lung diseases, including those observed in 92 patients with idiopathic pulmonary fibrosis. They showed intraluminal organization of exudate with fibrosis to be a common finding in several different diseases. Fibroblasts and myofibroblasts migrated through defects in the alveolar wall, leading to "intraluminal buds" that could progress to obliteration of the alveolus and fusion of adjacent alveolar structures. Basset et al. found intraluminal buds in 13 of 92 patients and mural incorporation in 69 of 92 patients with idiopathic pulmonary fibrosis. The mechanism of fibrosis in idiopathic pulmonary fibrosis may in part result from coalescence of collapesed alveolar septa and incorporation of organizing intraalveolar exudate into the interstitium.[5]

Clinical Features

Idiopathic pulmonary fibrosis usually occurs in middle-aged men and women. The insidious onset of dyspnea, the most common symptom, is usually progressive to

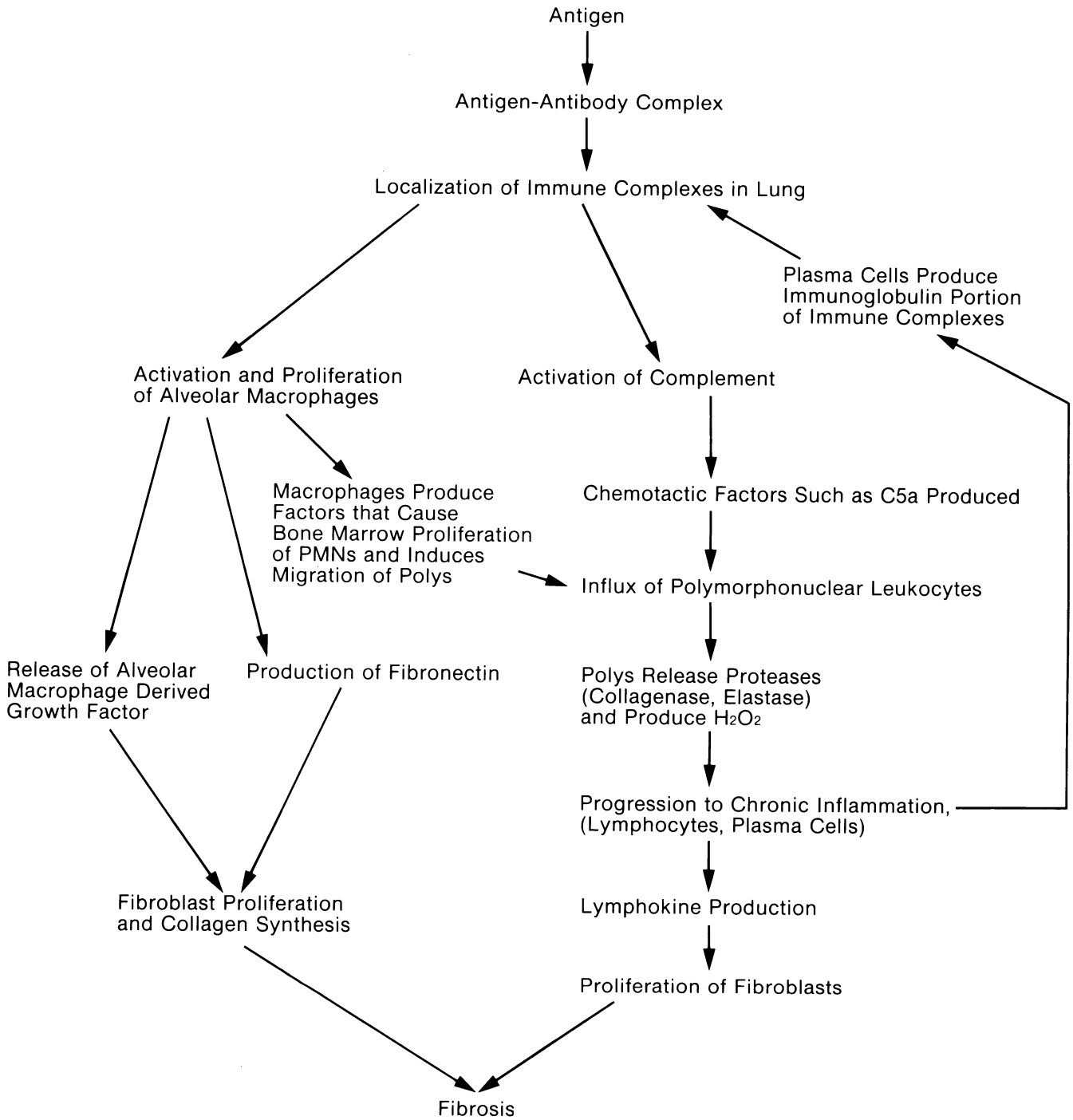


Fig. 18–1. Diagram of possible relationships between immunopathogenic factors thought to be important in development of pulmonary fibrosis.

a point at which patients may become unable to perform the activities of daily living. Clubbing of the digits and inspiratory rales are common signs. Extrapulmonary symptoms such as fatigue, weight loss, and arthralgias occur in 25–40% of patients, especially in those whose pulmonary fibrosis is associated with a collagen vascular syndrome.

Abnormalities appearing in laboratory tests may include a low-titer positive antinuclear antibody, abnormal liver function tests, and an elevated erythrocyte sedimentation rate. When associated with a collagen vascular disease, laboratory test abnormalities are more frequent and depend on which specific syndrome is involved, such as systemic lupus erythematosus, derma-

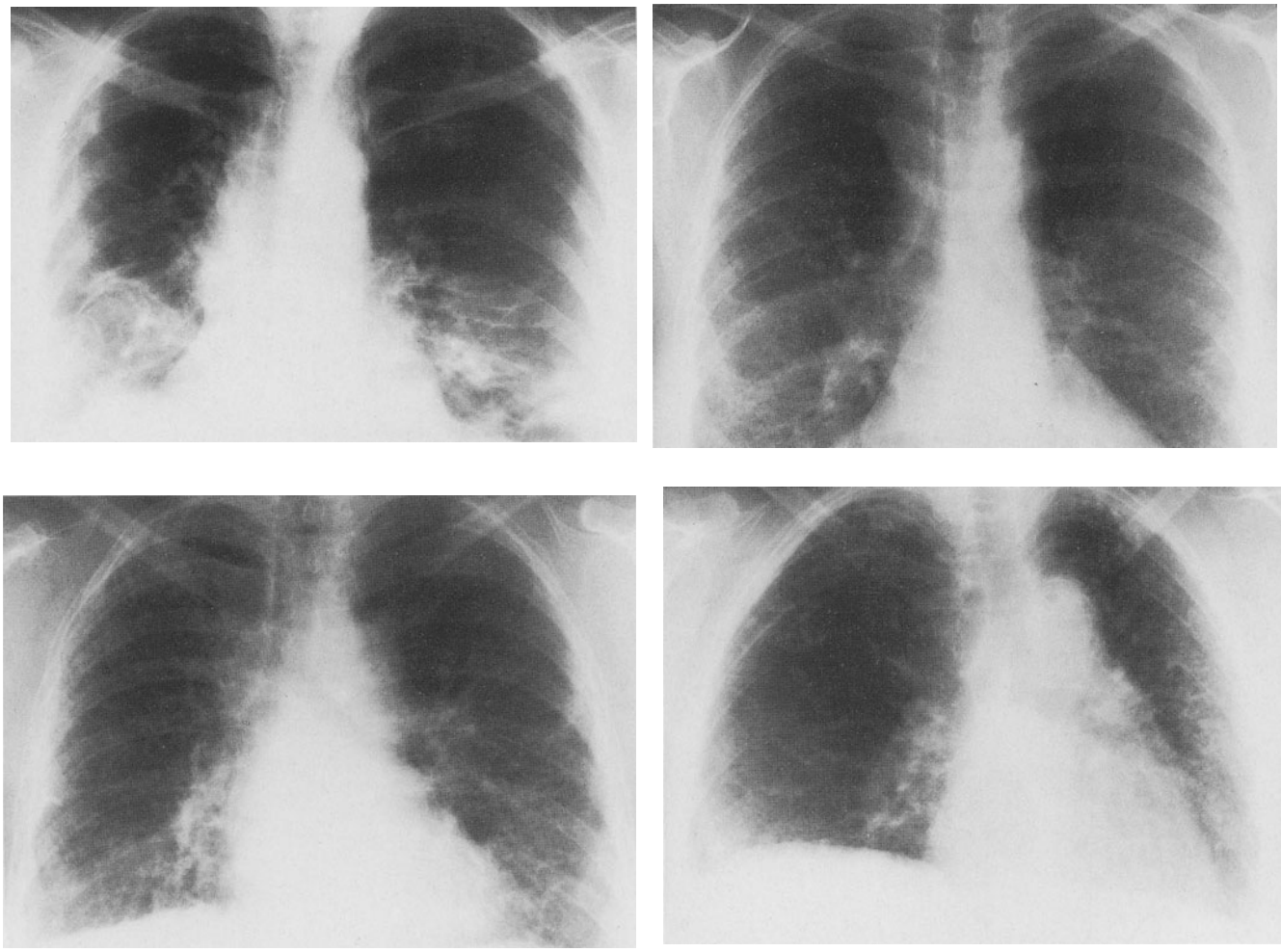


Fig. 18–2 A–D. Chest radiographs from four patients with idiopathic pulmonary fibrosis. Note variability and that infiltrate appears most prominent in lower lobes.

tomyositis, or mixed connective tissue disease.

Pulmonary function tests typically show a restrictive defect that is characterized by a decrease in total lung capacity, forced vital capacity, residual volume, diffusion capacity of carbon monoxide, and arterial oxygen concentration. The reduction in diffusion capacity and decreased arterial oxygen saturation is thought to be caused by a decrease in pulmonary capillary volume and by ventilation-perfusion abnormalities. With exercise, the arterial oxygen saturation decreases sharply.

Chest radiographs usually show diffuse bilateral infiltrates that appear most severe at the bases of the lungs with sparing of the apices, and are often referred to as interstitial, alveolar, or reticulonodular. There is always some variability in radiographs from patient to patient (Fig. 18–2), and we have shown that the apparent increased involvement in the lower lobes results from only the greater lung volume in the lower lobes and not from more severe disease in this region.[94]

Patients with acute diffuse alveolar damage usually have clinical features of the adult respiratory distress

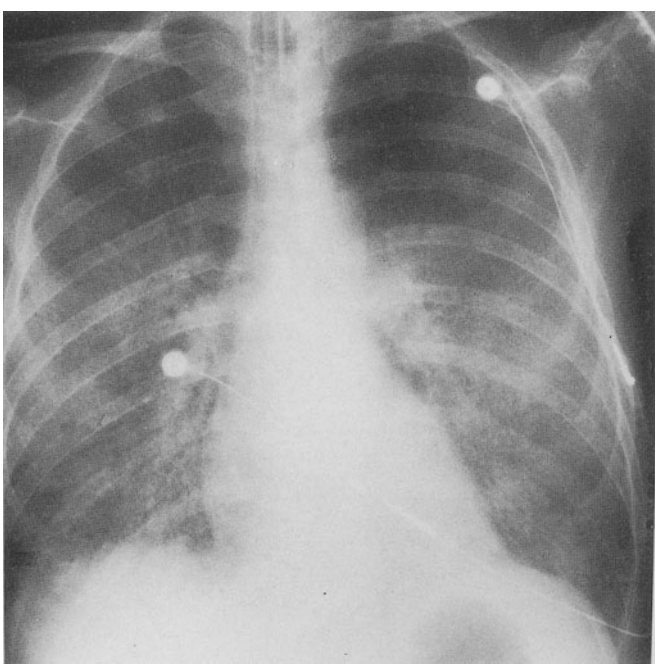


Fig. 18–4. Right and left lung from a person dying of idiopathic interstitial pulmonary fibrosis. Note nodular pleural surface, which is similar to surface of cirrhotic liver.

syndrome.[95] They are critically ill and require ventilatory assistance that delivers fixed concentrations and volumes of oxygen. Other than signs and symptoms of respiratory insufficiency, the clinical features depend on the etiology of the syndrome. Chest radiographs frequently show a diffuse alveolar infiltrate involving all lobes equally that is sometimes described as a "white-out" (Fig. 18–3).

Fig. 18–3. Chest radiograph from patient with adult respiratory distress syndrome. Note diffuse ground glass appearance of pulmonary parenchyma.

Pathologic Features

The gross pathologic changes of the lungs from patients with idiopathic pulmonary fibrosis vary, depending on which stage of the disease the lung is biopsied. In the early stages there may be few discernible macroscopic

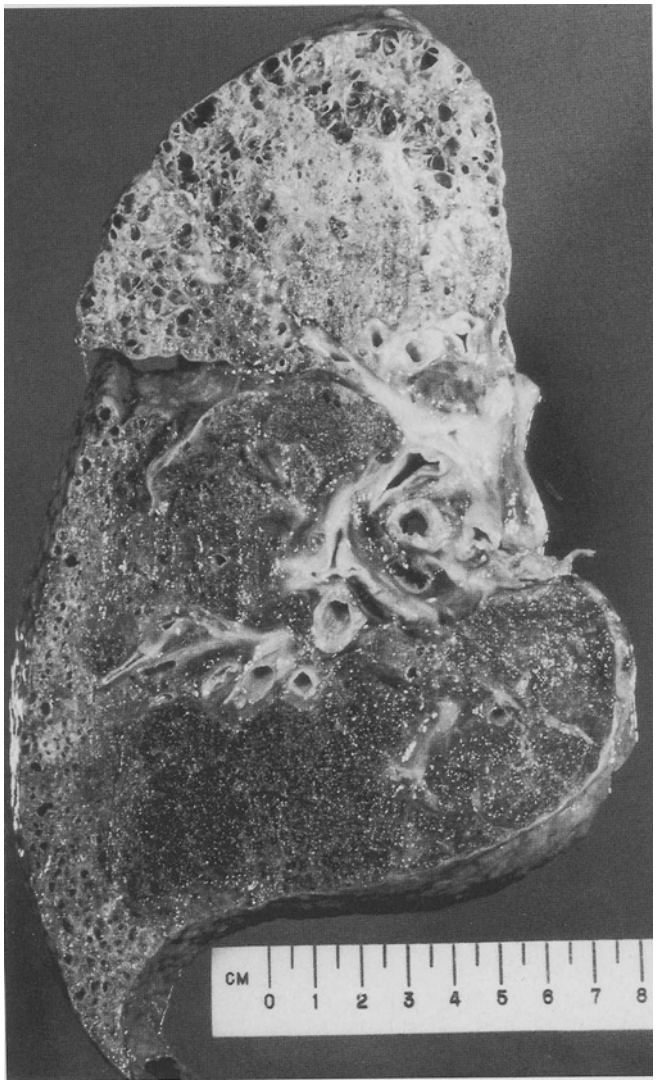


Fig. 18–5. Cut surface of right lung shown in Fig. 18–4. Note fibrosis and honeycombing in peripheral 2–3 cm and that more central parenchyma, especially in lower lobe, is relatively normal. Scale in centimeters.

