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I D I O P A T H I C P U L M O N A R Y F I B R O S I S

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Diffuse involvement of the pulmonary interstitium with abnormal fibrous tissue is a process which occurs in many settings. Although there are many possible etiologies for pulmonary fibrosis, in the majority of individuals a clear cause cannot be determined and a diagnosis of idiopathic pulmonary fibrosis (IPF) results. Despite limited knowledge concerning the inciting event, recent advances in biomedical technology offer great promise for increasing our understanding of IPF. This review will focus on current concepts of the pathogenesis of IPF. However, an understanding of the clinical presentation of the disease and the physiologic derangements which result from the accumulation of abnormal fibrous tissue in the lung is first essential.

Clinical Presentation

In 1944 Hamman and Rich (1) described four individuals who presented with rapid onset of progressive dyspnea and expired within one to six months after the onset of symptoms. At post mortem examination each patient had marked pulmonary fibrosis and cor pulmonale. The term "Hamman-Rich Syndrome" has often been applied uniformly to cases of IPF. However, it is clear that in many patients pulmonary fibrosis follows a more chronic course (2-10). Thus, in any patient presenting with a history of progressive dyspnea of uncertain duration and a chest roentgenogram showing diffuse reticular, nodular, or honeycomb infiltrate, a diagnosis of IPF should be considered. However, these complaints and radiographic findings have a lengthy differential diagnosis (**Table 1, see Appendix A**) and a diagnosis of IPF depends on a precise history and a histologic picture of diffuse fibrosis. Indeed, previous studies (11) have demonstrated that a clinical history is often the most useful diagnostic device. The absence of known exposure to drugs or other agents capable of producing pulmonary fibrosis is required as histology usually cannot differentiate between various etiologies of fibrosis.

The prevalence of IPF is unknown but is estimated to be three to five cases per 100,000 population (12). There is a slightly increased prevalence in males (13) and the disease usually occurs in the fourth to sixth decade of life though all age groups may be affected.

Breathlessness is the predominant presenting complaint, found in virtually 100% of patients (14). The dyspnea develops with minimal exertion and is usually accompanied by a non-productive cough. Physical examination often reveals clubbing, basilar rales and an augmented pulmonic heart sound (7, 14).

Initial laboratory evaluation is remarkable for resting arterial hypoxemia without an increase in hemoglobin or hematocrit

(15). Although a variety of "immunologic" abnormalities have been described in the literature (elevated sedimentation rate, cryoimmunoglobulins) these are nonspecific and provide little clinical value (16-19). The major abnormalities observed on initial work-up pertain to aberrations of pulmonary function (Table 2) and provide a perspective for understanding the importance of regulating the proliferation of fibrous tissue in the lung.

Table 2

Physiologic Abnormalities in IPF

1) Reduced vital capacity and lung compliance
2) Small airways obstruction
3) Resting hypoxemia and arterial desaturation with exercise
4) Reduced diffusion capacity
5) Increased work of breathing

Physiologic Abnormalities in IPF

The spirometric hallmark of IPF is a reduction in vital capacity which correlates well with a reduction of total lung capacity and decreased lung compliance (14, 20). Although routine spirometry does not show evidence of obstruction, the small airways may be narrowed as a consequence of peribronchiolar fibrosis. When tests of small airways function are performed, 70% of patients with IPF show evidence of small airways obstruction (21). The abnormal airways physiology is of interest; however, the major consequence of the disorder relate to hypoxemia and increased work of breathing.

Patients with IPF have an abnormal arterial pO2 (58-75 mm Hg) at rest which is believed to result from ventilation perfusion imbalance (22, 23). However, during exercise, patients with IPF develop marked hypoxemia (4, 14). This is clearly related to a fall in lung diffusion capacity, (D_LCO). Recent series have found that the mean D_LCO of patients with IPF was 46% of predicted (14). Diffusing capacity can be subdivided into two components: the diffusability of the pulmonary membrane (Dm) and the pulmonary capillary blood volume (θVc). The reduction in D_LCO in IPF is predominantly one of decreased Dm, suggesting that alterations in the alveolar-capillary membrane are primarily responsible (24).

During exercise the time a red blood cell spends traversing the pulmonary capillary bed decreases to 0.5 seconds or less. In patients with IPF this is insufficient to allow equilibration between alveolar and arterial pO2 because of the diffusion abnormality. Patients thus develop arterial hypoxemia with

relatively minor exercise with a resultant severe functional limitation (Figure 1).

Figure 1

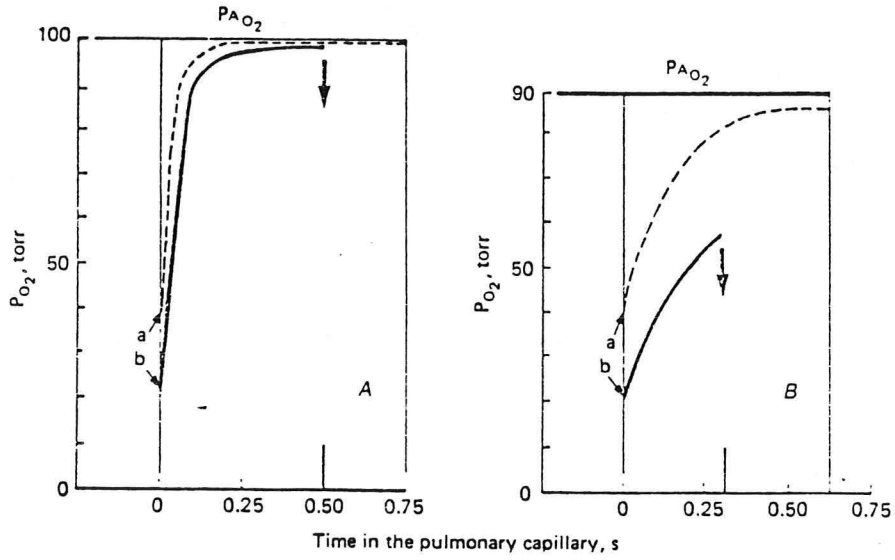


Figure 1 Oxygenation of pulmonary capillary blood at rest (---) and during exercise (-) in normals (A) and IPF (B). a and b denote the $\bar{p}O_2$ of mixed venous blood at rest and during exercise respectively.

Exacerbating this diffusion abnormality is an increased O_2 cost of breathing (increased work of breathing). Most patients with IPF have a marked increase in minute ventilation both at rest and during exercise. This results from a preferential increase in respiratory rate rather than tidal volume (25). The increased rate is believed to result from abnormally large afferent stimulation of the respiratory center by mechanical receptors in the pulmonary parenchyma and can be ameliorated by blockade of vagal afferents (26). While the minute ventilation is increased, much of this increase is "wasted" ventilation as physiologic deadspace is elevated in 60% of patients with IPF (27, 28). The combination of an increased respiratory rate, a high dead space and decrease in lung compliance results in a work of breathing which is 2-3 fold greater than in normal individuals (Figure 2) (29).

Figure 2

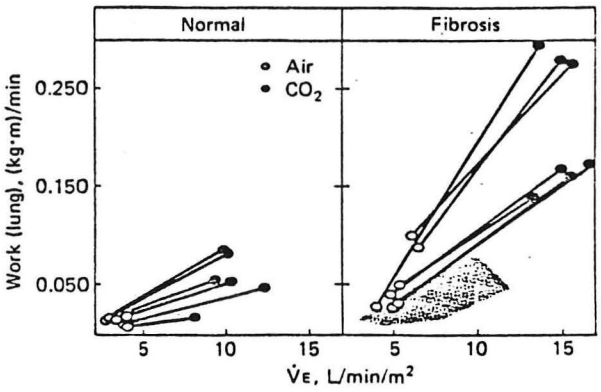


Figure 2 Work of breathing at given levels of minute ventilation in normals (left) and IPF (right). Increased minute ventilation was seen both at rest and following inhalation of CO_2 in IPF with a disproportionately increased work of breathing.

Thus, during exercise patients with IPF are caught in a vicious cycle of an increased work of breathing requiring increased amounts of oxygen supply to respiratory muscles in the setting of arterial hypoxemia. One can hypothesize that significant selective pressure has occurred throughout evolution to tightly regulate the production of fibrous tissue in the lung. Indeed the structural integrity of the normal alveolus is crucial to optimizing gas exchange.

Normal Alveolar Structure

The adult lung contains 300 x 10^6 alveoli with an internal diameter of 200 to 300 um and walls 5 to 10 um thick (30). The air surface is bordered by Type I and Type II epithelial cells, both of which rest on basement membrane (Figure 3). Type I cells line the majority of the alveolar surface and are incapable of replication. Type II cells are twice as numerous as Type I cells, synthesize surfactant, are capable of replication and may differentiate into Type I cells.

