IPF

and the
Idiopathic Interstitial Pneumonias

Medical Grand Rounds
University of Texas Southwestern Medical Center
August 20, 1998

This is to acknowledge that John Fitzgerald, M.D. has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program.

Biographic information

Name: John E. Fitzgerald, M.D.

Rank: Assistant Professor of Medicine

Division: Pulmonary and Critical Care Medicine

Special interests: Interstitial lung disease

Introduction

Idiopathic pulmonary fibrosis (IPF), also known as cryptogenic fibrosing alveolitis (CFA), is a clinical term encompassing a group of inflammatory and fibrosing lung disorders of unknown etiology which share a similar presentation.[1,2,3,4,5] IPF predominantly affects persons between 40 and 75 years of age.[1,4,6,7] It is a chronic form of interstitial lung disease which produces progressive respiratory insufficiency in most subjects, often culminating in death.[2,6,8] Worldwide, both the prevalence and the mortality attributed to this disorder are increasing, especially in older patients.[9,10,11] The peak incidence of disease now appears to be in the seventh and eighth decades of life, a significant change from early reports.[4,7,12] Estimates of disease prevalence have ranged from 3 to 29 cases per 100,000, and there is a slight male predominance (approximately 1.5:1).[4,7,11,13,14] The overall five year survival after diagnosis is 40-50 percent.[4,6,8,15]

The clinical features of IPF are summarized in Table 1. The most prevalent symptom in idiopathic pulmonary fibrosis is the insidious onset of progressive exertional dyspnea. This is seen in about 90 percent of patients.[1,2,4,5,15] Sometimes individuals relate a more abrupt onset of breathlessness, but serial radiographs often reveal that the disease has been present for months or years in these cases. Over a third of patients are profoundly limited at the time of presentation, able to walk less than 100 yards before becoming breathless.[4] A chronic cough, which is generally non-productive in the absence of concomitant tobacco abuse, is reported by 70 to 85 percent.[1,4,5,15] Up to half of IPF patients report some sort of constitutional symptoms such as fever, weight loss, malaise or arthralgias.[5] Fever, specifically, has been noted in 15 to 20 percent.[16,17] Approximately five percent of patients are asymptomatic at the time of diagnosis.[4]

Table 1
Clinical Features of Idiopathic Pulmonary Fibrosis

Symptoms	**Physiologic Alterations**
exertional dyspnea	↓ lung volumes
cough	↑ elastic recoil
	↓ DLCO
Signs	exercise desaturation
velcro rales	
digital clubbing	**Radiographic findings**
↑ P2, S3, JVD, edema	reticular or ground glass opacities
cyanosis	basilar and subpleural predominance
tachypnea	honeycombing frequent

Physical examination is remarkable for the presence of mid to late inspiratory crackles ("velcro rales") in up to 95 percent.[1,2,5] Digital clubbing is seen in 25 to 66 percent.[1,4,15] As the disease progresses, signs of cor pulmonale may become evident. These include an accentuated pulmonic component of the second heart sound (loud P2), a right ventricular heave, S3 gallop, cyanosis, jugular venous distention and peripheral edema.

Common laboratory abnormalities in IPF include elevated antinuclear antibody titers and/or rheumatoid factor levels in 20 to 25 percent, elevated globulin fractions, and circulating immune complexes.[1,4,8,18,19,20] In one series, 24 (9%) of 268 patients had serum precipitins to avian proteins identified, but only seven had a documented bird exposure.[4] Notwithstanding, chronic hypersensitivity pneumonitis can mimic IPF clinically, radiographically and even histologically is some cases.

Chest radiographs typically indicate diffuse or basilar predominant reticular or reticulonodular infiltrates.[1,5] A few individuals (less than 10 percent) exhibit ground glass or "hazy" opacities.[5] An associated reduction in lung volumes is usual, except in patients with concomitant airways disease.[2] A normal or near-normal chest film is noted in 2 to 12 percent.[1,4,21]

Pulmonary function testing classically reveals a restrictive process associated with reduced lung volumes, increased elastic recoil, and a low diffusing capacity for carbon monoxide.[1,2,12,22,23,24] Early in the disease process, resting arterial blood gases may be fairly normal, but exercise desaturation is very common.