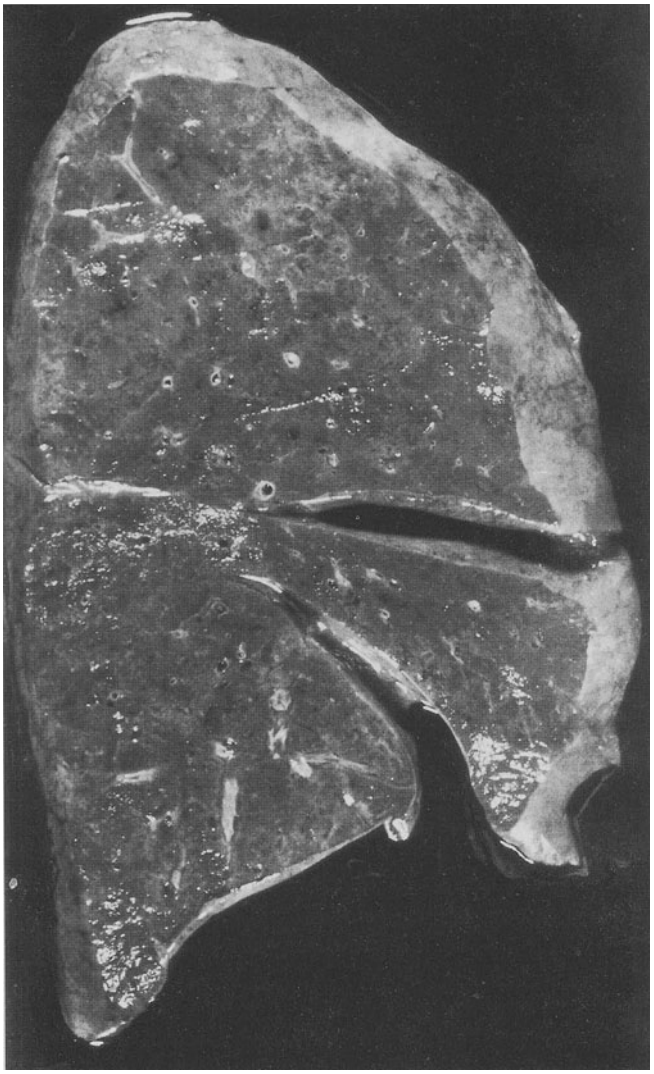


Fig. 18–6. Cut surface of right lung shows acute diffuse alveolar damage. Lung weighs more than 1,000 g, is reddish gray, and has consistency of liver.

changes. The lungs from a person dying from pulmonary fibrosis show reproducible abnormalities. The lungs are two to three times their usual weight and are stiff. The pleural surface is diffusely nodular, much like the surface of a cirrhotic liver (Fig. 18–4). When sectioned, the most peripheral 2–3 cm of lung tissue is strikingly abnormal, with the more proximal or central parenchyma appearing normal or only mildly abnormal (Fig. 18–5). The peripheral parenchyma shows obliteration of the delicate alveolar lung architecture, with replacement by dense grayish-white to yellow-tan fibrous tissue. The nodular pleural surface is due to irregular scarring of the underlying parenchyma. The irregular scarring with obstruction of bronchi and bronchioles and destruction of parenchyma leads to cystically dilated spaces in the scarred parenchyma, referred to as honeycombing.

As shown in Figs. 18–4 and 18–5, the changes are just as severe in the upper as in the lower lobes, but the greater volume of lung tissue in the lower lobes accounts for the apparent localization of the disease to the lower lobes in chest radiographs. That the disease is most severe in the peripheral parenchyma means that any open lung biopsy is, to some degree, nonrepresentative. In a diffuse disease such as pulmonary fibrosis, our surgeons are specifically requested to not biopsy the region that shows the greatest gross abnormality. Although Newman et al.[96] found that the lingula may

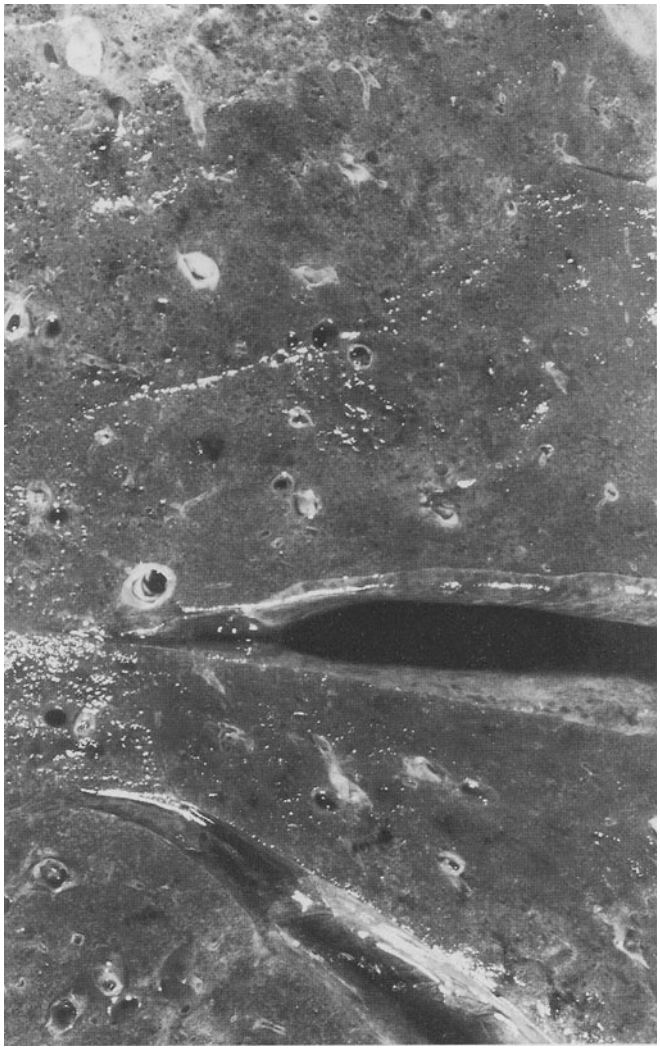


Fig. 18–7. Greater magnification of cut surface of lung shown in Fig. 18–6. Note accentuation of bronchiolar and alveolar architecture resulting from bronchiolar and alveolar septal distortion caused by necrosis and hyaline membrane formation.

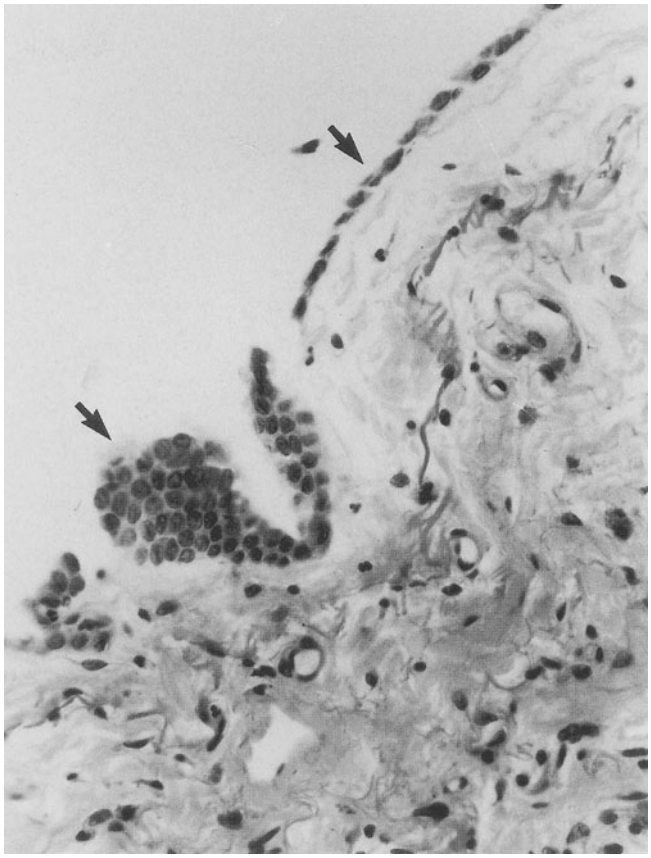


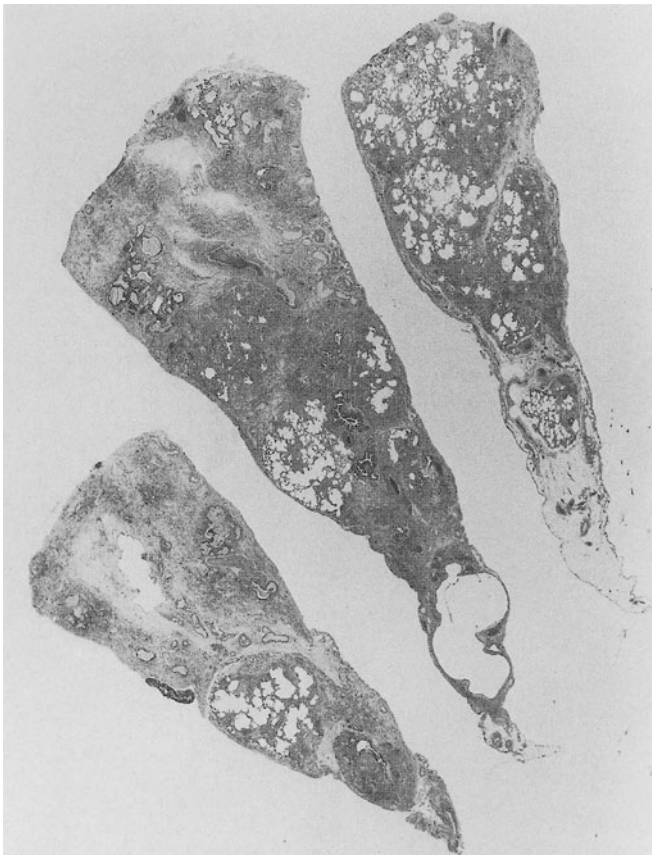
Fig. 18–8. Visceral pleura is slightly thickened. Note reactive hypertrophy and hyperplasia of surface mesothelial cells (*arrows*). ×330.

show mild fibrosis and other abnormalities in patients without diffuse lung disease, in our experience this alteration is usually mild. In this author's experience, the lingula is as abnormal as other peripheral lung tissue in patients with idiopathic pulmonary fibrosis, an observation supported by the report of Wetstein showing that lingular biopsies are representative in several types of lung disease including idiopathic interstitial fibrosis.[96a]

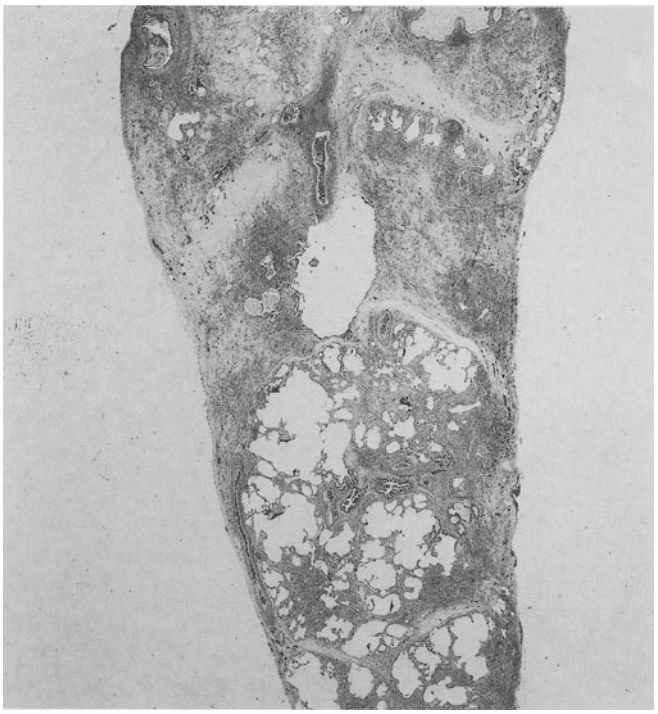
In acute interstitial pneumonitis characterized by acute diffuse alveolar damage, the lungs macroscopically are diffusely and uniformly abnormal. Each lung usually weighs more than 1,000 g, and the pleural surfaces are smooth but may show fibrinous adhesions. The parenchyma is reddish gray to tan and has a meaty consistency similar to liver (Fig. 18–6). The bronchiolar and/or alveolar architecture is accentuated by the alveolar septal necrosis and hyaline membranes (Fig. 18–7).

The most conspicuous histologic feature of idiopathic pulmonary fibrosis is its variability. In every open lung biopsy or autopsy lung section, there is a wide spectrum of changes. The pleura is frequently thickened, and shows an increase in vascularity with hypertrophy and hyperplasia of mesothelial lining cells (Fig. 18–8). The peripheral lung tissue shows a haphazard pattern of fibrosis, inflammation, occasional smooth muscle proliferation, elastic tissue fragmentation and/or synthesis, alveolar and bronchiolar lining cell hypertrophy, and hyperplasia and honeycoming (Figs. 18–9 through 18–14).