Figure 3

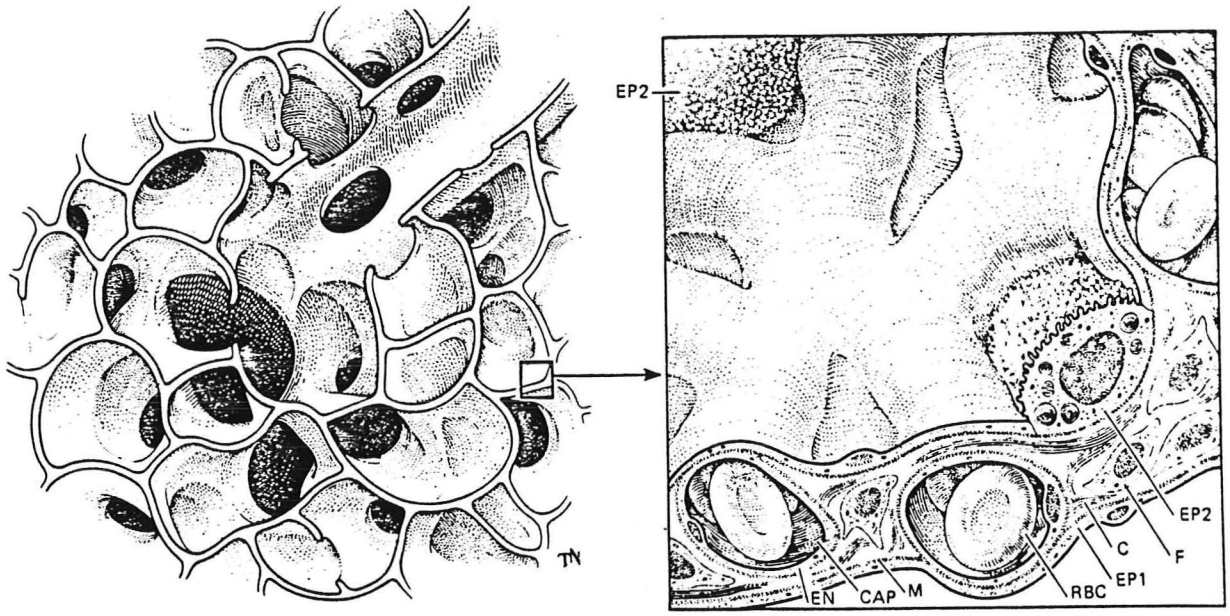


Figure 3 Structure of the alveolus. The cut surface demonstrates the type I (EP1) and type II (EP2) epithelial cells, endothelial cells (EN), basement membrane (M), red blood cells (RBC) in the capillaries (CAP), fibroblasts (F), and connective tissue (C). Inflammatory cells are not shown.

The pulmonary capillaries are comprised of a single layer of endothelial cells resting on a continuous basement membrane. Although the endothelial and epithelial basement membranes are separate they fuse at locations where capillaries are closest to air spaces. The space between the alveolar epithelium and capillary endothelium comprises the pulmonary interstitium.

The interstitium contains both non-cellular connective tissue components, and a variety of parenchymal cells including fibroblasts, macrophages and lymphocytes. In addition circulating blood cells may be recruited under certain circumstances into the interstitium.

Several abnormalities of lung architecture have been observed in patients with IPF and largely reflect a continuum of injury and fibrosis. Considerable confusion exists in the literature

concerning the morphologic changes observed in IPF. Early in the disorder a patchy alveolitis with mild to moderate thickening of the alveolar walls is observed (31-36). As the process continues, Type I cells are lost and a proliferation of Type II cells occurs. The cellular population of the interstitium and alveolus expands and at this point the confusion begins. A variety of interstitial lung diseases may have similar morphologic findings and the diagnosis of "chronic interstitial pneumonia" is often found in the Pathology literature.

Liebow and Carrington differentiated between "usual interstitial pneumonitis " (UIP) and "desquamative interstitial pneumonitis" (DIP) (37-42) (Table 3). UIP is characterized by an often uneven distribution and extreme variation in histologic features from one area of the lung to another. In contrast, DIP is a relatively uniform lesion which is best differentiated by hyperplasia of Type II cells and filling of distal air spaces with large "desquamated" mononuclear cells which on electron microscopy appear to be classical alveolar macrophages (43). In addition the lesions of DIP generally show less fibrosis than UIP and the interstitial infiltrate tends to be sparser. Alveolar lining cells in DIP are uniformly round or cuboidal Type II cells in contrast with the variable component of round, columnar, ciliated or even squamous cells seen in UIP.

Table 3

Characteristics of UIP and DIP

	UIP	DIP
Distribution of lesion	Variable	Uniform
Interstitial infiltrate	Marked	Sparse
Fibrosis	++	+
Alveolar lining cells	Variable	Type II cells
Response to Steroids	Poor	Fair

Although biopsies from patients with IPF may exhibit features similar to DIP or UIP, most clinicians view these changes as nonspecific. In contrast many pathologists believe UIP and DIP are distinct entities and there is a somewhat better response to steroid therapy in patients with DIP (44). For the sake of simplicity it is probably best to view UIP and DIP as part of the spectrum of IPF.

In the final stages of IPF, honeycombing is produced by marked restructuring of distal air spaces and obliteration of small airways with resultant formation of macroscopic cysts separated by areas of dense interstitial fibrosis (45). The list of diseases that can lead to a "honeycomb lung" is extensive and

biopsy at this stage usually contributes little to the diagnosis of a specific etiology.

Thus, the histologic findings in IPF are often nonspecific. However, several important observations are made on more detailed analysis of biopsy specimens. Specifically patients with IPF have been noted to have:

1. Derangement of normal collagen metabolism.
2. The presence of abnormal inflammatory cells in the alveolus during various stages of IPF.
3. Proliferation of fibroblasts in the interstitium.

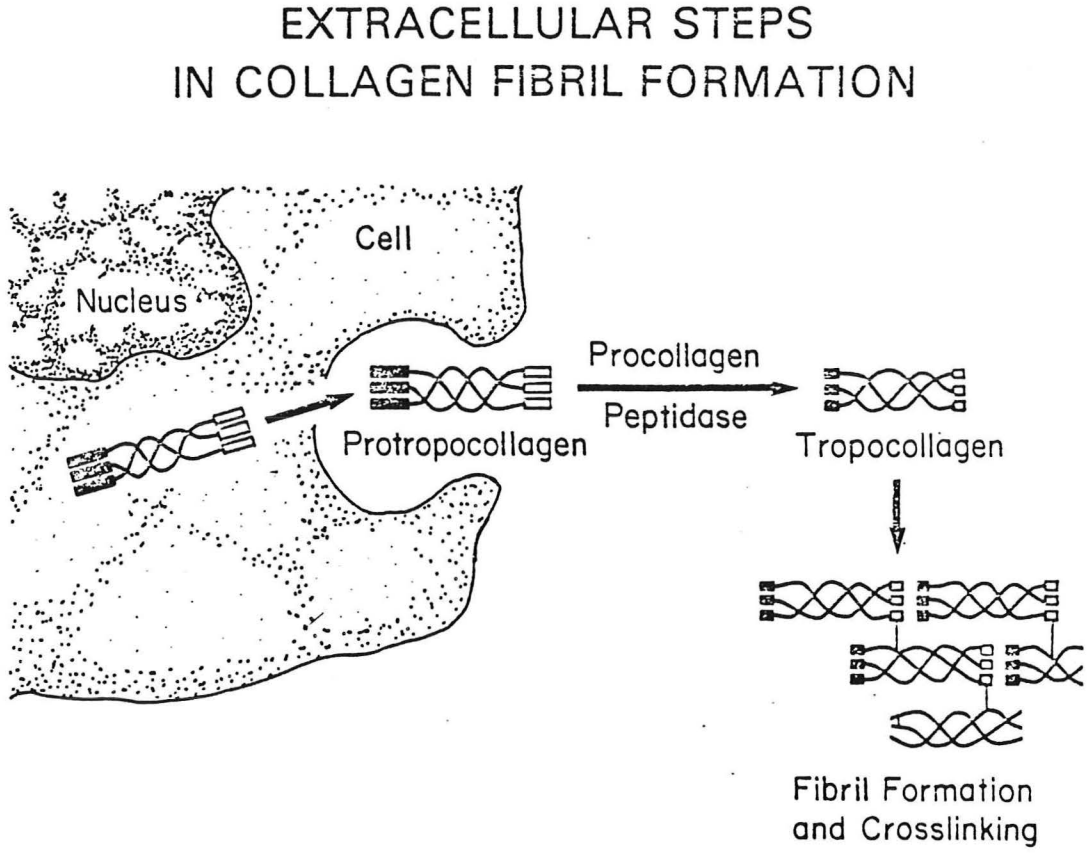
Each of these observations may be central to the pathogenesis of IPF and have been the focus of extensive investigation in the last decade. Therapeutic strategies have been formulated on the basis of this research and it is therefore important to review each facet in detail.

Collagen Homeostasis in the Lung

Collagen is the most abundant constituent of the interstitial connective tissue matrix comprising 60-65% of the total non-cellular mass. Collagen exists in several forms in the interstitium and differences in the inherent properties of the molecules are important to an understanding of fibrosis.