Our current understanding of the natural history of IPF is limited, and it has been heavily biased by data from tertiary care populations. The clinical course of individuals with this disease is, in fact, quite variable. Many patients demonstrate a slow but relentless decline in pulmonary function with gradual progression of radiographic opacities over a period of years with or without therapy.[2] Others show a stair-step pattern of deterioration with periodic flares of disease activity interrupted by sometimes sustained periods of stability. Still others exhibit a profound and rapid decrement in function, the so-called accelerated phase of pulmonary fibrosis, leading to death in a matter of weeks.[25,26] A few patients even survive for decades with sometimes severe but ostensibly quiescent disease.

Another level of complexity is generated by the variable histopathologic patterns associated with IPF, with each subgroup possessing a fairly distinct natural history of its own.[27,28,29] Usual interstitial pneumonia (UIP) is the most common histologic lesion identified, accounting for more than 80-90 percent of fibrosing alveolitis cases in most series.[27,30,31] The poor prognosis of UIP is largely responsible for the pervasive nihilism which surrounds the diagnosis of idiopathic pulmonary fibrosis. This has resulted in widespread misconceptions regarding the importance of biopsy confirmation in IPF and the potential benefits of treatment. A recent review of over 100 patients with IPF from the Mayo Clinic, however, emphasized the heterogeneous nature of this clinical syndrome.[15] Remarkably, only 62 percent of their patients demonstrated a UIP lesion after careful pathologic review. Thus, it may not be appropriate to consider the clinical term "IPF" as synonymous with the pathologic diagnosis of usual interstitial pneumonia.

Table 2
Histopathologic Diagnoses in 102 Patients with Idiopathic Pulmonary Fibrosis

Histopathological Diagnosis	%
Usual interstitial pneumonia	62
Nonspecific interstitial pneumonia	14
Desquamative interstitial pneumonia	8
Bronchiolitis obliterans organizing pneumonia	4
Bronchiolitis	4
Respiratory bronchiolitis-interstitial lung disease	2
Acute interstitial pneumonia	2
Chronic eosinophilic pneumonia	1
Hypersensitivity pneumonitis	1
Honeycomb change only	1
Scarring and pneumonia	1

From: Bjoraker JA, et al. AJRCCM 1998; 157: 199

Approach to the Patient with Diffuse Parenchymal Lung Disease

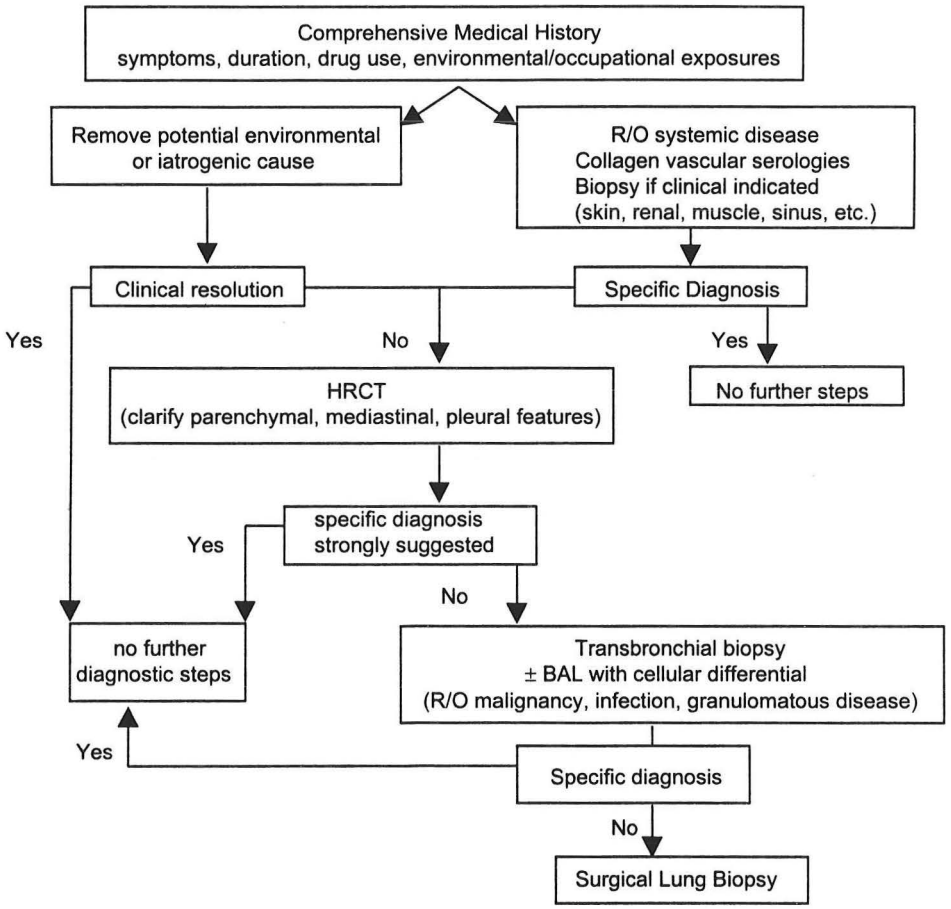
Importantly, a patient can only be considered to have IPF when a careful evaluation has excluded all other known causes of diffuse parenchymal lung disease. After identifying an individual with clinical and radiologic features of interstitial lung disease, a comprehensive medical history must be obtained. Particular attention should be paid to potential occupational, avocational, and environmental exposures, no matter how distant. A detailed accounting of prior medication use is also required to eliminate the possibility of drug-induced disease.[32] A history of heavy tobacco abuse may make certain considerations more likely (eosinophilic granuloma, respiratory bronchiolitis, desquamative interstitial pneumonia) or less likely (hypersensitivity pneumonitis). Rarely, a family history will be helpful in eliciting the correct diagnosis (familial IPF, sarcoidosis, neurofibromatosis, Hermansky-Pudlak syndrome, tuberous sclerosis, storage diseases). Finally, specific inquiries should be made regarding extrapulmonary manifestations of sarcoidosis and collagen-vascular disease.