In this author's opinion, the suggestion that the disease necessarily progresses from an "active cellular phase" to an end stage relatively "acellular fibrotic phase" is not borne out by the histologic changes. In our study of open lung biopsies from 37 lobes in 20

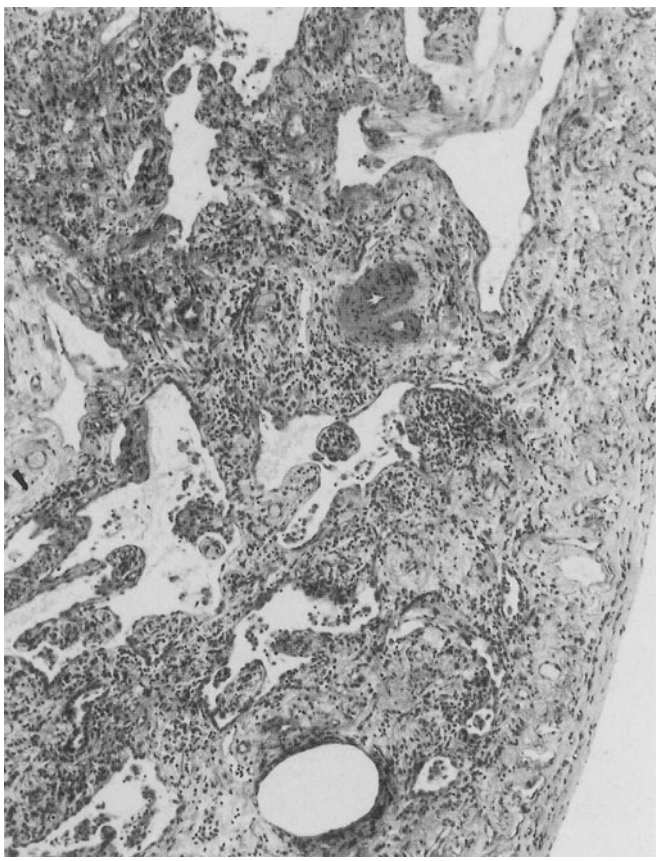


18-9

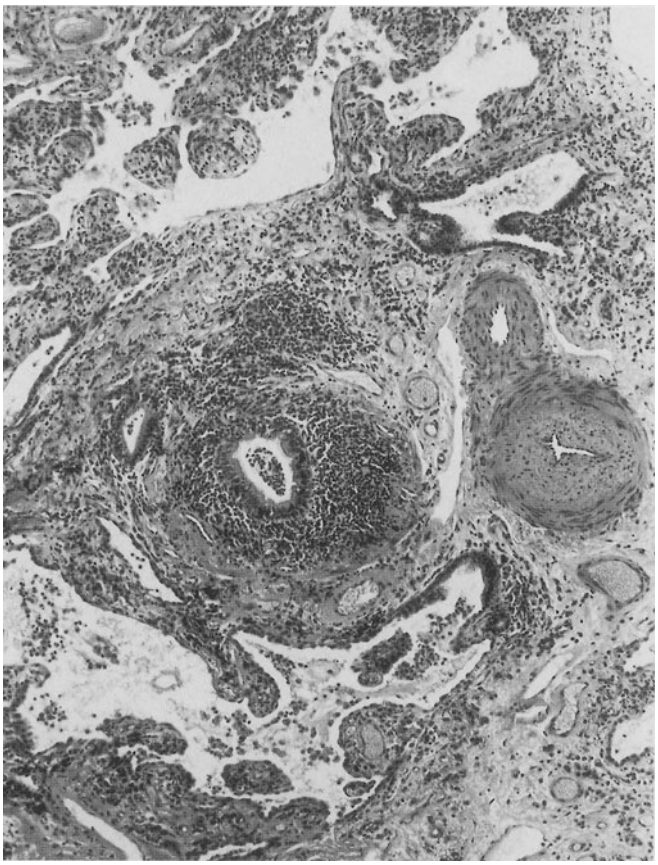


18-10

Fig. 18–9 and Fig. 18–10. Representative sections of open lung biopsy show distortion of usual pulmonary architecture and variability of the abnormality. Fig. 18–9, ×4; Fig. 18–10, ×8.

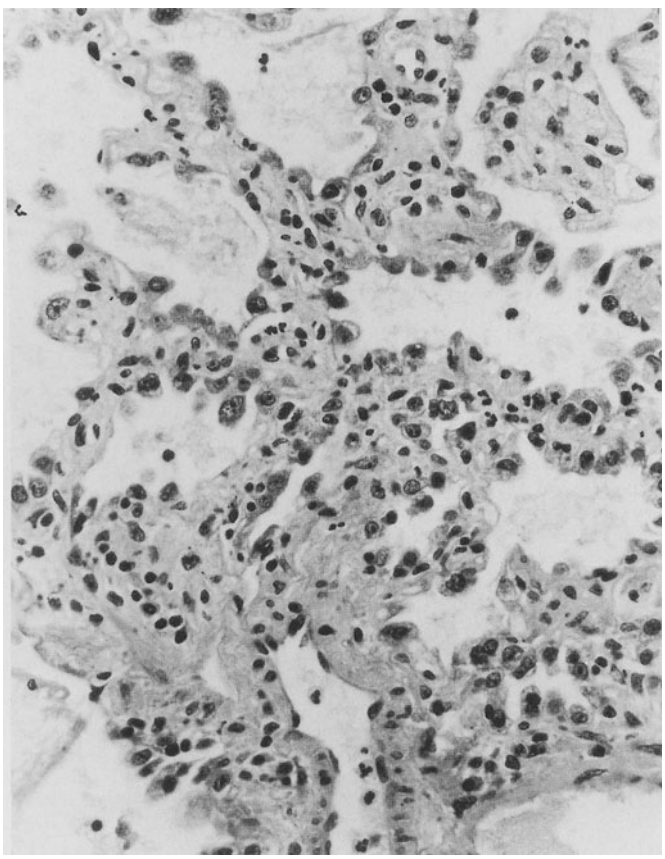


18-11

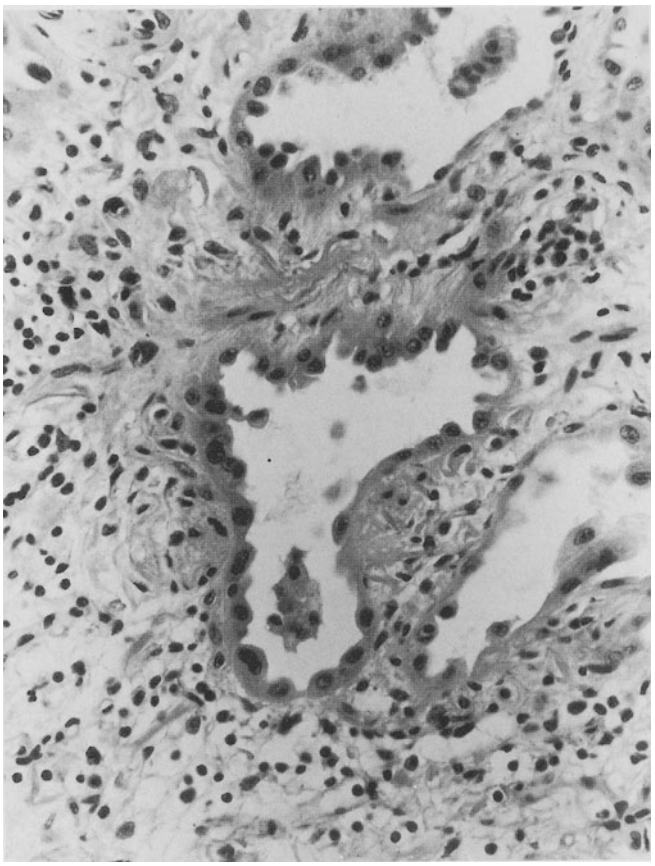


18-12

Fig. 18–11 and Fig. 18–12. At slightly greater magnifications, disorganization of peripheral lung tissue is evident. Moderate interstitial fibrosis is associated with a chronic inflammatory cell infiltrate. ×75.



18-13



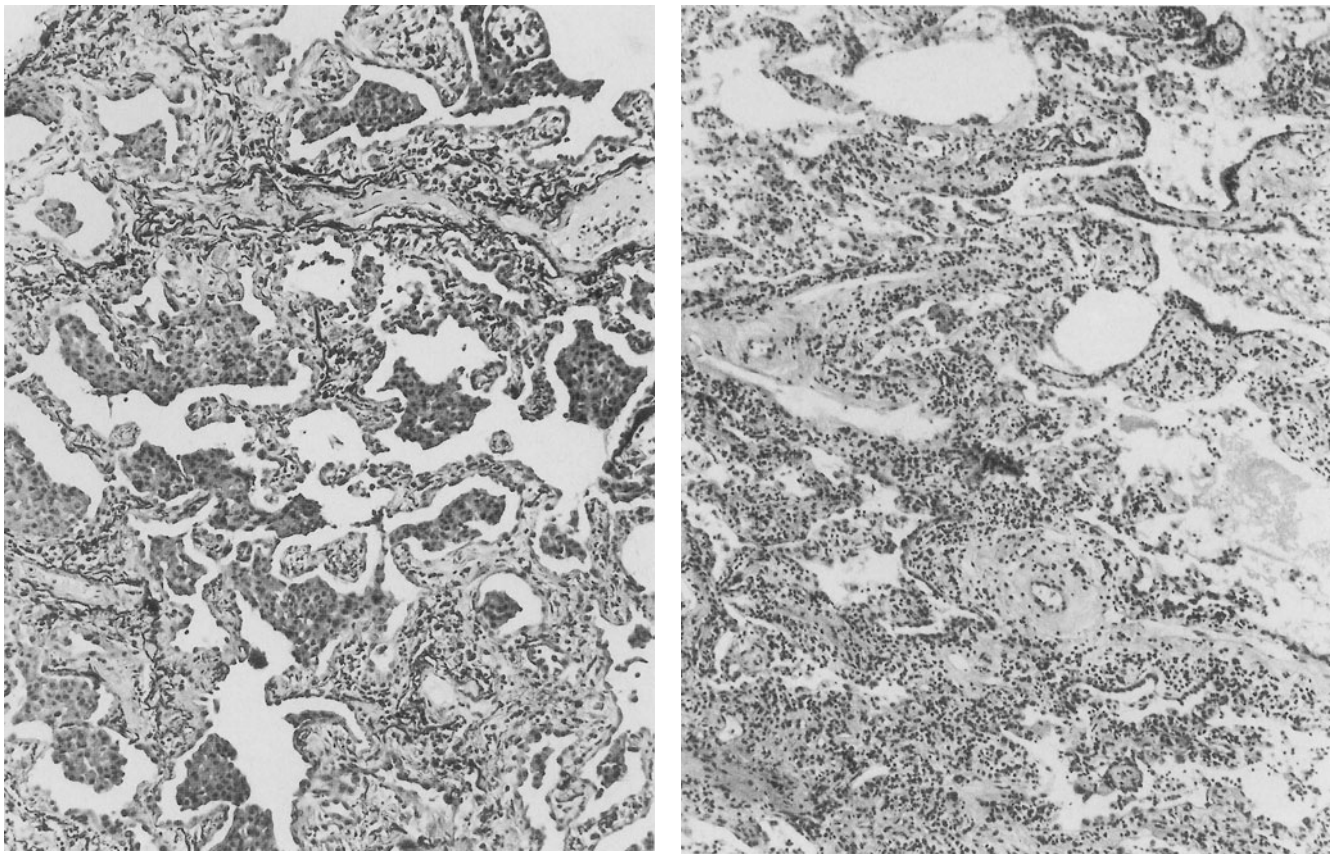
18-14

Fig. 18–13 and Fig. 18–14. Interstitial fibrosis and chronic inflammation are obvious at this magnification. Note alveolar lining cell hypertrophy and hyperplasia. ×330.

patients, we found significant variation in histologic changes. Individual regions of the same biopsy frequently show more than one of the patterns of interstitial pneumonitis as described by Liebow and Carrington[11] (Fig. 18–15). In each open biopsy we give a semiquantitative estimation of the average severity of fibrosis on an arbitrary O to 4+ scale (Fig. 18–16). Intimal fibrosis and medial hypertrophy of small pulmonary arteries are seen in most cases (Fig. 18–17). Likewise, occasional obliteration of small bronchi or bronchioles by granulation or fibrous tissue, bronchiolitis obliterans (Fig. 18–18), is a common finding. This author prefers the Movat pentachrome stain to delineate the histologic changes; with this stain, elastic tissue stains black, young connective tissue green, collagen yellow, and smooth muscle red. The most dramatic histologic feature using this stain is the marked fragmentation and/or increase in elastic tissue (Fig. 18–19). In some cases, smooth muscle proliferation is a prominent feature (Fig. 18–20).

Immunohistochemistry and electron microscopy are effective tools in further characterizing the pathologic changes in idiopathic fibrosis. Using monoclonal antibodies directed against low or high molecular weight cytokeratin, epithelial membrane antigen, or human milk fat globule protein, the hypertrophied and hyperplastic alveolar and bronchiolar lining cells are accentuated (Fig. 18–21). Ultrastructurally, the marked disorganization of the lung tissue is better seen (Figs. 18–22 and 18–23). Atypia of alveolar lining cells is prominent (Fig. 18–24), with most of these atypical cells representing alveolar type II cells (Fig. 18–25). As they become reactive, the number of lamellar bodies usually decreases. Some will show intranuclear tubular inclusions, which can also be seen by light microscopy (Figs. 18–26 and 18–27). Occasionally these cells will engulf other cells such as erythrocytes and polymorphonuclear leukocytes and some will show accumulation of "alcoholic hyaline," which represents aggregates of intermediate cytokeratin filaments (Fig. 18–28). A neoplastic proliferation of these reactive cells probably accounts for the increased incidence of peripheral lung adenocarcinoma in patients with idiopathic fibrosis.[97–100]

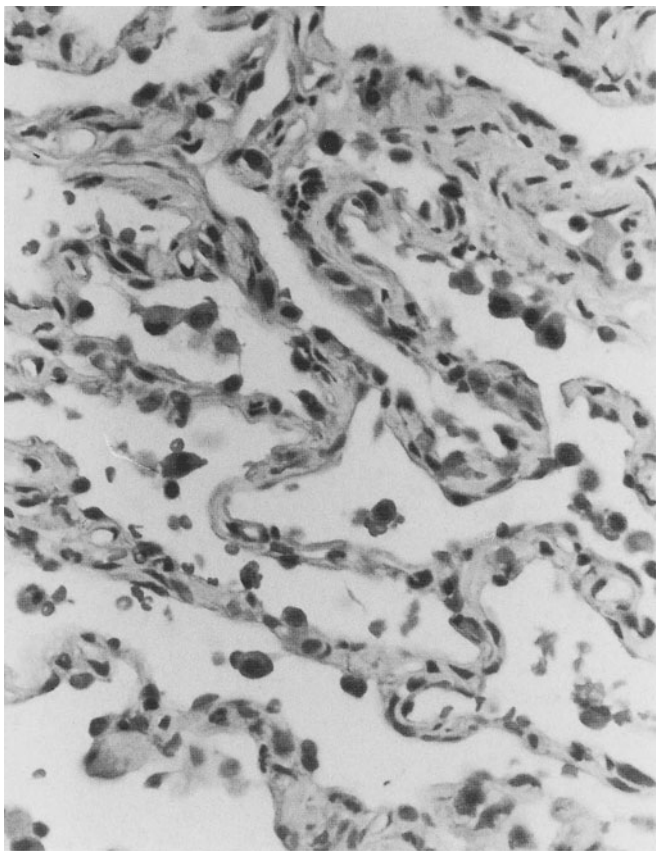
Immunohistochemical identification of the intermediate filaments vimentin and desmin, panleukocyte antigen, and muscle-specific actin is helpful in identifying alveolar macrophages, interstitial mesenchymal cells, inflammatory cells, and smooth muscle cells. Demon-



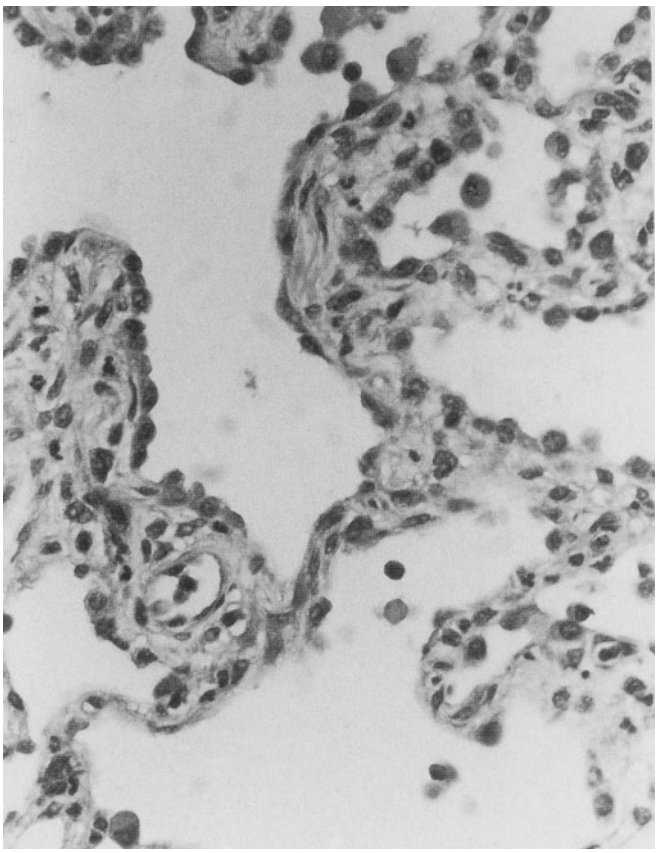
A B

Fig. 18–15 A,B. Open lung biopsy shows significant variability in histologic appearance. **A.** Note "desquamative" pattern with accumulation of intraalveolar macrophages. **B.** Note more lymphocytic interstitial pneumonitis pattern characterized by an intense interstitial infiltrate of lymphocytes and plasma cells. ×75.