The fundamental unit of collagen is the tropocollagen molecule which by its ability to copolymerize with other tropocollagen molecules is capable of forming the cytoskeleton of the interstitium. Tropocollagen is composed of three alpha chains in a right-handed helical arrangement (46-48). The different types of collagen are distinguished by a variation in the combination of the 5 known alpha chains. Each α chain has a different primary amino acid sequence and is the product of a different gene. Collagen mRNA is large (MW $>1.6 \times 10^6$ daltons) (49) and is translated to a pro-α chain (MW 1.5×10^5 daltons). The pro-α chain contains the α chain in the middle (MW 9.5×10^4) surrounded by N-terminal and C-terminal noncollagenous regions. Following translation glycosylation of the pro-α chain occurs in the endoplasmic reticulum. Triple helix formation then occurs through an interaction of both collagenous and noncollagenous regions and the molecule (now known as protropocollagen) is then secreted (Figure 4). During secretion the N-terminal noncollagen region is cleaved by pro-collagen peptidase at the cell surface, (which in the lung is usually the fibroblast). Further proteolytic activity removes the C-terminal peptide and the remaining 3 α chains with short, non-helical peptides at each end, then polymerize to form a collagen fibril. The fibril is then stabilized by cross-linking (48).

Figure 4



The most abundant collagen in the lung is Type I which contains two α 1 chains and one α 2 chain. Type I collagen comprises 60-70% of total interstitial collagen in normal individuals. It is easily visible on light microscopy as a blue fibril with a Masson Trichrome stain. Type I collagen is highly organized with cross-banded fibers 50-1000 nm in diameter running parallel to the basement membrane. It is the least compliant form of collagen found in the interstitium (50).

Type III collagen usually accounts for 30-40% of interstitial collagen. Type III collagen is not easily visualized on light microscopy and is detected on electron microscopy as randomly dispersed fibrils 150-250 nm in diameter (51). Type III collagen, by mechanisms which are poorly understood, influences the way that Type I collagen forms fibrils.

In patients with IPF the major abnormality of collagen homeostasis appears to be an alteration of the ratio of Type I:Type III collagen (Table 4). Although there is some controversy in the literature, the total amount of collagen in biopsy specimens from IPF lung is grossly normal. Early in the disorder there may be an increase in Type III collagen (52). However, as the disease progresses the ratio of Type I to Type III collagen increases (35).

Table 4

Abnormalities of Collagen Homeostasis in IPF

Normal amount of <u>total</u> collagen
Early increase in Type III collagen
Later increase in the ratio of Type I:Type III collagen

Several recent studies suggest that Type III procollagen metabolism is abnormal in the lungs of patients with IPF (53-57). The N-terminal Type III procollagen is usually cleaved as the molecule is secreted from the fibroblast. Occasionally the N-terminal peptide is not cleaved and is deposited in the intracellular matrix. Compared to normal volunteers or patients with sarcoidosis, an interstitial lung disease where fibrosis occurs but is uncommon, patients with IPF have significantly increased Type III procollagen N-terminal peptide in BAL (58) (Figure 5). The mechanisms responsible for this are unclear but may relate to increased degradation of Type III collagen in the matrix of the lung.

Figure 5

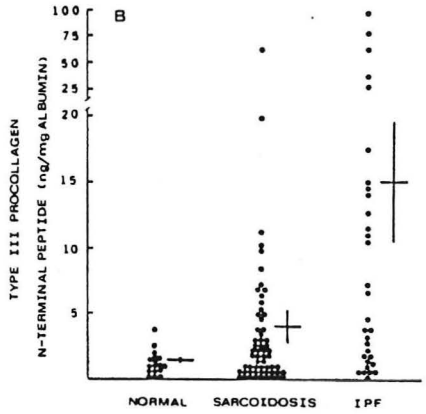


Figure 5 Type III procollagen aminoterminal peptide-related antigen levels in bronchoalveolar lavage fluid of normal subjects, patients with sarcoidosis, and patients with IPF expressed per mg of lavage fluid albumin.

Degradation of collagen presumably occurs continually in the normal lung as the concentration of collagen does not change despite continued synthesis (59). Once collagen is in the triple helical form it is very resistant to proteolytic attack and can be degraded only by collagenase (60, 61). Several cells present in the lung including alveolar macrophages, fibroblasts and neutrophils contain collagenase (62). Although release of collagenase by these cells may play a role in lung injury, collagenase may also function in lung repair. Indeed permanent fibrosis is not an invariable reaction to injury in the lung. Many toxic substances are capable of causing diffuse alveolar damage acutely. Although fibrosis may occur transiently, persistent and permanent fibrosis usually does not result. Humans who are afflicted with the Adult Respiratory Distress Syndrome develop pulmonary fibrosis 1-2 weeks following the initial insult. However, survivors of ARDS have normal lung function one year later suggesting that fibrous tissue has been degraded.

Intra-tracheal instillation of bleomycin in animals causes a marked acute inflammatory response, an increase in collagen synthesis 4-15 days after the initial injury and the development of pulmonary fibrosis eight weeks later. In contrast, instillation of intra-tracheal elastase produces an identical acute inflammatory reaction, similar changes in collagen synthesis

and the development of emphysema where there is no fibrosis. Thus, the regulation of collagen metabolism following an initial acute injury is likely central to the pathogenesis of fibrosis. However, because the injury in patients with IPF may be of a more chronic nature, considerable effort has been devoted to possible mechanisms of chronic injury. The contribution of inflammatory cells, which are present in increased numbers in the BAL of IPF patients, has been the major focus of this research.

"Injury" and Alveolitis in IPF

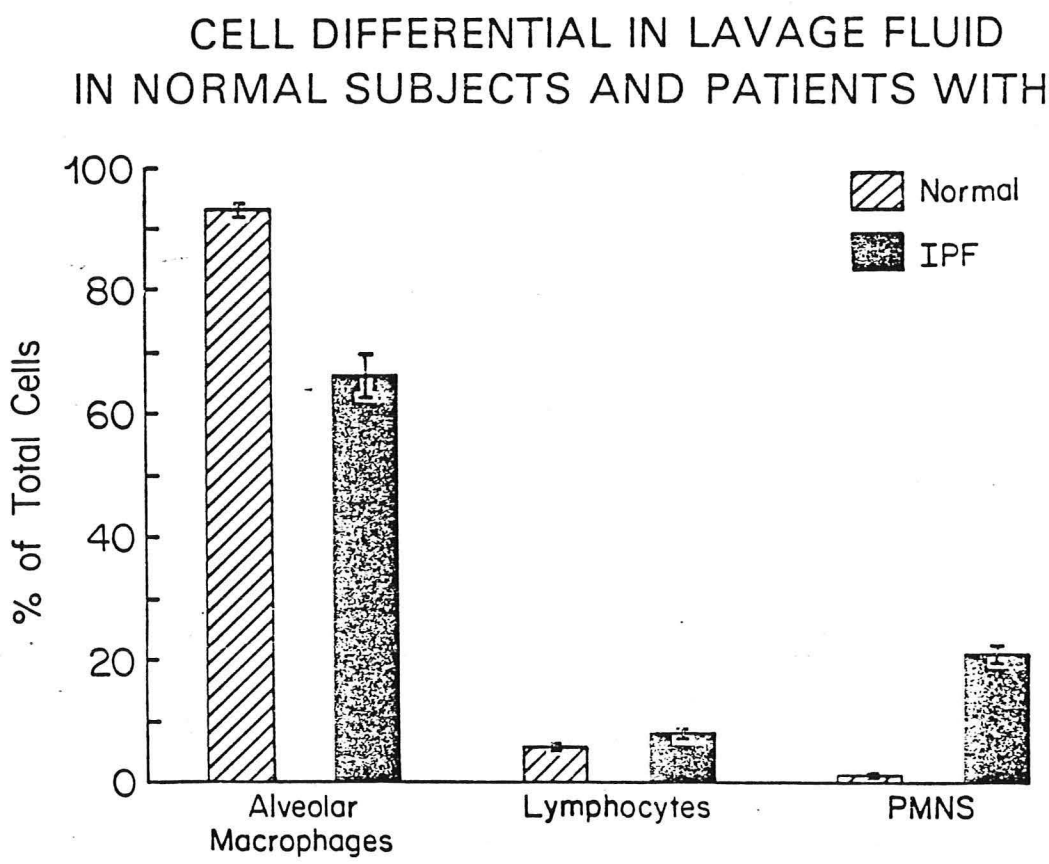
The development of bronchoalveolar lavage (BAL) roughly ten years ago allowed for the repetitive sampling of cellular components of the lower respiratory tract in a safe and practical manner. The use of BAL in a variety of interstitial lung diseases including IPF has offered new insight into the pathogenesis of these diseases. Compared to normal, non-smoking subjects a variety of alterations in the alveolar milieu have been described in IPF. Predominantly, these changes are reflected by an increased number of inflammatory cells, including polymorphonuclear leukocytes (PMN) in the alveolar spaces. The contribution of these cells to the development of an "alveolitis" resulting in injury to alveolar epithelium, basement membrane and interstitium is currently a subject of debate. Most interest in the past decade has focused on the role of PMN in this pattern of injury. It would be helpful therefore to review the evidence implicating the neutrophil as the primary "culprit" in IPF.