Fig. 18–16 A–D. In each open biopsy showing histologic changes of interstitial pulmonary fibrosis, we assess average degree of fibrosis on an arbitrary scale of 0 to 4+: 0, normal tissue with no interstitial fibrosis; 1+, interstitial fibrosis **(A)** is characterized by slight widening of alveolar septa with relatively normal alveoli; 2+, interstitial fibrosis **(B)** is characterized by slight-to-moderate fibrous thickening of alveolar septa; 3+, fibrosis **(C)** shows moderate to marked septal thickening with a moderate distortion of the usual architecture including obliteration of alveoli; 4+, fibrosis **(D)** is characterized by complete obliteration of alveoli by dense fibrous tissue. In each grade of fibrosis there usually is some degree of chronic inflammation and alveolar lining cell hypertrophy and hyperplasia. ×330.



A



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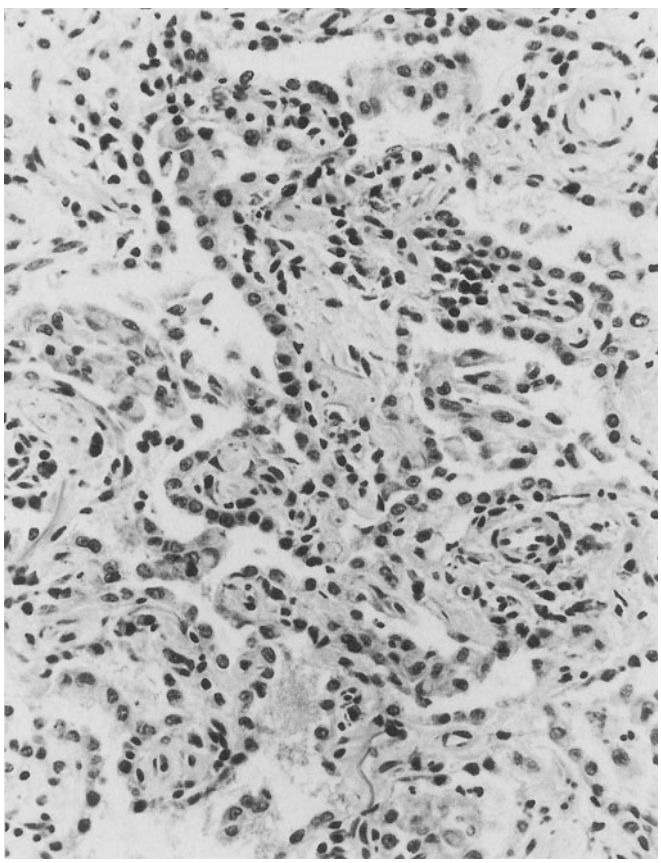

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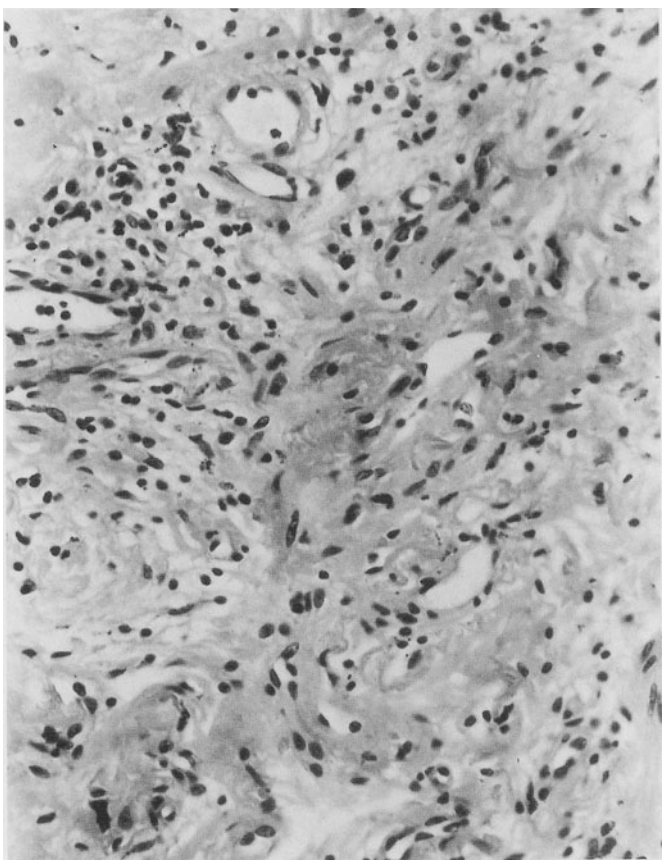

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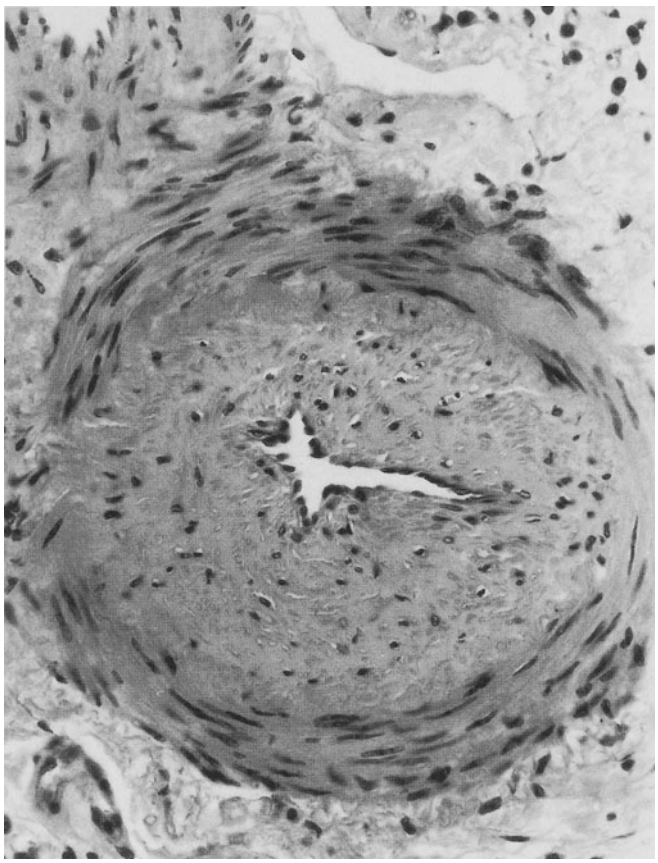
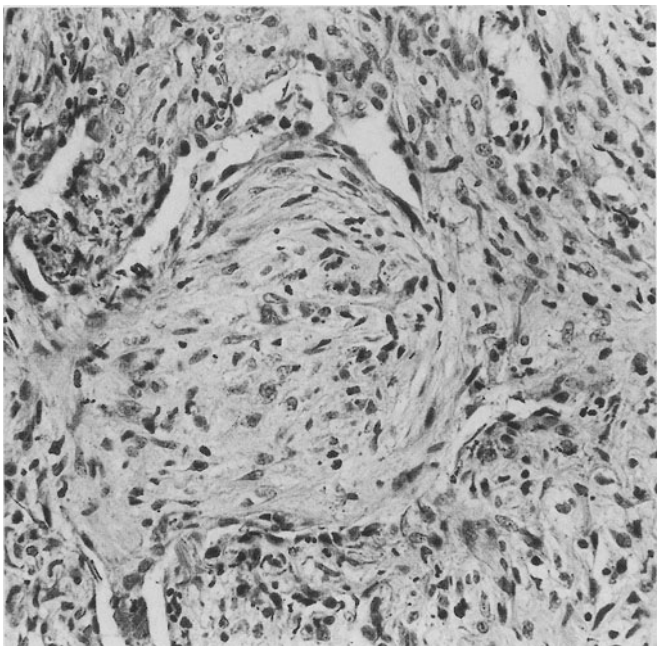


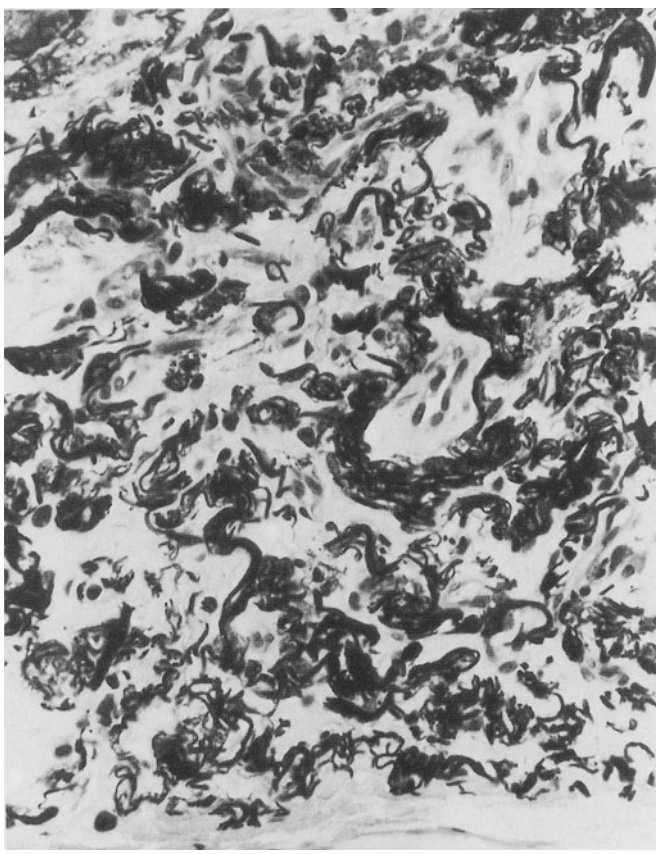
18-17



18-18

Fig. 18–17. In most cases of pulmonary fibrosis, small pulmonary arteries and veins show some degree of muscular hypertrophy and intimal fibrosis. ×550.

Fig. 18–18. Focal bronchiolitis obliterans characterized by granulation tissue or fibrous tissue in lumen of bronchiole, is a common finding in cases of idiopathic pulmonary fibrosis. ×330.



18-19

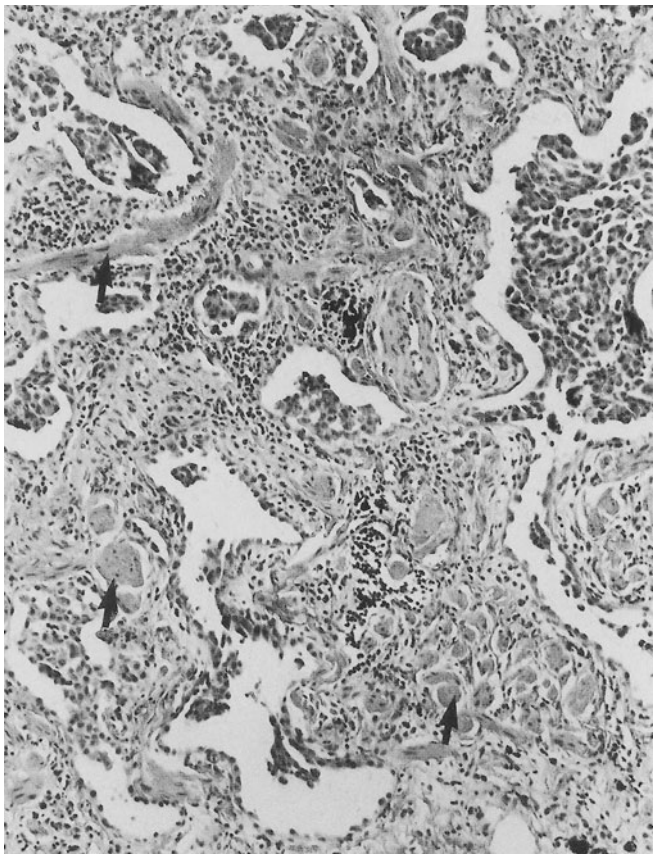
Fig. 18–19. Peripheral lung tissue stained for elastic tissue (*black*) shows apparent increase and/or fragmentation of the elastic fibers, which could be secondary to collapse of parenchyma. ×330.

Fig. 18–20. Regions of smooth muscle proliferation (*arrows*) not obviously associated with vessels or bronchi are seen in some cases of pulmonary fibrosis. ×75.

Fig. 18–21. Peripheral fibrotic lung tissue immunostained for low molecular weight cytokeratin vividly shows hypertrophied and hyperplastic alveolar lining cells and accentuates thickened interstitium. Pleural mesothelial cells (*arrow*) are also seen. ×550.

Fig. 18–22. Low power electron micrograph shows marked disorganization of peripheral lung tissue characteristic of idiopathic pulmonary fibrosis. In this region is seen a mixed interstitial inflammatory cell infiltrate with hypertrophy and hyperplasia of alveolar lining cells, most of which are alveolar type II cells (*arrows*). Interstitial collagen (COL) and elastic tissue (ET) are increased in interstitium. ×6,500.

Fig. 18–23. Lung tissue shows dense interstitial collagen (COL) and elastic tissue (ET) formation with little inflammation and no alveolar lining cell changes. ×6,500.



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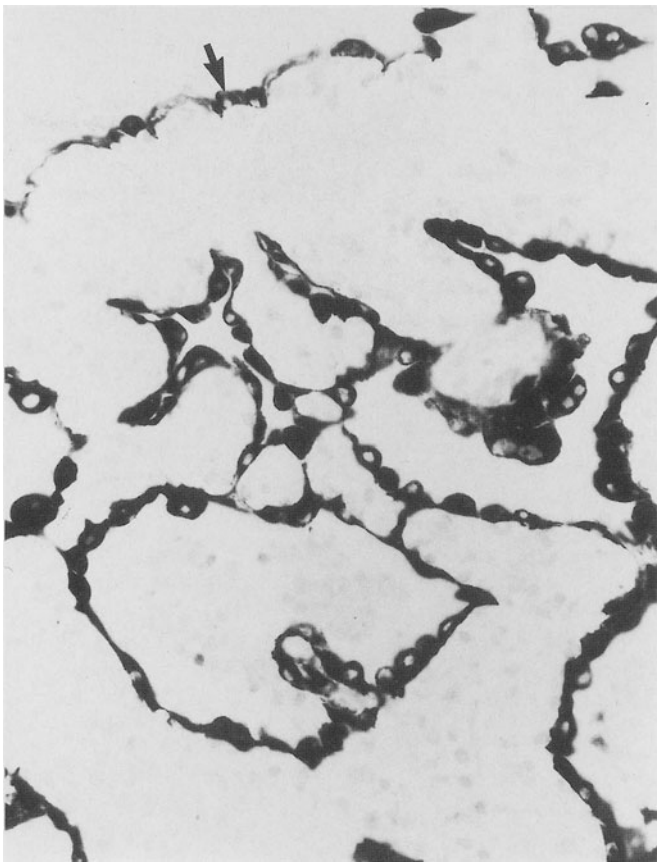

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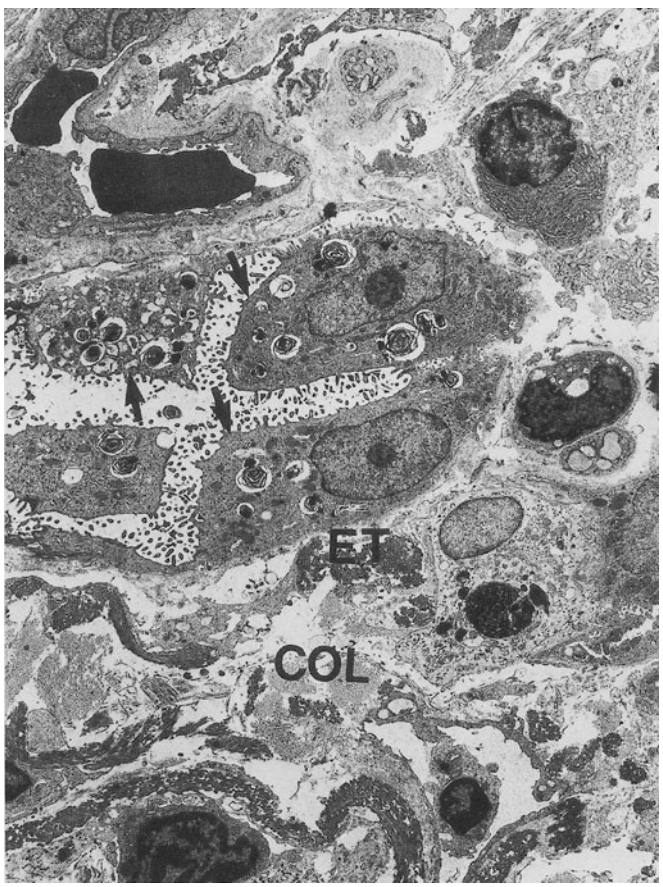

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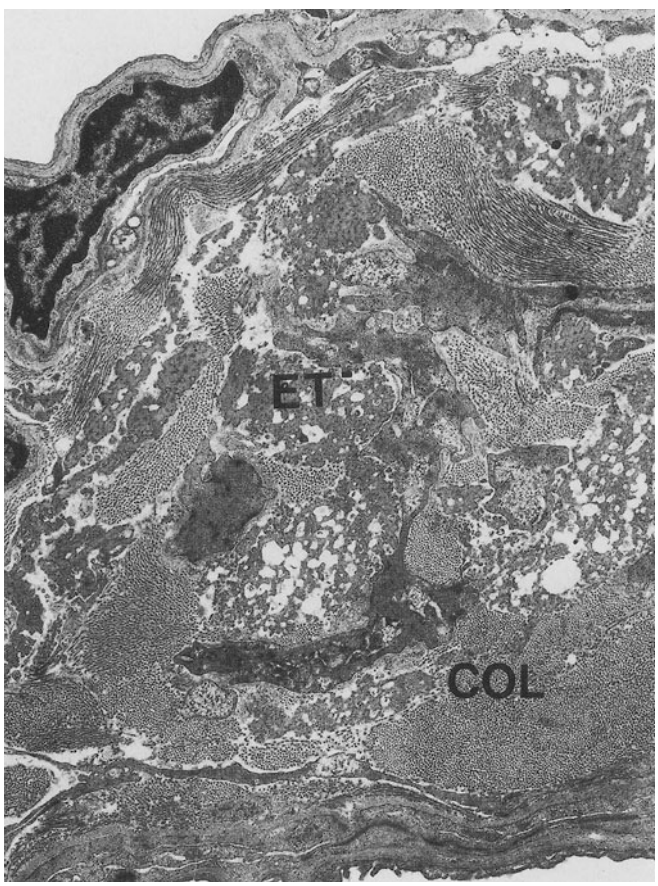

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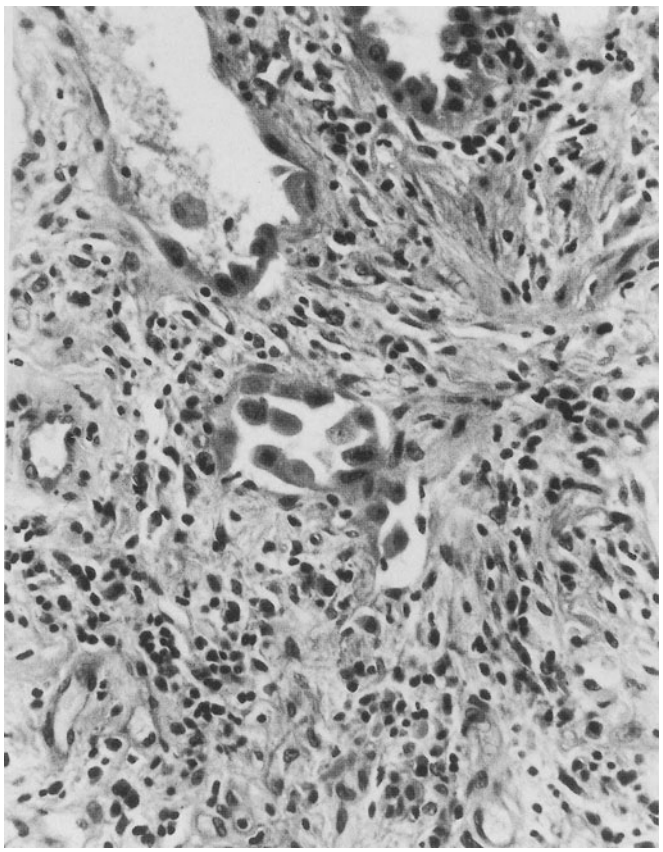

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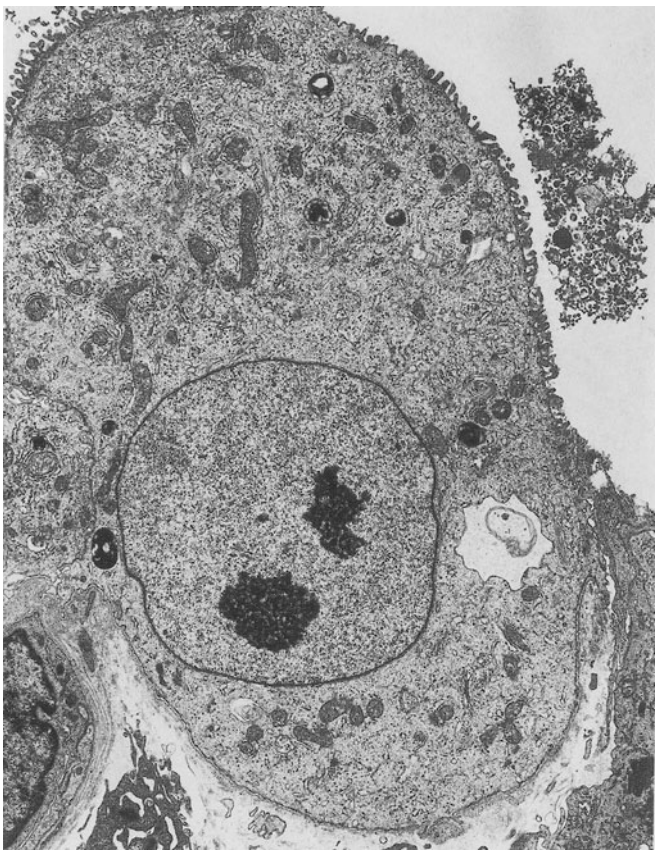

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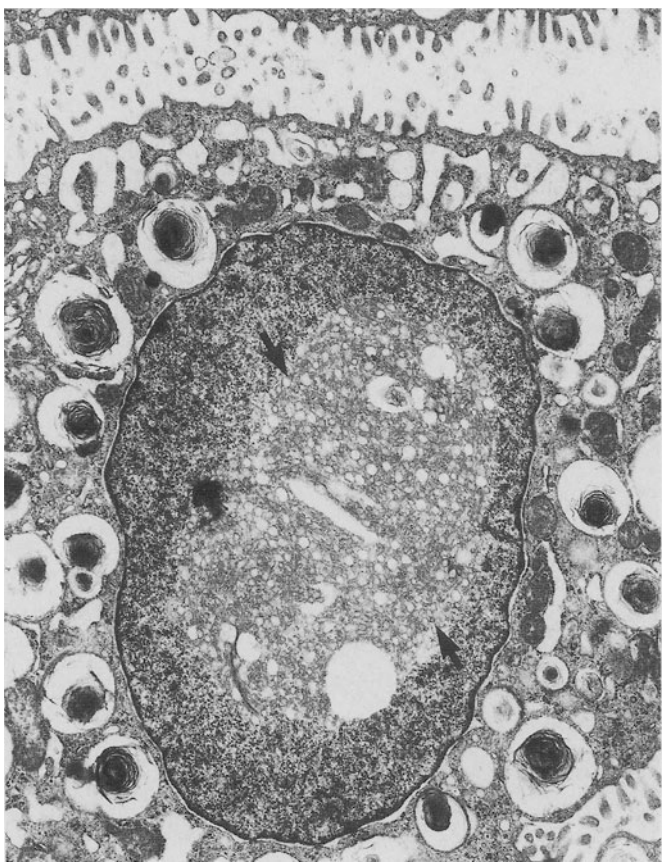
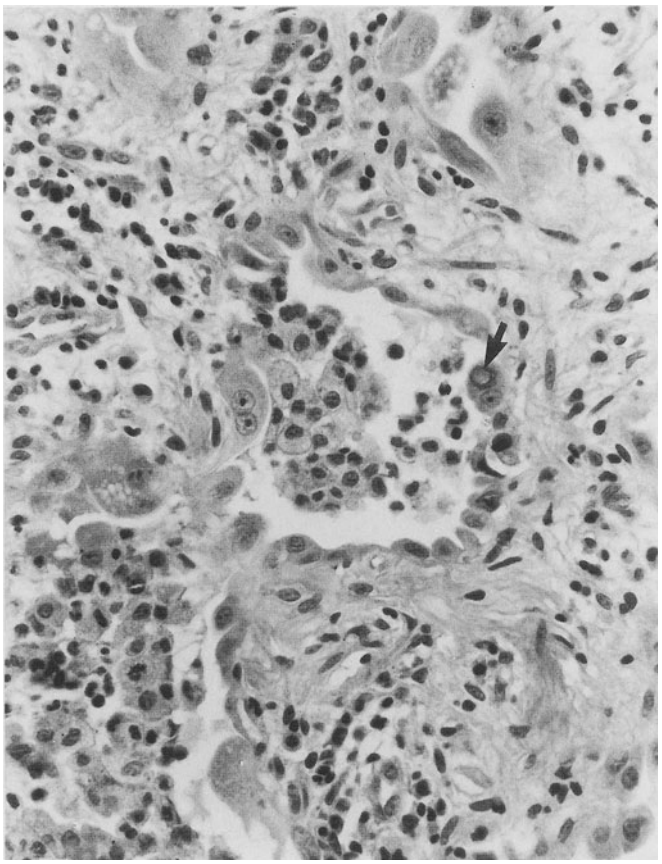


18-26



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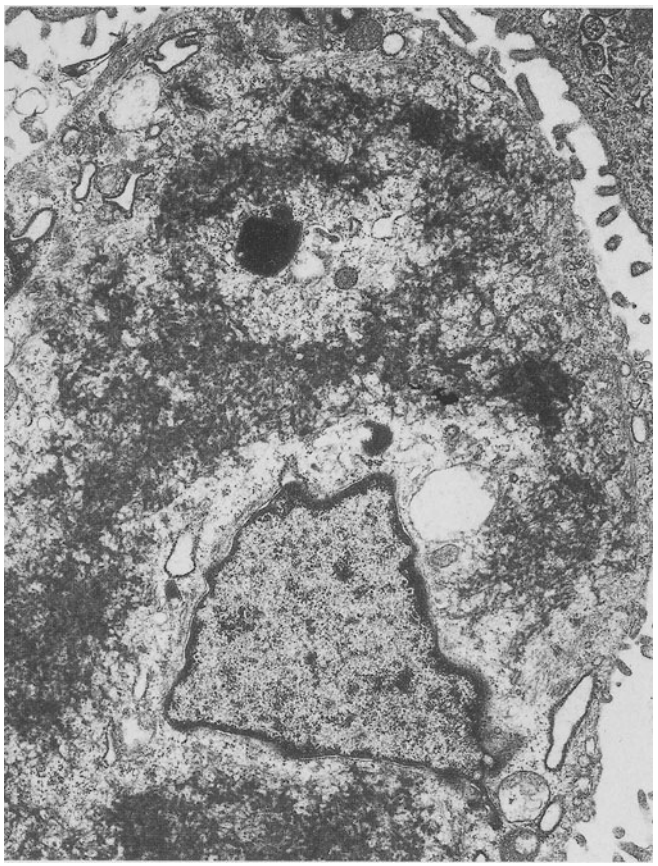


Fig. 18–28. Reactive alveolar lining cell contains aggregates of electron-dense intermediate filaments that represent cytokeratin. In H and E-stained sections, these have the appearance of "alcoholic hyaline" as seen in liver cells. ×16,500.