Evidence Supporting the Role of PMN in IPF

Early studies using BAL (63, 64) found that the number of neutrophils obtained from patients with IPF was significantly increased compared to non-smoking normal subjects (Figure 6). The total number of all cells obtained, including alveolar macrophages, was also significantly increased. In addition, patients who were treated with steroids and showed an objective clinical response were found to have a fall in the number of neutrophils obtained on subsequent BAL (65). This suggested that neutrophils were important in ongoing injury and that once the neutrophil component of the alveolitis was suppressed improvement occurred. Other evidence supporting the primary role of PMN was provided by studies showing elevated levels of neutrophil products, including collagenase and myeloperoxidase, in the BAL fluid of patients with IPF (62). Other studies demonstrating damage of connective tissue components and lung parenchymal cells by PMN in vitro suggested that PMN had the ability to injure lung tissue, primarily through the production of toxic oxygen compounds and proteases (66, 67). The mechanisms by which PMN were recruited to the lung were unclear in these studies, though most investigators implicated chemotactic factors released by alveolar

macrophages (which will be discussed in a later section). Thus, considerable evidence in these studies suggested that PMN were important in the pathogenesis of IPF.

Figure 6



Evidence Against the Role of PMN

Although PMN are clearly capable of producing injurious substances, subsequent research has cast doubt on the central role of PMN. First, several other BAL studies have suggested that PMN may accumulate relatively late in the disease (68, 69). In an excellent longitudinal study of patients with biopsy proven IPF, Watters and colleagues (69) (Table 5) found the number of neutrophils in lavage to be heterogeneous. Indeed, in patients with biopsies and clinical findings suggesting relatively recent onset of disease, PMN were not particularly numerous (1-10% of total cells) compared to those individuals with more advanced disease (23% of cells). Thus, the concept that accumulation of PMN early in the disease causes injury leading to fibrosis may be incorrect.

Table 5

Correlation of BAL Differential With Simultaneous Clinical Impairment

	Impairment			
	Mild	Moderate	Severe	Incapacitated
Patients (n)	4	11	9	2
PMN % (mean)	1	10	7	23
Lymphocytes % (mean)	32	14	17	6
Macrophages % (mean)	66	72	69	55
Eosinophils % (mean)	2	3	7	17

ARRD 135:696, 1987

Another troublesome point is that subsequent studies (70) have failed to show a clear improvement in the neutrophil alveolitis in patients who improve with Prednisone. Indeed, some of the authors of the original study (65) have recently published data (71) showing that Prednisone had no effect on the number of neutrophils obtained by BAL.

Other evidence questioning the role of PMN is provided by several studies where lung histology correlated poorly with BAL findings (72). Although PMN were increased in lavage samples, biopsy specimens often showed few neutrophils in the interstitium under light microscopy. This would suggest that although PMN are recruited into the air spaces they are not present in the interstitium, the site where the pathologic process is most acute. Indeed, the recent study by Watters (69) (Figure 7) demonstrated no correlation between the severity of alveolar septal inflammation or the presence of honeycombing and the number of neutrophils present in BAL.

Figure 7

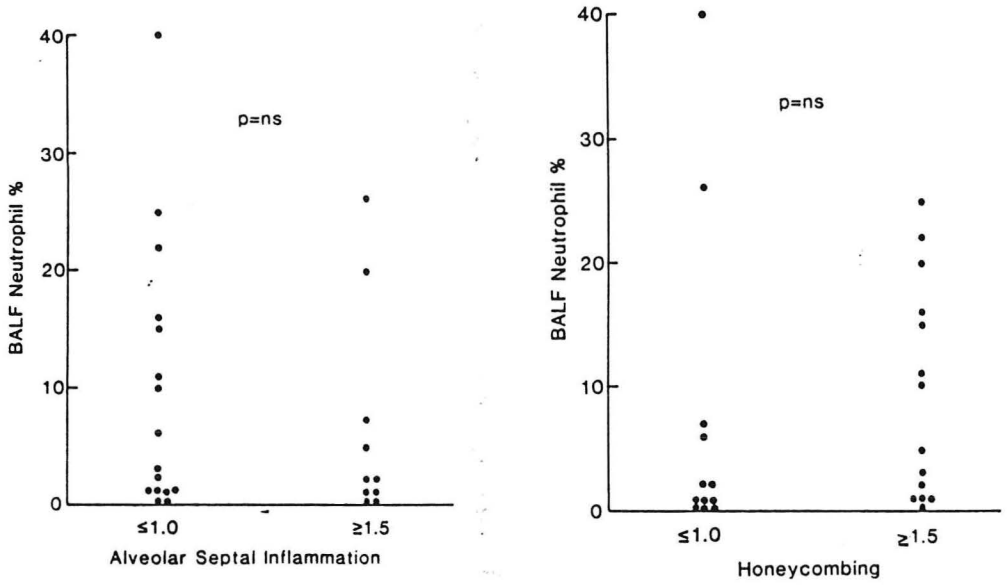


Figure 7 Elevated BALF neutrophils (%) did not significantly differentiate absent-to-mild from moderate-to-severe alveolar septal inflammation (A) or honeycombing (B).

Although collagenase has been found in increased amounts in BAL from patients with IPF, the significance of this is unclear. First, other cells besides PMN (specifically AM) in the lung contain collagenase. Secondly, collagenase preferentially degrades Type I and Type II collagen (60, 61). As discussed previously, the abnormalities of collagen homeostasis in IPF appear to be characterized by an increase in Type I collagen and alterations in the metabolism of Type III collagen. It is thus somewhat difficult to reconcile this with an effect of collagenase.

Finally, although PMN are capable of injuring tissue, the mere presence of PMN does not infer that PMN are injurious. Resting PMN are poorly responsive to nonparticulate stimuli with regard to production of oxygen radicals or proteases (73, 74). Recent studies have shown that intra-alveolar deposition of leukotriene B_4 (a chemotactic substance produced by alveolar macrophages) in human volunteers caused a marked increase in the number of neutrophils present in BAL within several hours (75). No evidence of altered vascular permeability was detected acutely suggesting that PMN can be rapidly recruited into human alveoli without the production of an acute injury. Indeed, perhaps the strongest evidence against a primary role for PMN in IPF comes

from a human model of chronic neutrophil alveolitis-the cigarette smoker.

Cigarette smokers have a significant increase in the number of PMN's obtained by BAL (5-8% of total cells) compared to normal non-smoking subjects. The characteristic pattern of lung injury seen in these individuals is not fibrosis, but rather emphysema. Considerable evidence suggests that elastase released by PMN is responsible for this disorder: Animal models of emphysema can easily be induced by the intra-tracheal instillation of neutrophil elastase and humans with a deficiency of alpha-1-anti-proteinase are predisposed to the development of the disease. It would seem unlikely that a chronic neutrophil alveolitis is the initiating event in both emphysema and fibrosis, two processes whose structural abnormalities are completely divergent.

The role of PMN in IPF is therefore unclear. A contributory role for PMN in the pathogenesis of this disease is possible and can not be excluded. However, there is enough evidence against PMN as the primary effector of injury to suggest that more important mechanisms of pathogenesis exist.

Lymphocytes in IPF

One possible cellular effector of injury which has received relatively little attention is the lymphocyte. Although early studies of BAL (63, 64) did not find an increase in lymphocytes, several subsequent studies (68, 69, 76) have shown an elevation of lung lymphocytes in IPF. In contrast to the situation with PMN, the increase in lavage lymphocytes does correlate with an increase in interstitial lymphocytes (72). More importantly a lymphocyte alveolitis appears to be present early in the course of the disease.

In normal individuals roughly 10% of BAL cells are lymphocytes. In patients with clinical evidence of early IPF Watters, et al (69) (Table 5) found a mean BAL lymphocyte count of 32% and only 1% PMN. In contrast, patients with severe physiologic abnormalities and a history suggestive of a more prolonged course had only 6% lymphocytes and 23% PMN in lavage. This suggests that based on clinical grounds a lymphocytic alveolitis is a relatively early event in IPF. Pathological correlation in this study is even more impressive (Figure 8). A significant correlation was observed between the degree of lymphocytosis and alveolar septal inflammation. Conversely, there was a negative correlation between the degree of honeycombing and the number of lymphocytes in BAL. Taken together these observations suggest that lymphocytes accumulate prior to the development of marked fibrosis and thus could play an important role in the production of injury.

Figure 8

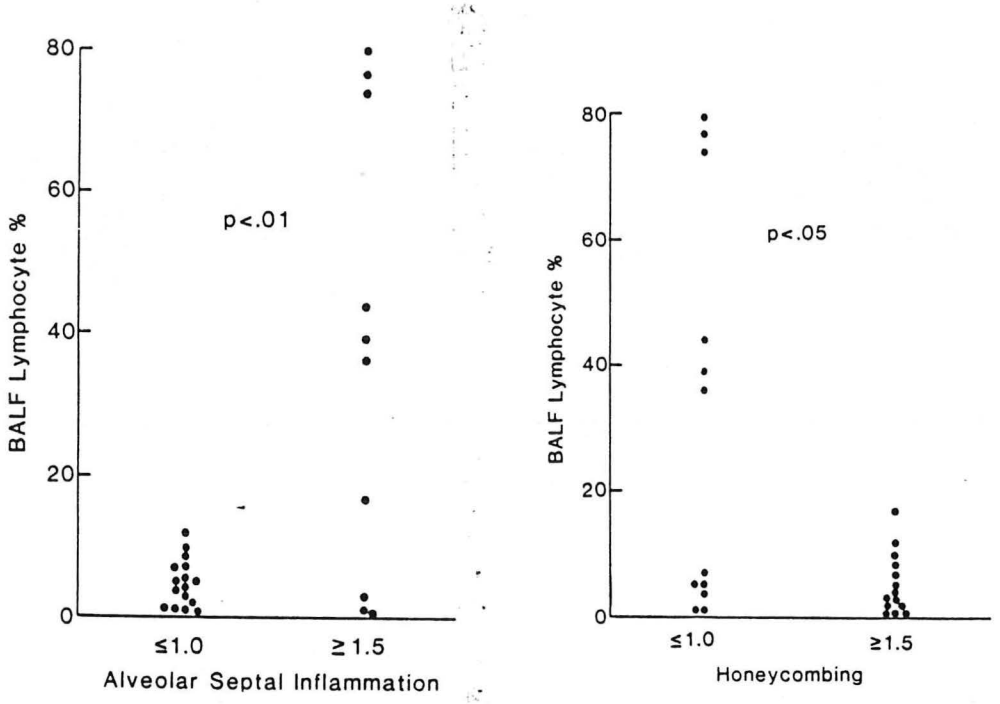


Figure 8 BALF lymphocytosis was associated with moderate-to-severe alveolar septal inflammation (A) and with absent-to-mild honeycombing (B).

There are several mechanisms by which lymphocytes could induce fibrosis (Table 6). Previous studies have demonstrated (77) that cytotoxic lymphocytes can be primed by the introduction of haptens into the lung and that an allergic contact dermatitis can be induced following intradermal injection of the same hapten. These cells could conceivably be recruited to the lung if a second intrapulmonary exposure occurred. Indeed, evidence now exists to support this: Animals rendered immune by cutaneous exposure to haptens developed pulmonary fibrosis following a single challenge of intra-alveolar hapten (78). In addition to a direct effect of cytotoxic lymphocytes, it is now recognized that these cells contain proteases (79). Recent studies have shown that interleukin-2 activated peripheral blood lymphocytes synthesize a serine protease as they develop cytotoxicity and that this protease is capable of degrading connective tissue components (80). A third mechanism by which T lymphocytes may mediate injury in IPF is by providing help for B cell proliferation. Several studies (81, 82) have demonstrated the accumulation of immune complexes in the lungs of patients with IPF and the number of

antibody-producing B cells present in the BAL of these patients is markedly increased (83, 84). The presence of immunoglobulin and immune complexes could induce injury by a) activation of PMN to produce toxic oxygen compounds, b) fixation of complement following attachment to the epithelial or endothelial surface, c) enabling lymphocytes to kill parenchymal cells via antibody dependent cellular cytotoxicity.

Table 6

Mechanisms of Injury By Lymphocytes

Direct cytotoxic effect
Release of proteases
Stimulation of immunoglobulin production with resultant

1. Activation of PMN
2. Fixation of complement
3. Antibody dependent cellular cytotoxicity

Thus, considerable evidence suggests that lymphocytes are involved in the early phase of inflammation in IPF. The mechanisms responsible for the development of a lymphocyte alveolitis remain unknown.

Another possible interpretation of these studies, however, would be that lymphocytes actually protect against the development of fibrosis. Patients with extensive fibrosis in IPF tend to have normal numbers of lymphocytes in BAL while those with only inflammation have a lymphocyte alveolitis. Indeed, evidence to support this hypothesis comes from sarcoidosis, another chronic interstitial lung disease characterized by a lymphocytic alveolitis. Although patients with sarcoid have extensive granulomatous inflammation, the development of fibrosis is relatively uncommon. In those patients with sarcoid and fibrosis the number of BAL lymphocytes tends to be reduced. The mechanisms by which lymphocytes may actually impede fibrosis will be discussed shortly.

Macrophages in IPF

The majority of interest in alveolar macrophages initially focused on the role of AM in recruiting neutrophils into the lung in IPF. AM from patients with IPF spontaneously release a low molecular weight chemotaxin, possibly leukotriene B4. AM are also capable of releasing a high molecular weight chemotaxin (85-88). The neutrophil chemotaxin also attracts blood monocytes and eosinophils. Resting AM from normal subjects do not release these

factors but can be stimulated to produce chemotaxins by a variety of surface active molecules.

Evidence exists that immune complexes may be responsible for the stimulation of AM in IPF. First, deposits of immunoglobulin and complement have been demonstrated in the alveolar walls in IPF biopsy specimens (14, 16, 89). Secondly, immune complexes have been demonstrated in BAL fluid from patients with IPF and when lavage fluid is incubated with normal human AM, these cells release a neutrophil chemotaxin (90). Third, AM from patients with IPF have their IgG Fc and C3b receptors occupied suggesting the presence of immune complexes on the cell surface (90, 91). Finally, AM from these patients demonstrate intracytoplasmic IgG suggesting that immune complexes have been phagocytosed.

Another important aspect of AM function in this disease is the central role that macrophages may play in fibroblast regulation. Macrophages produce a variety of mediators which may either inhibit or stimulate fibroblast proliferation. Indeed, the control of fibroblast growth is likely essential to the pathogenesis of IPF.

Fibroblasts in IPF

Fibroblasts normally account for 35-40% of cells in the pulmonary interstitium (92, 93). Considerable evidence suggests that abnormalities of fibroblast biology are present in IPF: First, fibroblasts are markedly increased in number in biopsy specimens from IPF (94). Second, fibroblasts are the major source of Type I collagen production in the lung and Type I collagen is increased in IPF (95, 96). Third, fibroblasts in biopsy samples from patients with IPF have dilated endoplasmic reticulum and abundant intracellular procollagen by immunofluorescent microscopy suggesting that they are metabolically active. Finally, recent evidence suggests that a significant number (10-15%) of fibroblast clones derived from IPF biopsy specimens rapidly proliferate in culture (97). Thus, the abnormal proliferation of fibroblasts in the lung with a resultant increase in Type I collagen synthesis is a hallmark of IPF.

Fibroblast replication requires a series of exogenous growth factors delivered temporally at appropriate points in the cell cycle. Pledger, et al (98) suggested that two major categories of growth factors existed based on their temporal specificity: "Competence" factors act early in G1, help the cell traverse G1, and render the cell responsive for a variable number of hours to "progression" factors. Progression factors act later in G1 and signal the cell to continue through the cell cycle and replicate. Optimal replication requires both competence and progression factors delivered in sequence. However, a "competence" factor may

be delivered by the extracellular matrix when it allows the fibroblast to attach and spread (99).

Several observations suggest that mononuclear phagocytes are important providers of growth factors for fibroblasts. First, mononuclear phagocytes accumulate in an area of injury prior to the recruitment and proliferation of mesenchymal cells including fibroblasts (100). Secondly, mononuclear phagocytes are capable of releasing other growth factors for cell replication such as interleukin-1 and colony stimulating factor (101). Third, supernatants obtained from cultures of mononuclear phagocytes harvested from scar tissue induce fibroblast proliferation. Thus, AM could play an important role in stimulating fibroblast replication. Indeed, several fibroblast growth factors are produced by AM.

Production of Fibroblast Growth Factors by AM

Fibronectin

Fibronectin is a 440,000 dalton glycoprotein component of the extracellular matrix with specific domains that bind to the fibroblast surface (102-104). Fibronectin, at concentrations in the nanomolar range can stimulate resting fibroblasts to replicate in a dose-dependent manner (105). Alveolar macrophages produce fibronectin which is capable of acting as a chemo-attractant for lung fibroblasts. Additionally, AM from patients with fibrotic lung disease release large amounts of fibronectin spontaneously (105). However, for optimal stimulation, a progression factor must be supplied.

Alveolar Macrophage Derived Growth Factor (AMDGF)

Stimulated human AM release a progression factor capable of inducing fibroblast replication. Alveolar macrophage derived growth factor (AMDGF) is an 18,000 dalton protein which induces fibroblast DNA synthesis within 12 hours and cell division within 48 hours (106). While resting AM do not normally produce AMDGF, stimulation of these cells with a variety of agents, including immune complexes causes release of the growth factor. AMDGF acts as a progression factor and produces fibroblast replication only following a priming step with a competence factor. The AM of patients with a variety of interstitial lung disorders have been shown to release AMDGF spontaneously (107) (Figure 9). However, it is of note that AMDGF is elevated in diseases, such as sarcoidosis, where fibrosis is relatively uncommon. This suggests that factors in addition to AMDGF are important in regulating fibroblast proliferation in the lung. Indeed, AMDGF production did not change following therapy with either steroids or cytoxan despite a clinical improvement in some patients.