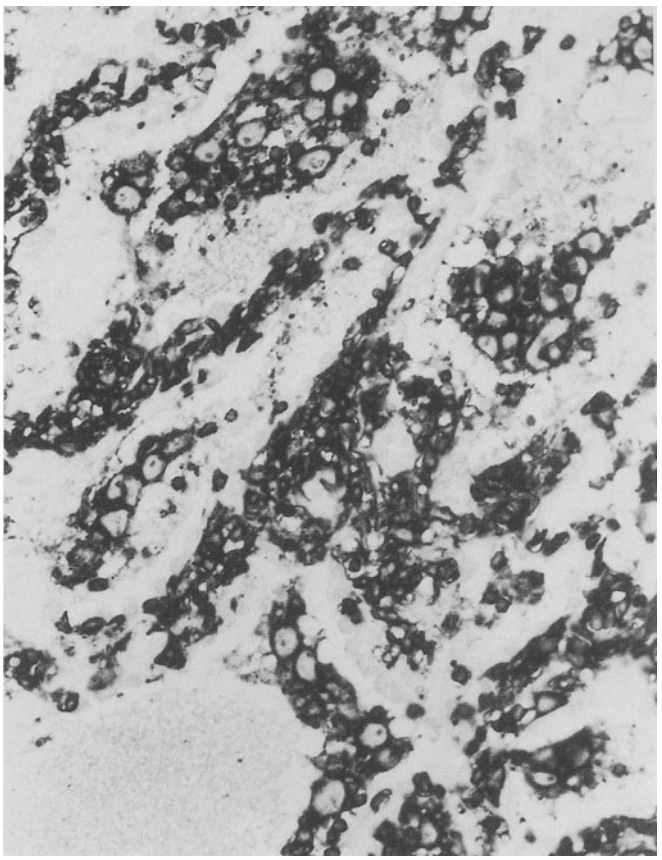


Fig. 18–29. Lung tissue immunostained for pan leukocyte antigen shows numerous, predominantly interstitial, "positive" (*black*) staining cells, mostly lymphocytes and macrophages. ×330.

Fig. 18–24. Atypical alveolar lining cells, obvious in this peripheral lung tissue, can result in a false-positive sputum cytology. ×330.

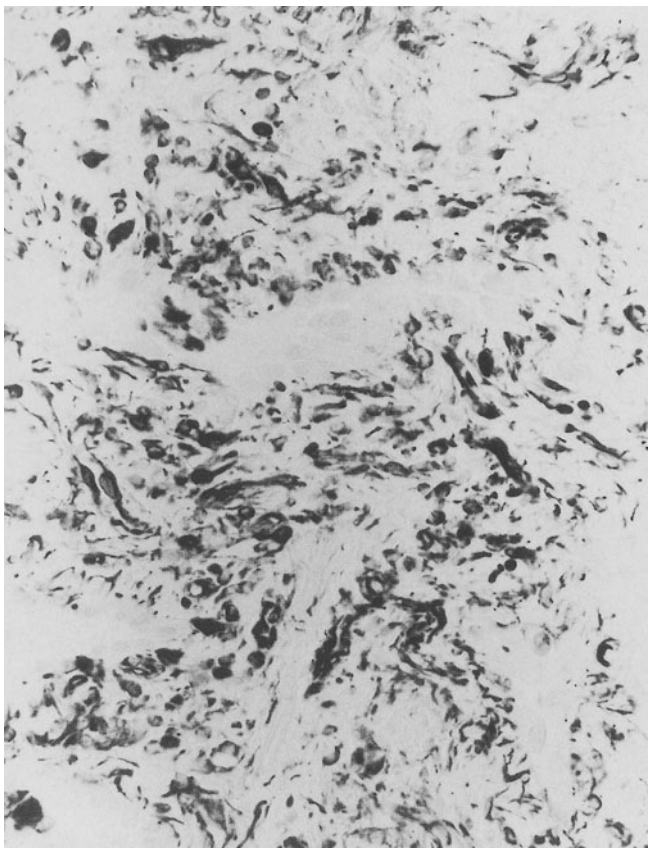
Fig. 18–25. Reactive alveolar lining cell with large nucleus and prominent nucleoli probably represents a type II pneumocyte although it lacks well-formed lamellar bodies in its cytoplasm. ×10,500.

Fig. 18–26. Reactive alveolar type II cell contains intranuclear tubular inclusion (*arrows*). Thought to be derived from the inner nuclear membrane, these are frequently seen in bronchiolo-alveolar cell carcinomas but are not specific for malignancy. ×10,500.

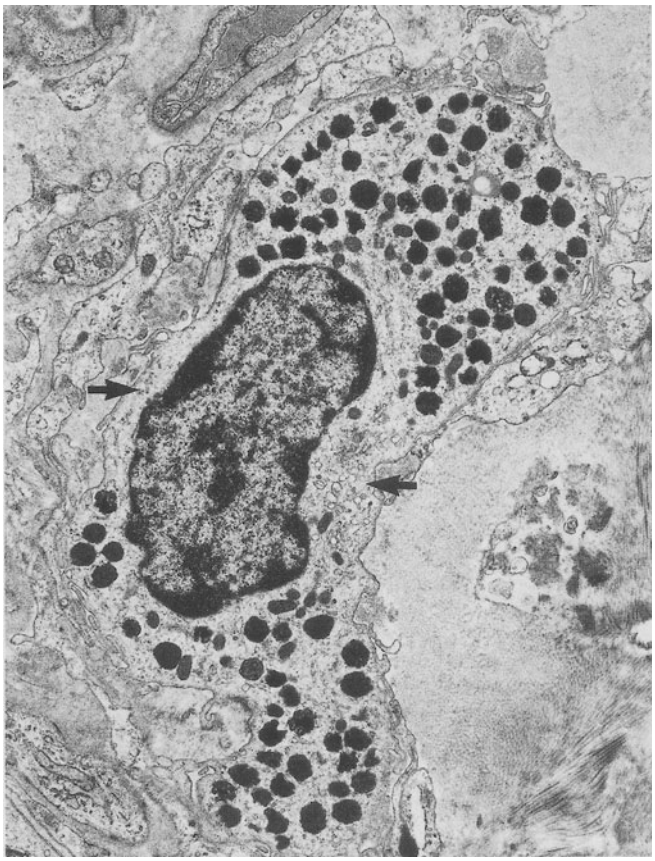
Fig. 18–27. Intranuclear inclusion seen in Fig. 18–26 can be recognized by light microscopy as a ground glass-like inclusion (*arrow*) that may stain with periodic acid–Schiff reagent. ×330.

stration of these cells via immunohistochemistry is usually not necessary for diagnosis but is useful in identifying various cell types (Figs. 18–29 and 18–30). An experimental study of bleomycin-induced pulmonary fibrosis in rats showed that the interstitial cells exhibited immunostaining for vimentin and not desmin, suggesting that these cells are of fibroblast and not smooth muscle origin.[101]

Other cells that can be identified in the interstitium of fibrotic lungs ultrastructurally or immunohistochemically but are not observed in hemotoxylin and eosin-stained light microscopic sections are mast cells (Fig. 18–31) and Langerhans cells. Mast cell hyperplasia has recently been noted in cases of bleomycin-induced pulmonary fibrosis, although its exact role in the development of fibrosis is uncertain.[102] Langerhans cells are unique dendritic histiocytes of bone marrow origin that occur normally in the skin and other organs[103] and are present in most cases of idiopathic pulmonary fibrosis.[104–107] They can be identified ultrastructurally because of their pathognomonic cytoplasmic Langerhans cell granules or immunohistochemically by the



18-30



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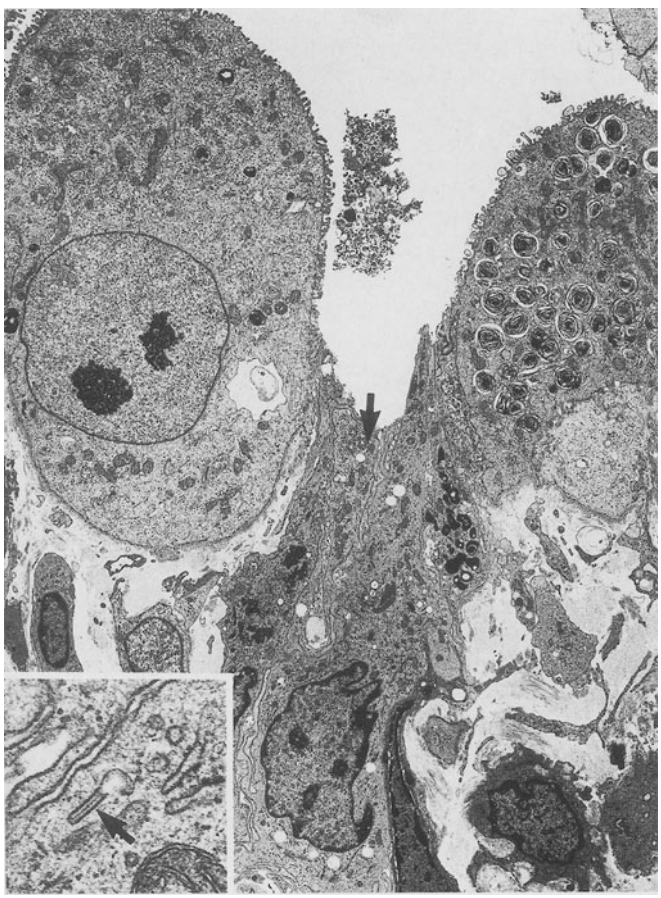


18-32

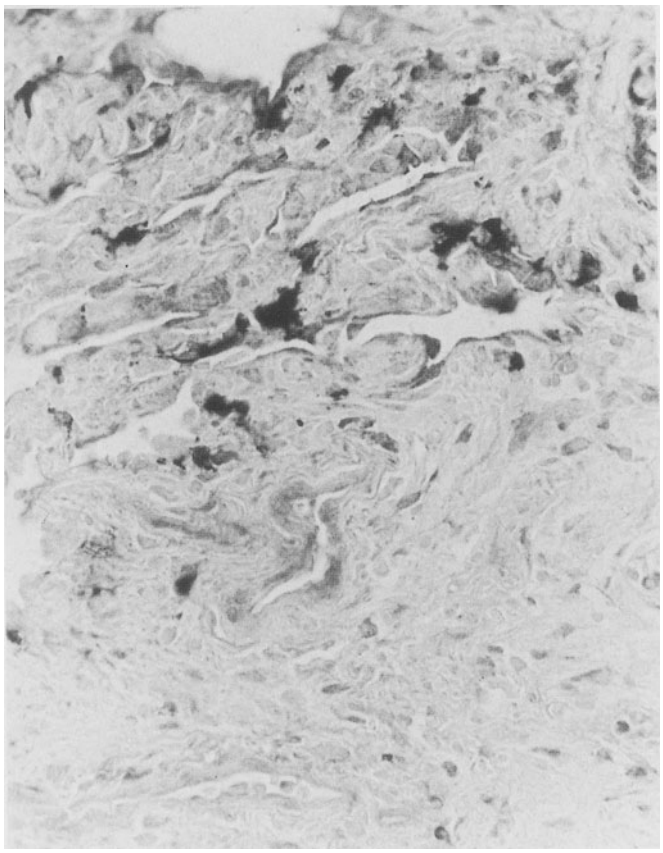
presence of S–100 protein (Figs. 18–32 and 18–33). Unlike pulmonary histiocytosis X in which Langerhans cells (histiocytosis X cells) usually occur in nodular aggregates,[108–110] (see Chapter 14) these cells are typically associated with reactive alveolar lining cells or are in association with interstitial lymphocytes. Langerhans cells function by presenting antigens to T lymphocytes, and in the skin are important in sensitization to and perhaps eradication of contact antigens. Their exact function in idiopathic pulmonary fibrosis is unknown but presumably is immunologic.

As previously stated, as many as 20% of cases of

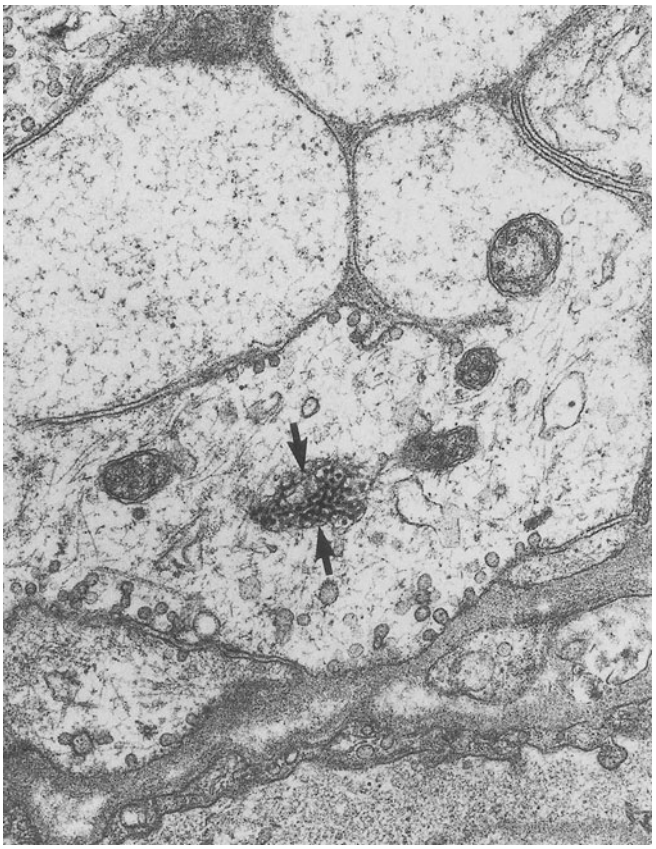
Fig. 18–30. Lung tissue immunostained for the intermediate filament vimentin shows numerous "positive" (*black*) cells, a combination of fibroblasts, endothelial cells, and inflammatory cells. ×330.

Fig. 18–31. Mast cell (*arrows*) seen by electron microscopy is frequent in most cases of pulmonary fibrosis but is usually not visible in H and E stained sections. ×6,500.

Fig. 18–32. Langerhans cell (*arrow*) wedges between reactive alveolar type II cells in this example of pulmonary fibrosis. ×6,500. Inset: Typical Langerhans cell granule (*arrow*) present in cytoplasm of Langerhans cell at higher magnification. ×26,500.