Figure 9

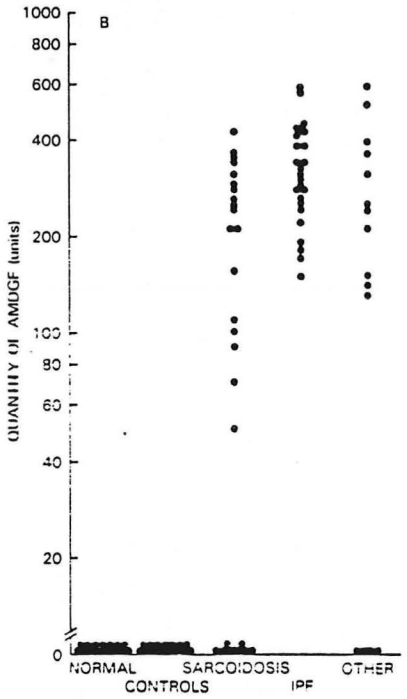


Figure 9 Spontaneous release of AMDGF by alveolar macrophages from patients with interstitial lung disease.

AMDGF has not been well characterized despite being first described in 1981. No specific receptor for the factor has been identified and it has been suggested that this growth factor contains contaminating amounts of platelet derived growth factor (PDGF) (108). In addition the effect of AMDGF on fibroblasts may involve the release of other intermediary mediators, such as fibroblast growth factor, from the fibroblast itself.

Platelet Derived Growth Factor (PDGF)

Platelet derived growth factor (PDGF) was first isolated from the alpha granules of platelets (109-111) but has since been found in several other cell types. PDGF is a 29,000-33,000 dalton

dimeric glycoprotein composed of an A chain and B chain linked by disulfide bonds. The sequence of the biologically active B chain has been identified and the molecule exerts its effect through a cell receptor thought to be a tyrosine kinase (112, 113). Apart from its ability to attract and activate fibroblasts, PDGF also is a chemoattractant for smooth muscle cells, cells which accumulate in the interstitium in IPF.

Although the classical form of PDGF has a molecular weight of 29,000, several investigators (108, 114) have isolated a 13,000 dalton molecule in the supernatants of macrophage cultures which binds to fibroblasts, acts as a competence factor and is antigenically similar to PDGF.

Several cell types present in the lung including endothelial cells, arterial smooth muscle cells and activated monocytes produce PDGF. However, the most abundant source of PDGF in the lung appears to be the alveolar macrophage. The B chain of PDGF is coded for by a 30kb gene located on chromosome 22. This gene, designated the C-sis proto-oncogene is an analogue of the retroviral V-sis oncogene originally isolated from a simian sarcoma virus. Although this gene appears important in the malignant transformation of fibroblasts by this virus, there is no evidence thus far to suggest that fibroblasts in IPF are malignantly transformed. Indeed, expression of the 4.2kb mRNA transcript of the C-sis gene is found in normal AM and monocyte-derived macrophages (115) and recent studies show that PDGF like molecules are released by AM (116).

Isolation of a 29,000-31,000 dalton molecule with PDGF activity produced by AM from patients with IPF has recently been demonstrated by Martinet, et al (116). In contrast to platelet derived PDGF, this molecule does not contain an A chain and is a homodimer rather than a heterodimer. A significant number of patients with IPF spontaneously released PDGF compared to low levels of release in normal subjects (Figure 10). In addition, normal AM could be stimulated by immune complexes to produce PDGF. The release of PDGF by alveolar macrophages may therefore be important in providing a competence factor for fibroblast proliferation in IPF. One should be cautious, however, in over-interpreting this data as PDGF levels remained elevated in patients treated with Prednisone who had a clinical response. Indeed, it is likely that PDGF production is elevated in other chronic lung diseases (such as sarcoidosis) where fibrosis is uncommon. Thus, PDGF may be only one of a number of factors affecting fibroblast proliferation and metabolism.

Figure 10

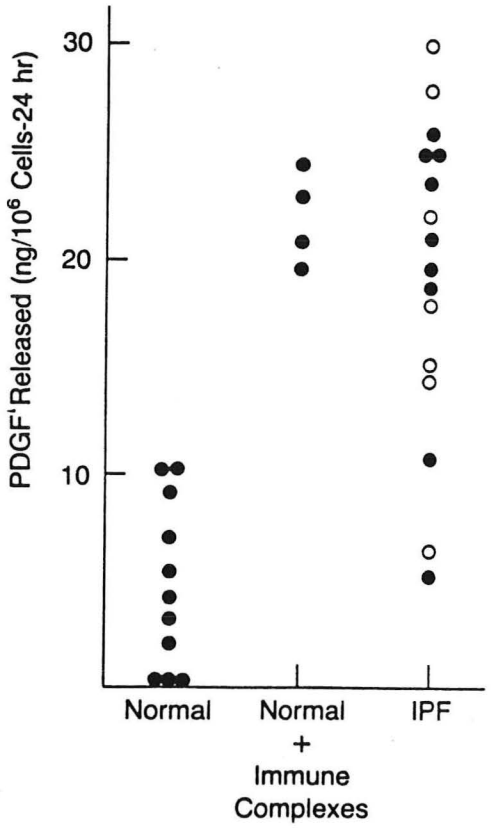


Figure 10 Exaggerated spontaneous release of platelet-derived growth factor (PDGF) by alveolar macrophages from patients with idiopathic pulmonary fibrosis.

In summary then, AM produce two known competence factors (fibronectin and PDGF) and one progression factor (AMDGF) suggesting that AM may stimulate fibroblast growth in IPF. However, the role of AM is complex and AM are also capable of inhibiting fibroblast replication.

Inhibition of Fibroblast Proliferation by Cytokines from AM and Lymphocytes

Blood mononuclear phagocytes are capable of releasing several substances capable of inhibiting both fibroblast proliferation and collagen synthesis. Amongst these are a) a small (<1400 dalton) molecule released following mitogen stimulation (117) b) a 12,000-20,000 dalton molecule which inhibits both skin and lung fibroblast growth c) Prostaglandin E_2 (PGE_2) (118).

Alveolar macrophages produce a factor with a MW >12,000 which suppresses both fibroblast proliferation and collagen synthesis (118). This substance appears to act by increasing fibroblast cAMP formation and PGE_2 production. The effect of this factor can be blocked by indomethacin and suppression requires relatively high concentrations to overcome the growth factors simultaneously released by AM (119). Thus a "balance" between stimulatory and suppressive factors by AM may be important in regulating fibroblast proliferation.

Perhaps a more important source of suppressive cytokines in IPF is the lymphocyte. Studies (120, 121) from several laboratories have disclosed that supernatants from proliferating lymphocytes are suppressive to fibroblast proliferation. More detailed characterization of these factors has focused on the interferons. Alpha and beta interferon do not stimulate the proliferation of quiescent lung fibroblasts and act to inhibit the growth of rapidly proliferating cells (122). In contrast, gamma interferon <u>stimulates</u> resting fibroblasts to proliferate but <u>inhibits</u> the growth of rapidly dividing fibroblasts (122). The inhibitory effect of the interferons does not depend on PGE_2 production and cannot be blocked by indomethacin. The possible biologic significance of suppression of fibroblast proliferation by interferon is suggested by studies in IPF and sarcoidosis which demonstrate that increased numbers of lymphocytes have a negative correlation with the degree of fibrosis.

It is clear that both stimulatory and inhibitory signals for fibroblast replication are present in the pulmonary milieu (Table 7). Although there are a variety of possible hypotheses to accommodate the role of these cytokines in the pathogenesis of IPF, the picture remains muddled. However, recent data suggests that the response of fibroblasts to these substances is heterogeneous and this observation may be the key to the pathogenesis of IPF.

Table 7

Stimulatory and Inhibitory Signals for Fibroblast Replication in the Pulmonary Milieu

Cell	Stimulatory	Inhibitory
Alveolar macrophage	Fibronectin PDGF AMDGF	PGE_2 >12,000 dalton molecule Tumor necrosis factor
Lymphocyte	Gamma Interferon (Resting Fibroblasts)	Gamma Interferon (Dividing Fibroblasts) Alpha + Beta Interferon
Fibroblast	Fibroblast Stimulatory Factor	PGE_2 cAMP

Fibroblast Heterogeneity and the Pathogenesis of IPF

Several lines of evidence suggest that morphological and functional heterogeneity exists amongst human fibroblasts: Fetal lung fibroblasts are heterogeneous with regard to size and proliferative capacity (123); dermal fibroblast clones differ in their responsiveness to both PGE_2 and mononuclear cell cytokines (124); human gingival fibroblasts differ in their ability to synthesize collagenous and noncollagenous proteins (125); density fractionated human lung fibroblasts are heterogeneous in regard to size and proliferative response to serum (126). Thus, the concept that a selective clone of fibroblasts may proliferate in IPF is attractive.

A recent study by Jordana, et al (97) obtained clones of fibroblasts from control lung tissue and IPF biopsy specimens. Proliferation of IPF fibroblast cell lines was significantly greater than those of control lung fibroblast lines (Figure 11). Subcloning of these lines disclosed that 15% of IPF clones showed a distinctly rapid growth rate. It is not inconceivable that clonal differences in lung fibroblast response to cytokines occurs and indeed preliminary evidence exists to support this (127).

Figure 11

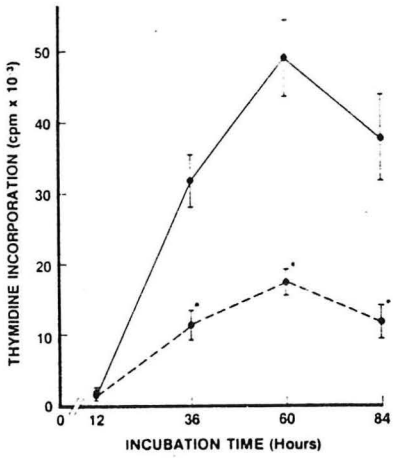


Figure 11 In vitro thymidine incorporation of human adult lung fibroblasts. Results expressed as mean ± SEM of 4 control (dashed line) and 4 pulmonary fibrosis (solid line) fibroblast cell lines.

Keeping the aforementioned in mind it is possible to construct a hypothesis for the pathogenesis of IPF: The initial event in IPF is a local cellular and humoral immune response against a persistent inhaled foreign protein (virus, fungus, etc...) which results in the accumulation of lymphocytes and the production of immunoglobulin in the lung. Release of cytokines (gamma interferon) and the presence of immune complexes activate macrophages to produce chemotaxins for PMN and produce fibroblast growth factors. This early stage of IPF is characterized by an alveolitis of neutrophils and lymphocytes and a mild increase in the number of lung fibroblasts. During this phase injury to connective tissue components may occur. Over a period of time the counterbalance of growth and inhibitory factors selects out a "clone" of fibroblasts which are relatively resistant to suppression by these inhibitory factors. These fibroblasts may be only a small subpopulation of normal fibroblasts and could differ in the types of collagen they produce. Once a crucial mass is reached (perhaps when the production of interferon by lymphocytes decreases), these fibroblasts become the predominant replicating cell in the interstitium and severe fibrosis occurs.

To test this hypothesis several lines of investigation would seem important. First, a more detailed knowledge of the molecular basis of collagen biosynthesis by fibroblasts is needed. Second,

further analysis of fibroblast clones to look for expression of the C-sis gene, perhaps by in situ hybridization, would seem in order. Finally, more detailed knowledge of fibroblast self-regulation, particularly the release of endogenous stimulating factors by fibroblasts is required. It is likely that thoughtful and patient use of molecular and cellular techniques in IPF will ultimately yield a clearer explanation for the abnormalities observed in this disease.

Diagnosis and Management of IPF

As mentioned previously (Table 1) the differential diagnosis of bilateral reticular, nodular or honeycomb infiltrate on chest x-ray is extensive. The patient with IPF may have little to distinguish his clinical presentation from a variety of other interstitial lung disorders. It is likely that most patients with unexplained interstitial lung disease will initially undergo a bronchoscopy with transbronchial biopsy. However, the ability of bronchoscopy to definitively diagnose the entities listed in Table 1 is quite variable. In general, bronchoscopy will yield a definitive diagnosis in only a few of these disorders (sarcoidosis, malignancy, tuberculosis, fungal or parasitic infection). The finding of "fibrosis" on transbronchial biopsy is nonspecific.

The issue of open lung biopsy in patients thought to have IPF is controversial. Often, patients with a negative bronchoscopy and progressive interstitial lung disease will be treated with a trial of steroids emperically. The decision to pursue an open lung biopsy in these patients is so individualized that no general recommendations can be made. However, the treating physician must realize that in the absence of an open lung biopsy a definitive diagnosis has not been established and therapy may be misdirected.

Therapy of IPF has generally involved treatment with either corticosteroids or cytotoxic drugs. There are no controlled trials comparing these agents in the literature, though anecdotal reports of patients responding to Cytoxan after failing to improve with Prednisone exist (68, 76). Overall roughly 30-50% of patients with IPF have an objective response to therapy (68, 69, 76). The optimum dose of these agents is unknown but recent published series have utilized the following schedules:

Prednisone (69) 1.5 mg/kg/day (maximum 100/mg/day) for 6 weeks, followed by 1.0 mg/kg/day for 6 weeks, then 0.5 mg/kg/day for 3 months, then a slow taper to 0.25 mg/kg/day. The optimal duration of therapy after 6 months is unknown.

Cytoxan (71) 1.5 mg/kg/day until discontinuation.

Most data suggests that patients with IPF who are going to improve with therapy do so by 6 months and that the clinical status at 1 year of follow-up is the same at 6 months (69).

Use of BAL to Predict Response to Therapy

Several studies have looked at the BAL fluid differential to predict which patients will respond to therapy. Haslam, et al (76) reported that 6/8 patients with elevated BAL lymphocytes demonstrated an improvement with Prednisone therapy. In contrast of 9 patients who failed to improve with Prednisone only 1 had increased lymphocytes. This study suggested that elevated BAL lymphocytes could be used to predict a response to Prednisone. A subsequent study (68) by these investigators also suggested that a BAL lymphocytosis predicted a response to Prednisone therapy (Table 8). Patients who responded had elevated lymphocytes on initial BAL (mean 22%) compared to nonresponders (mean 3%). Subsequent BAL showed a decrease in lavage lymphocytes in the responders. In both studies by this group of investigators, lavage differentials did not predict a response to Cytoxan.

Table 8

Percentage of BAL Cells Initially
and at Follow-Up (FU) After Therapy

	Prednisone				Cytoxan			
	Improved		Unimproved		Improved		Unimproved	
	1st	FU	1st	FU	1st	FU	1st	FU
mean Lymphs %	22	5	3	4	3	4	2	3
mean Neutrophils %	20	10	21	42	8	10	23	13

ARRD 135:26, 1987

The study by Watters, et al (69) in which all patients had biopsy proven pulmonary fibrosis also suggests that patients with elevated BAL lymphocytes are more likely to respond to therapy (Figure 12). Five of the 7 patients who responded to Prednisone in this study had an elevated BAL lymphocyte count. In contrast only 2/14 patients with normal BAL lymphocyte counts improved with therapy. The number of PMN or eosinophils in this study did not predict a response.

Figure 12

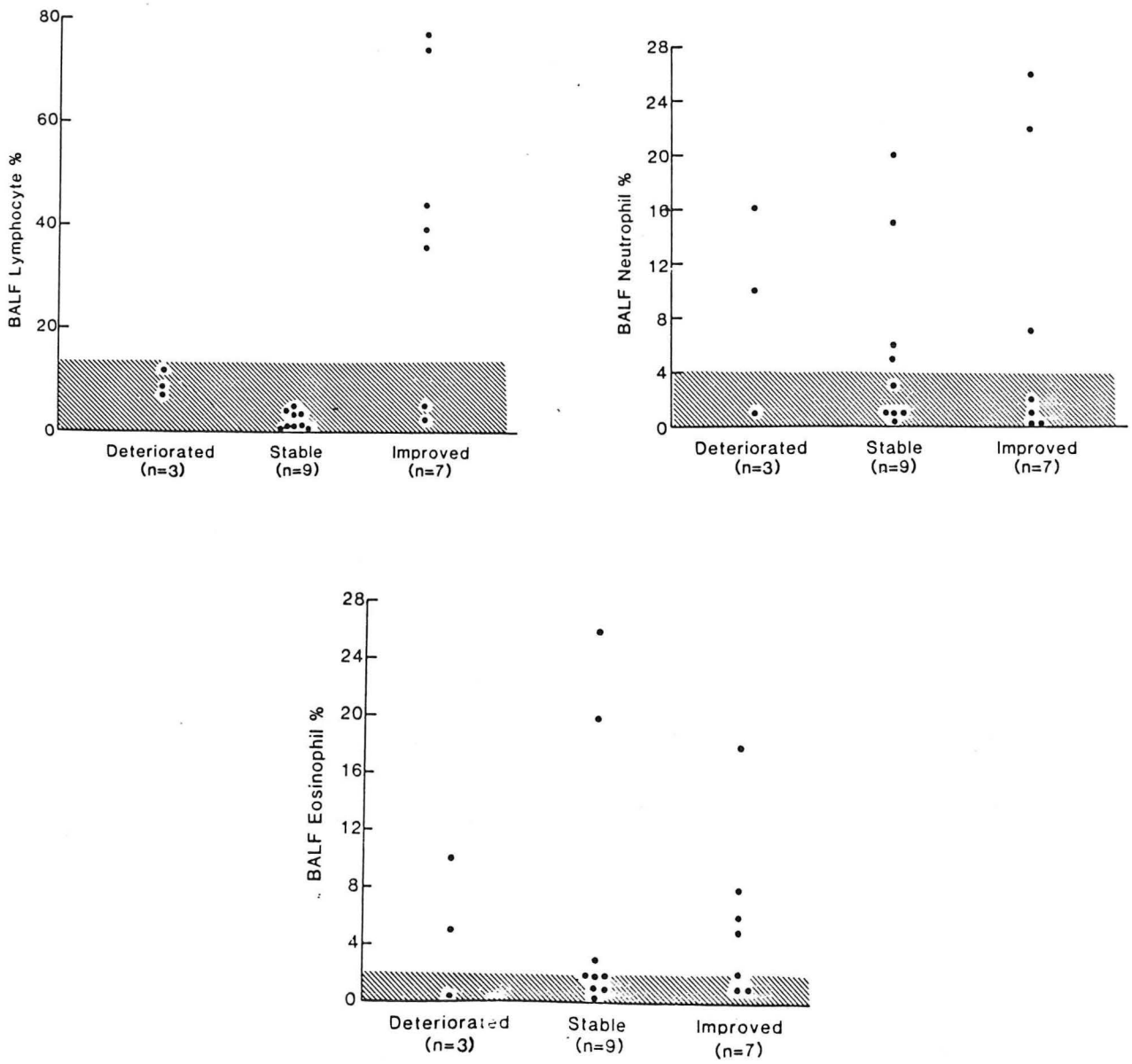


Figure 12 The relationship between initial pretherapy BALF cellular content and response to 6 months of therapy. Shaded areas represent the mean + 2 SD of healthy volunteers.