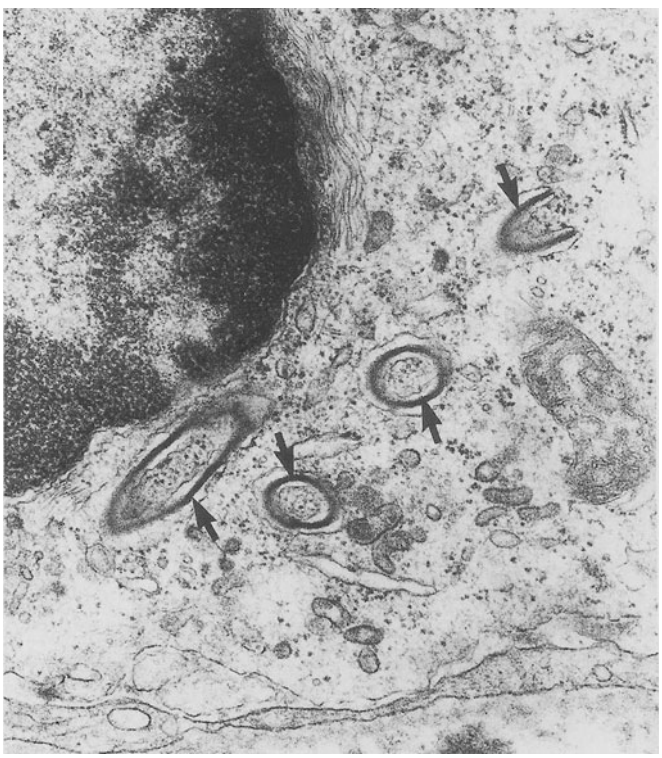


18-33



18-34

pulmonary fibrosis may be associated with a collagen vascular disease. We have recently found that those cases associated with a collagen vascular syndrome or with a viral infection showed marked alveolar septal capillary endothelial cell swelling with intracellular tubuloreticular structures and cylindrical confronting cisternae (Figs. 18–34 and 18–35).[111,112] As reviewed, these changes are caused by inferferon,[111,112] and we have postulated that the primary mechanism of injury in collagen vascular disease and viral-associated pulmonary fibrosis is endothelial cell damage.[107]

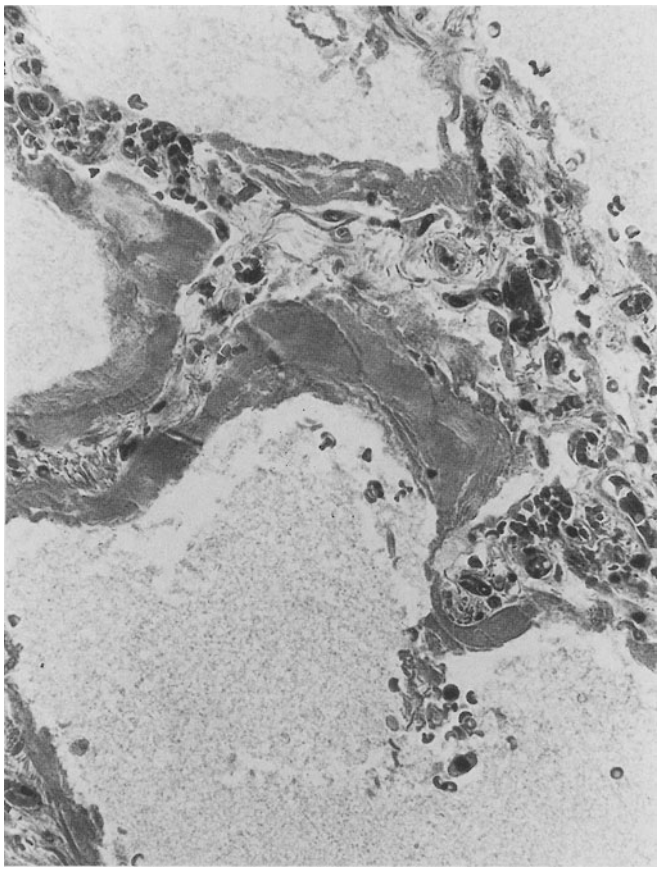


18-35

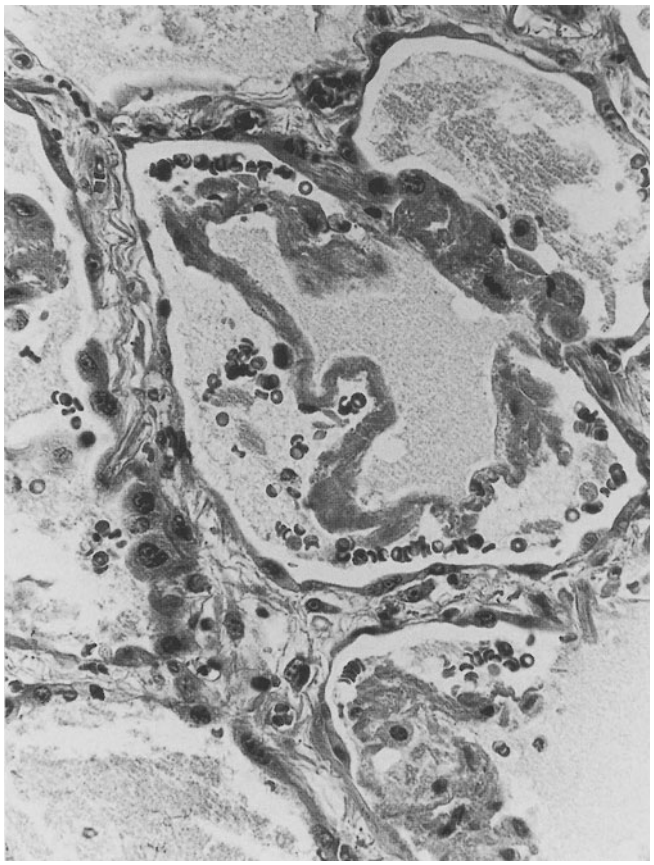
Fig. 18–33. Fibrotic lung tissue immunostained for S-100 protein shows several "positive" (*black*) cells with dendritic processes that represent Langerhans cells as shown in Fig. 18–32. ×330.

Fig. 18–34. Tubuloreticular structure (*arrows*) in cytoplasm of swollen endothelial cell from patient with interstitial fibrosis associated with mixed connective tissue disease. ×16,500.

Fig. 18–35. Cylindrical confronting cisternae (*arrows*), also known as test tube and ring-shaped structures, are present in cytoplasm of endothelial cell from patient with interstitial pulmonary fibrosis associated with systemic lupus erythematosus. Cylindrical confronting cisternae and tubuloreticular structures are formed in response to elevated levels of interferon in these conditions. ×16,500.



18-36



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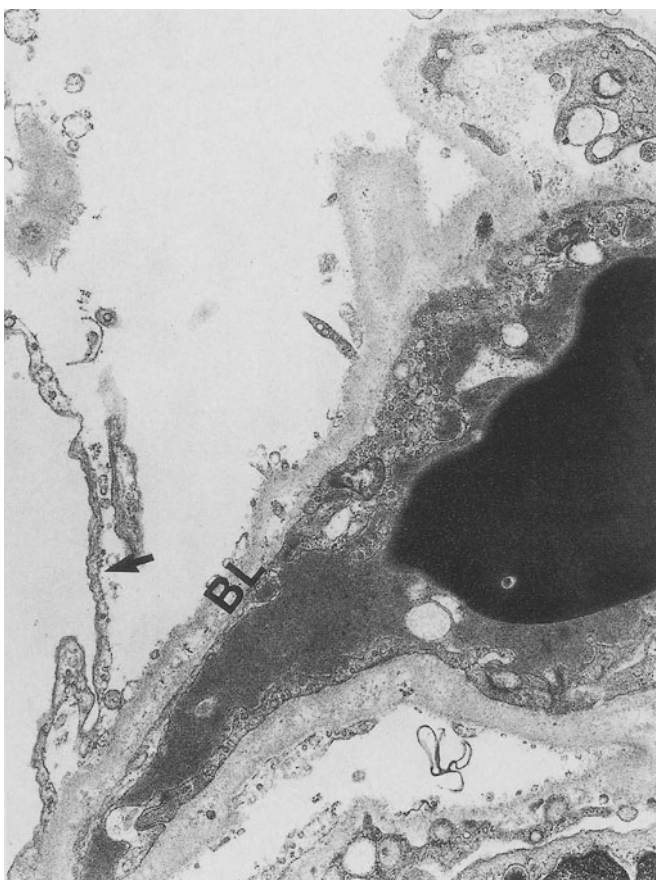

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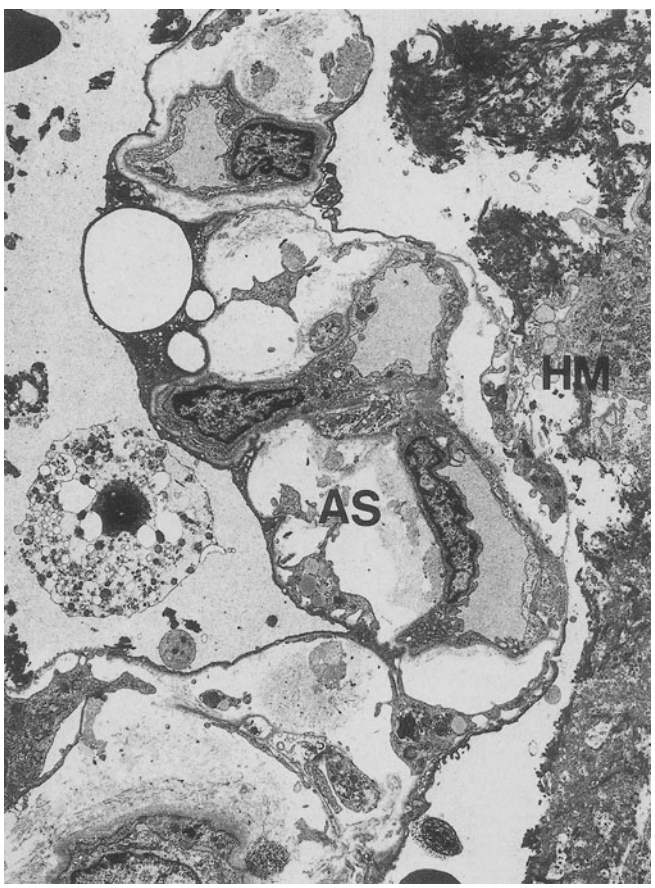

18-39

In acute diffuse alveolar damage, there is marked alveolar septal edema with variable degrees of necrosis of alveolar lining cells and hyaline membrane formation (Figs. 18–36 and 18–37). The alveolar lining cells are frequently lifted off the basal lamina (Fig. 18–38). Hyaline membranes are composed of a mixture of degenerating cells, fibrin, and other serum proteins (Fig. 18–39). Acute interstitial pneumonitis, may represent progression of alveolar damage and is characterized by extensive interstitial fibroblast proliferation with little collagen deposition plus alveolar type II cell hypertrophy and hyperplasia.[5a]

Differential Diagnosis

In most instances, the diagnosis of idiopathic pulmonary fibrosis is straightforward. The clinical history of insidious dyspnea of unknown cause, a diffuse bilateral interstitial infiltrate on chest radiograph, and the typical pathologic changes described in this chapter all add up to the diagnosis.

The problem for clinician and pathologist is to exclude other known causes of fibrosis. Chronic hypersensitivity pneumonitis can progress to chronic fibrosis indistinguishable from idiopathic fibrosis; a careful clinical history is most important. The end stages of pulmonary histiocytosis X can macroscopically and microscopically be identical to idiopathic fibrosis. In pulmonary histiocytosis X, the disease usually occurs in a younger age group and is frequently biopsied in the acute stage of the disease. In the end stages it may be difficult, if not impossible, to identify aggregates of histiocytosis X cells. Viral pneumonia can progress rapidly or insidiously to pulmonary fibrosis. Again, the history is critical and serologic or viral culture studies may help elucidate this etiology. Also, ultrastructural examination will characteristically show endothelial cell swelling and intracytoplasmic tubuloreticular structures. Another potential cause, or association, of pulmonary fibrosis is the acquired immune deficiency syndrome (AIDS). A case of pulmonary fibrosis without superimposed opportunistic infection has been reported,[113] as has lymphocytic interstitial pneumonitis.[114,115] The same ultrastructural features seen in collagen vascular disease and viral-associated fibrosis, namely endothelial cell swelling, tubuloreticular structures and cylindrical confronting cisternae, may also be seen in the lung tissue from patients with AIDS. In AIDS, this is also probably caused by interferon, which is elevated in the serum of patients with this syndrome.[116]

In chronic, postobstructive pneumonitis, histologic changes identical to those seen in idiopathic pulmonary fibrosis may be present. There may also be, however, a significant number of foamy macrophages. Such a change is usually unilateral and the cause of the obstruction, such as a neoplasm, is usually obvious. Bronchiolitis obliterans organizing pneumonia, an entity that may have several etiologies or be idiopathic, may be confused with idiopathic fibrosis.[117,117a] Unlike patients with pulmonary fibrosis, there is complete recovery in 65% of subjects. Histologically there is more intraalveolar and intrabronchiolar organizing fibrous tissue than is seen in cases of idiopathic fibrosis.

A description of the patterns of pulmonary fibrosis seen in various disease conditions was published in 1986 and is helpful to the pathologist because it contrasts the patterns of fibrosis seen in many diseases and tells what patterns are specific and what are not.[117b]

In acute alveolar damage or acute interstitial pneumonitis, the problem is usually ruling out known causes of these conditions rather than considering a different diagnosis.

Approach to the Diagnosis

The handling of an open lung biopsy specimen is critical to making an accurate diagnosis (see Chapter 1). At our institution open lung biopsy specimens are received in sterile containers from the operating rooms. With today's surgical techniques, the cut edge or edges of the specimen are usually closed with metal staples. Often, there is enough tissue in association with the staples that can be used for routine bacteriologic and viral cultures. Most biopsy specimens that show the changes of interstitial fibrosis will be sufficiently stiff so that no inflation-type procedure will be necessary to maintain the overall architecture.

In some cases of pulmonary fibrosis, lung tissue has been reported to show deposits of immunoglobulin and complement, especially in cases associated with collagen

Fig. 18–36. Acute diffuse alveolar damage shows alveolar septal necrosis with hyaline membrane formation. ×330

Fig. 18–37. In this region of acute alveolar damage, hyaline membranes are still present but there has been some repair with epithelialization of injured alveoli. ×330.

Fig. 18–38. Cytoplasm of alveolar type I cell (*arrow*) is lifted from its underlying basal lamina (BL) in this case of diffuse alveolar damage. ×16,500.

Fig. 18–39. Hyaline membrane (HM), associated with degenerating alveolar septum (AS), is composed mostly of degenerating cellular debris and fibrin. ×6,500.

vascular diseases.[118–120] This author has only rarely found deposits of immunoglobulin and complement in frozen sections of fibrotic lung tissue studied by direct *immunofluorescence,* and our observations are supported by Corrin et al.[92] This could be caused by variation in the techniques we use in preparing the tissue or in interpretation. Hogan et al.[121] illustrated the difficulties encountered in performing and interpreting direct immunofluorescent studies on lung tissue.[121] Autofluorescence of elastic tissue and nonspecific fluorescence are frequently encountered. Presently we do not perform direct immunofluorescent studies on lung tissue unless a diagnosis of Goodpasture's syndrome is to be ruled out.