In summary, an elevated lymphocyte count on initial BAL suggests that the patient with IPF is more likely to respond to Prednisone therapy. Because Prednisone therapy producing improvement is associated with a fall in BAL lymphs, one might hypothesize that the net effect of lymphocytes in this responsive stage of the disease is to contribute to lung injury. However, a direct effect of Prednisone on fibroblast replication can not be excluded.

Another component of BAL which has been utilized to predict response to steroids in IPF is the content of phospholipids in lavage fluid. Patients with IPF have less than half the amount of total phospholipid in BAL seen in normal patients (128). A recent study (129) suggests that the ratio of phosphatidylglycerol to phosphatidylinositol is reduced in IPF. Patients with higher total phospholipids in this study were more likely to respond to therapy with Prednisone.

The utility of BAL in directing therapy of IPF is unclear. An emperic trial of steroids is usually indicated regardless of the initial BAL findings. However, some investigators have suggested that BAL may be useful in deciding to reinstitute therapy in a patient who after an initial response has been tapered off the drug. A recurrence of abnormal BAL cell counts may presage a deterioration in some patients (68). In addition, since patients who do not have an increase in BAL lymphocytes tend not to respond to steroids, one could argue that these patients should initially be treated with Cytoxan.

Newer Therapies for IPF

1) Colchicine - Colchicine has been shown to inhibit the secretion of many proteins. Colchicine has recently been shown to inhibit the release of both fibronectin and AMDGF from AM *in vitro* (130). Inhibition occurred at concentrations from 1 to 10 ng/ml, a range which can be obtained with routine doses *in vivo*. The *in vivo* efficacy of this therapy remains to be established. However, a recent trial (131) of Colchicine in patients with hepatic cirrhosis produced a significant increase in survival associated with an improvement in liver histology.

2) Gamma-Interferon - Because γ-IFN is now obtainable by recombinant techniques in large quantities, interest in fibroblast inhibition by γ-IFN has been generated. Although details of the study are not available, preliminary investigation of the use of aerosolized γ-IFN in patients with IPF are currently underway.

3) Lung Transplantation - The efficacy of unilateral lung transplantation in patients with pulmonary fibrosis has recently been reported (132). Patients had a significant improvement in symptoms and exercise tolerance post-operatively. The use of unilateral lung allografts is attractive as it avoids the necessity for cardiac transplantation required by combined heart-lung procedures. Advances in procurement and maintenance of lung tissue will, however, be required before this therapy can be broadly utilized.

Summary

Idiopathic pulmonary fibrosis is a disease which is seen by most practicing internists. Although it is relatively uncommon, its manifestations are serious and life-threatening. Death usually occurs within 3-6 years after the onset of symptoms (13, 133). The pathogenesis of IPF remains to be fully elucidated. However, significant advances in our understanding of disease mechanisms in IPF have occurred in a relatively short period of time. The histologic and biochemical abnormalities of increased fibroblast number and Type I collagen synthesis are firmly established. The mechanisms responsible for these abnormalities seem readily approachable by current cellular and molecular techniques. One may therefore anticipate that significant progress in understanding this disorder will occur in the next few years. If the temptation of premature clinical application can be avoided, it is likely that rational and innovative therapeutic strategies will result from basic research in IPF.

APPENDIX A

Table 1

DIFFERENTIAL DIAGNOSIS OF INTERSTITIAL PULMONARY DISEASES
(Compiled by Alan K. Pierce, M.D.)

I. Infectious
- A. Bacterial
  1. Miliary tuberculosis
  2. *Staphylococcus aureus*
  3. Salmonella species
  4. Streptococci
  5. *Klebsiella pneumoniae*
  6. Brucellosis
  7. Tularemia
  8. Shigella
  9. Pertussis
  10. Actinomycosis
  11. Nocardiosis
- B. Fungal
  1. Histoplasmosis
  2. Coccidioidomycosis
  3. Blastomycosis
  4. Crytpococcosis
  5. Aspergillosis
  6. Candidiasis
  7. Geotrichosis
  8. Sporotrichosis
  9. Mucor
- C. Viral
  1. Chickenpox
  2. Influenza
  3. Measles
  4. Psittacosis
  5. Cytomegalovirus
  6. Adenovirus
  7. Parainfluenza
  8. Coxackie virus
  9. ECHO virus
- D. *Mycoplasma pneumoniae*
- E. Rickettsial
  1. Q fever
  2. Rocky Mountain spotted fever
- F. Spirochetal
  1. Syphilus
- G. Parasitis
  1. Pneumocystis carinii

2. Schistosomiasis
3. Filariasis
4. Toxoplasmosis

II. Inhalational Diseases

A. Diseases of alveolar hypersensitivity (Extrensic allergic alveolitis)
1. Farmer's lung
2. Bagassosis
3. Pigeon breeder's lung
4. Mushroom worker's lung
5. Suberosis
6. Maple bark disease
7. Pituitary snuff disease
8. Smallpox handler's lung
9. Sisal worker's disease
10. Malt worker's lung
11. Sequoiosis
12. Hen-litter sensitivity
13. Lycoperdonosis

B. Inorganic dust pneumoconiosis
1. Silicosis
2. Coal worker's pneumoconiosis
3. Asbestosis
4. Talcosis
5. Siderosis (arc welder's disease)
6. Kaolin pneumoconiosis
7. Berylliosis
8. Aluminum pneumoconiosis (Shaver's disease)
9. Radiopaque dust pneumoconiosis
   a. Stannosis (tin oxide)
   b. Barium sulfate
   c. Rare earth (cerium, etc.)

C. Inorganic chemicals
1. Nitrogen dioxide (Silo-filler's disease)
2. Nitrogen oxide (electric welding)
3. Chlorine
4. Smoke inhalation
5. Phosgene
6. Mustard gas
7. Lewisite
8. Carbon tetrachloride
9. Acetylene
10. Picric acid
11. Ammonia
12. Sulfur dioxide
13. Bromine
14. Hydrogen fluoride
15. Nitric acid
16. Hydrochloric acid

III. Neoplastic
- A. Bronchioloalveolar carcinoma
- B. Lymphangitic carcinomatosis
  1. Bronchogenic
  2. Breast
  3. Stomach
  4. Thyroid
  5. Pancreas
  6. Larynx
- C. Micronodular hematogenous
  1. Renal cell
  2. Thyroid
  3. Sarcoma of bone
  4. Choriocarcinoma
- D. Hodgkins' disease
- E. Lymphosarcoma
- F. Leukemia

IV. Therapeutic Agents
- A. Oxygen toxicity
- B. Radiation therapy
- C. Drugs
  1. Nitrofurantoin (Furadantin)
  2. Hexamethonium
  3. Mecamylamine (Inversine)
  4. Hydrochlorothiazide (Diuril)
  5. Pteroylglutamic acid (Methotrexate)
  6. Busulfan (Myleran)
  7. Methysergide (Sansert)
  8. Bleomycin

V. Connective Tissue Diseases
- A. Scleroderma
- B. Rheumatoid arthritis
- C. Lupus erythematosis
- D. Periarteritis nodosa
- E. Dermatomyositis
- F. Sjögren's syndrome
- G. Wegener's granulomatosis

VI. Cardiovascular
- A. Pulmonary edema
- B. Hemosiderosis
- C. Rheumatic pneumonia
- D. Embolism from oily contrast media

VII. Aspirational
- A. Gastric juice
- B. Lipoid pneumonia
- C. Hemoptysis
- D. Post drowning

VIII. Airways Disease
- A. Cystic fibrosis

B. Bronchiectasis
C. "Small airways" disease
D. Acute bronchiolitis
E. Riley-Day syndrome

IX. Trauma
A. Blast injury
B. Lightning stroke pulmonary edema

X. Miscellaneous or Idiopathic
A. Sarcoidosis
B. Goodpasture's syndrome
C. Pulmonary alveolar proteinosis
D. Eosinophilic granuloma
E. Sickle cell anemia
F. Letterer Seiwe
G. Neimann Pick
H. Hand-Schuller-Christian
I. Pulmonary alveolar microlithiasis
J. Amyloidosis
K. Waldenstrom's macroglobulinemia
L. Tuberous sclerosis
M. Pulmonary myomatosis
N. Wilson-Mikity syndrome
O. Infectious mononucleosis
P. Mycosis fungoides
Q. Spider angiomas in cirrhosis
R. Idiopathic interstitial pulmonary fibrosis

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