Transbronchial biopsies obtained via fiberoptic bronchoscopy are usually too small to make a specific diagnosis of interstitial fibrosis.[122–124] Wall and colleagues[125] recently studied the specificity of pathologic diagnosis obtained via transbronchial biopsy and compared it to diagnosis made from open lung biopsy specimens. They performed transbronchial biopsies in 53 patients with radiographic evidence of diffuse disease, obtaining four to six tissue specimens from the regions of greatest radiographic abnormality. They found transbronchial biopsy specimens to yield specific diagnosis in 20 patients (37.7%), of whom 18 had either sarcoidosis or malignancy. In the remaining 33 patients, the histologic findings were reported as normal lung in 10, nonspecific abnormalities in 11, interstitial fibrosis in 9, and inadequate tissue specimens from 3 patients. Open lung biopsies from these 33 patients resulted in specific diagnosis in 92%. Wall et al. concluded that the transbronchial biopsy diagnosis of pulmonary fibrosis was often misleading and required open biopsy for confirmation.

Bronchoalveolar lavage via a fiberoptic bronchoscope was introduced in 1974[126] and has been suggested to be useful diagnostically and prognostically in certain pulmonary diseases such as idiopathic fibrosis and sarcoidosis. An estimated 1 million alveoli are sampled in a typical procedure. The usefulness of bronchoalveolar lavage is dependent on three basic assumptions: (1) the technique samples airspace inflammatory cells; (2) a correlation exists between the cells sampled and the type and distribution of inflammatory cells in the interstitium of the lung; and (3) bronchoalveolar lavage cell populations can be translated into diagnostic and even prognostic correlations, which are reproducible and more exact than those derived for pulmonary function testing, chest radiographs, and patient symptoms. The technique and cellular analysis of bronchoalveolar lavage fluid are covered in Chapter 1. The lingula or right middle lobe is the site most commonly lavaged, because fluid can be recovered from these locations when the patient is in a supine position. In normal, nonsmoking adults, approximately 100–150 $\times$ 10^3 cells

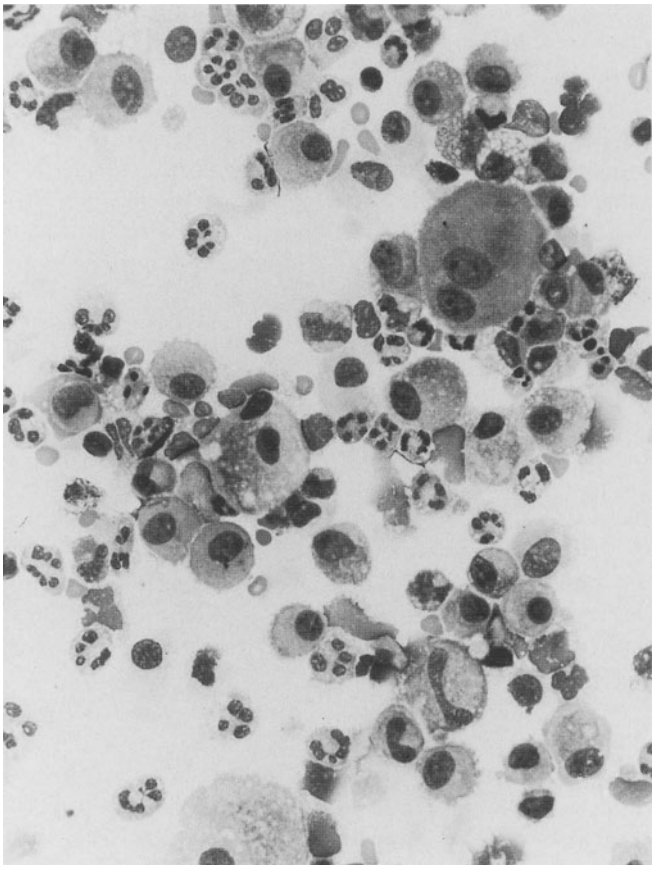

Fig. 18–40. Increased number of neutrophils (~ 20%) forms cellular component of bronchoalveolar lavage fluid from patient with idiopathic pulmonary fibrosis. ×330.

are present per milliliter of lavage fluid. Approximately 90% of recovered cells are macrophages, 10% are lymphocytes, and less than 1% are eosinophils and neutrophils. In cigarette smokers, there may be a two- to fivefold increase in total cells per milliliter due to an increase in macrophages and polymorphonuclear leukocytes; polys may reach 5% of the total number of cells.

There are several potential and known problems in interpreting lavage cellular data, such as the effect of lavage volume on cell counts[127] and variation between areas of the same lung.[128] Notwithstanding these problems, patients with idiopathic pulmonary fibrosis typically show a significant increase in neutrophils in their lavage fluid (Fig. 18–40). Gelb et al.[129] found elevated percentages of polys in 11 of 20 patients with fibrosing alveolitis. Whether the cellular population in the lavage fluid reflects that in tissue has been the subject of three studies. Davis et al.[130] performed a quantitative study on open lung biopsy specimens of airspace inflammatory cells from 28 patients with diffuse interstitial lung

disease including 14 patients with idiopathic pulmonary fibrosis. They found more inflammatory cells in the alveoli of patients with interstitial lung disease but found a significant variation in airspace cellular content in different tissue sections from the same person and significant differences in patients. Most interesting was their observation that polymorphonuclear leukocytes were so rarely seen in the airspaces that only lymphocytes were quantitated. A fourfold increase in lymphocytes was identified in airspaces of patients with pulmonary fibrosis, but no correlation could be made between airspace lymphocytes and interstitial inflammation. In the 19 patients who had lavage, a linear correlation was observed between lymphocytes in the airspaces and lavage fluid.

Hunninghake and colleagues[131] compared cells in lavage with open lung biopsy specimens in 9 patients with pulmonary fibrosis and 6 with sarcoidosis. Their approach was different than that of Davis et al. in that they teased cells from the tissue, passed them through a gauze filter, subjected the cells to ficoll-hypaque density centrifugation, and performed a differential cell count. They found an increased percentage of neutrophils in cells teased from the parenchyma of patients with pulmonary fibrosis, which correlated with cells identified in the lavage fluid. The third study was by Haslam et al.,[132] who compared cellular content of bronchoalveolar lavage fluid with open biopsy specimens in 21 patients with pulmonary fibrosis including 6 with collagen vascular diseases and 3 with asbestosis. In 12 patients, differential counts of cells extracted from lung biopsy specimens were compared to lavage cell populations, and a semiquantitative histologic assessment of each inflammatory cell was made for intraalveolar and interstitial cells. Haslam et al. found a significant correlation between inflammatory cells in lavage fluid and extraction samples, but found no correlation between semiquantitative scores of cell types observed either within alveolar spaces or in the lung interstitium and the differential or total cell counts of lavage samples and extract samples.

Thus, in these three studies often quoted as supportive of the theory that lavage cell populations reflect tissue cell populations, Haslam et al. found no correlation between the cellular infiltrate in tissue and that in lavage fluid, and Davis and colleagues found a correlation only between lymphocytes in tissue and lavage fluid and virtually never observed neutrophils. The exact source of the neutrophils in lavage fluid from patients with pulmonary fibrosis remains somewhat of a mystery. In this author's experience, open lung biopsies from patients with pulmonary fibrosis only rarely contain neutrophils in the interstitium or airspaces. When polys are observed, they are usually seen in distorted small bronchi, which are probably partially obstructed secondary to fibrosis (Fig. 18–41).

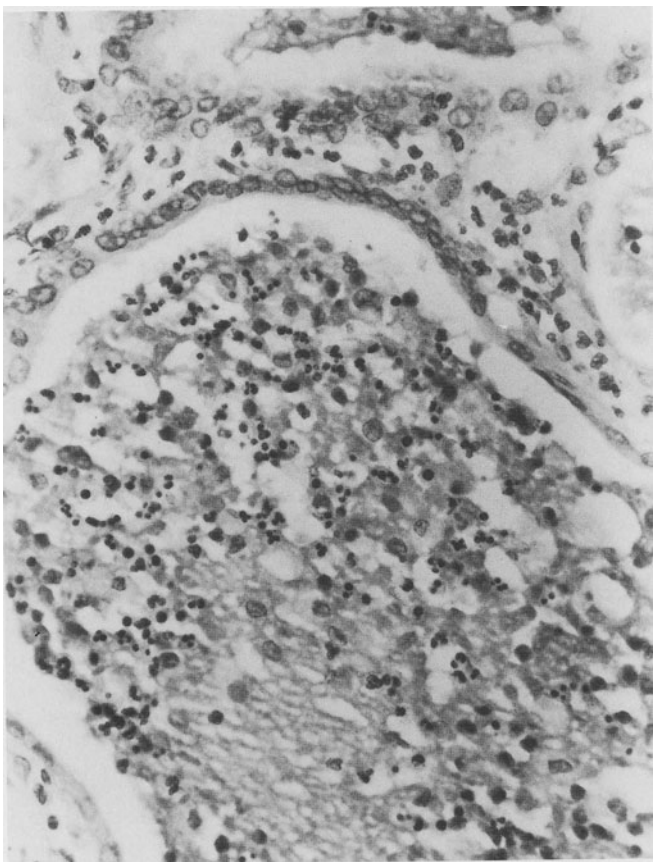

Fig. 18–41. Neutrophils are frequently observed associated with mucus in distorted small airways in cases of idiopathic pulmonary fibrosis. This may be the source of increased numbers of neutrophils in lavage fluid from patients with pulmonary fibrosis. ×330.

Clinical Pathologic Correlations

Idiopathic pulmonary fibrosis is usually a relentlessly progressive disease, and is characterized by progressive pulmonary dysfunction in an acute, subacute, or chronic pattern. About 20% of patients, however, will exhibit a stable fibrotic process with no progression. The main clinical problem is to determine which patients to treat, with what drugs, and for how long.

In general, treatment is ineffective in pulmonary fibrosis. In the study by Stack et al.[133] of 96 patients with idiopathic pulmonary fibrosis, the mean survival from time of onset of the first symptom to the time of death was 49.6 months. Survival was affected adversely by increasing age and increasing severity of signs and symptoms at the onset of the disease. In

our study[94] of 20 patients with diffuse interstitial pneumonitis treated with prednisone and/or azathioprine, we found that the degree of interstitial fibrosis was the single most important factor in separating those who responded to therapy versus those who did not. In the study of Carrington et al.[61] of the natural history and treated course of 40 patients with "desquamative interstitial pneumonitis" and 53 patients with "usual interstitial pneumonitis," approximately 22% with desquamative interstitial pneumonitis and none with usual interstitial pneumonitis showed spontaneous improvement without therapy. With prednisone therapy, 61.5% of desquamative interstitial pneumonitis patients and 11.5% with usual interstitial pneumonitis improved clinically. The mean survival in patients with desquamative interstitial pneumonitis was 12.2 years, and in usual interstitial pneumonitis patients it was 5.6 years. Their findings are similar to ours in that the patients with desquamative interstitial pneumonitis, according to their definition, lacked significant interstitial fibrosis.

In the study by Gelb and colleagues,[129] only 2 of 16 patients with "cellular disease" and none of 4 with a "pure fibrotic reaction" showed a response to corticosteroids. In the study by Rudd and co-workers[134] of 120 patients with cryptogenic fibrosing alveolitis, of whom 91 were treated, lymphocyte counts were significantly higher in bronchoalveolar lavage fluid in responders versus nonresponders, while neutrophils and eosinophils were highest in those who did not respond to therapy. Haslam et al.[135] found a similar negative therapeutic correlation with the number of neutrophils and eosinophils in lavage fluid. If our hypothesis is correct that polys are seen in distorted bronchi possibly obstructed secondary to fibrosis, this may also be a manifestation of the degree of fibrosis.

Several studies have addressed the clinical significance of serum immune complexes in patients with idiopathic fibrosis. In 1978, Dreisin and colleagues[78] found a correlation between the degree of inflammation in lung tissue and the the presence of circulating immune complexes. Those with elevated levels of circulating immune complexes and significant pulmonary inflammation showed a better response to corticosteroid therapy than those who lacked these features. In 1979, Haslam et al.[135] found no correlation between histologic changes in lung tissue and the presence or absence of immune complexes. Gelb et al.[129] also studied the association between serum immune complexes, histologic changes in lung tissue, and response to corticosteroid therapy in 20 patients with pulmonary fibrosis. They found elevated levels of immune complexes in 12 of 14 patients whose lung tissue showed significant inflammation. In all 12 patients, the elevated titers of immune complexes returned to normal within 2 months after beginning steroid therapy regardless of response to therapy. Only 2 of 16 patients whose lung biopsy showed significant inflammation and none of those with "pure fibrosis" improved with therapy. The authors concluded that immune complexes were associated with increased inflammation in the biopsy specimens but did not predict response to therapy.

More recently, Martinet et al.[136] performed a study to determine the clinical significance of circulating immune complexes in 16 patients with cryptogenic fibrosing alveolitis and 24 patients with collagen vascular-associated interstitial lung disease.[136] C1q binding, a measure of immune complexes in serum, was elevated in 62.5% of patients with collagen vascular disease and 31.3% of patients with idiopathic pulmonary fibrosis. Those patients with serum immune complexes tended to be younger and have a shorter duration of symptoms and less evidence of radiographic disease, but had similar mean values for total lung capacity, forced vital capacity, and forced expiratory volume than those without immune complexes in their serum. There was no correlation between responsiveness to corticosteroid therapy or length of survival with the presence of serum immune complexes.

In acute interstitial pneumonitis characterized by acute diffuse alveolar damage, most patients die of respiratory failure. Survival is dependent on the amount of lung tissue involved and the severity of injury. Unfortunately, the disease typically involves the entire lung. Those who survive usually are respiratory cripples with diffuse interstitial fibrosis requiring oxygen, although the condition is usually not progressive.

We have found that patients with interstitial fibrosis associated with collagen vascular syndromes, whose lung tissue and peripheral blood lymphocytes contain tubuloreticular structures, will frequently not respond to prednisone therapy but may show dramatic improvement with cyclophosphamide therapy.[137] When these patients clinically improve, the tubuloreticular structures seen in their lymphocytes disappear. The role of cyclophosphamide in treating idiopathic pulmonary fibrosis is still being evaluated.

In summary, idiopathic pulmonary fibrosis is a chronic progressive pulmonary syndrome usually occurring in middle-aged men and women. It is known by a variety of names, such as usual interstitial pneumonitis or fibrosing alveolitis, and may be associated with a collagen vascular disease or be a consequence of viral pneumonitis. Histologically, the lung shows a highly variable pattern of change including fibrosis, inflammation, alveolar lining cell hypertrophy, and thickening of small pulmonary vessels. The disease is usually progressive, leading to respiratory insufficiency and death, although patients whose disease is associated

with a collagen vascular disease may show a dramatic therapeutic response to cyclophosphamide.

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