On physical examination, the presence of basilar predominant mid to late inspiratory crackles ("velcro rales") and clubbing are suggestive of, but not specific for IPF. Identification of inspiratory squeaks may suggest bronchiolitis or hypersensitivity pneumonitis. Again, extrapulmonary findings may be particularly helpful in limiting the differential diagnosis.

Routine laboratory tests and collagen vascular serologies may suggest an underlying systemic disease, but antinuclear antibodies and an elevated rheumatoid factor are frequently identified in IPF patients.[1,4,8,18] When clinically indicated, a serum precipitin panel for common agents of hypersensitivity pneumonitis can be obtained.

High resolution computed tomography (HRCT) should be routinely employed in the assessment of diffuse parenchymal lung disease. Several HRCT patterns have been identified which may strongly suggest specific diagnoses such as eosinophilic granuloma, lymphangioleiomyomatosis, sarcoidosis, lymphangitic carcinomatosis, hypersensitivity pneumonitis and IPF.[33,34,35] HRCT will at least limit the differential diagnosis and assist in planning the appropriate biopsy procedure (bronchoscopic vs. surgical). Usually, bronchoscopy with saline lavage and transbronchial biopsies is performed next (especially when the CT reveals a bronchocentric pattern of involvement) to exclude granulomatous disorders, malignancy and atypical infectious etiologies. See Figure 1 for a schematic view of the approach to patients with diffuse parenchymal lung disease.

Figure 1
Approach to the Patient with Interstitial Lung Disease



Modified from: Raghu G. AJRCCM 1995; 151: 909

Only when this extensive evaluation is negative can a patient reasonably be said to have IPF. In fact, the diagnosis is only certain when a surgical lung biopsy is obtained.[2] A transbronchial biopsy demonstrating pulmonary fibrosis is never adequate to confirm this diagnosis, but surgical biopsies will provide a definitive diagnosis in over 90 percent of interstitial lung disease cases.[36] An open thoracotomy is occasionally required (because of bleeding, severe pleural disease, or inability to tolerate single lung ventilation), but most specimens are now obtained by video-assisted thoracoscopic surgery (VATS). VATS biopsies provide equivalent results with considerably less morbidity and a shorter recovery time.[37,38] Despite

technologic advances, though, practice trends around the world indicate an increasing reluctance on the part of physicians to subject their patients to these operative procedures. In 1990, Smith and Holbrook surveyed pulmonologists in California and found that two thirds of patients with suspected IPF underwent transbronchial biopsy as part of the diagnostic evaluation.[39] Forty-two percent of these were recommended for open lung biopsy if a nonspecific result was obtained. In contrast, more recent data from the New Mexico ILD registry indicated that only 38 percent of IPF patients underwent even a transbronchial biopsy, and a mere 11 percent had an open biopsy.[11] A large scale study from the United Kingdom indicated similar findings.[4] Twenty-eight percent had transbronchial biopsies, with only 12 percent referred for surgical biopsy. It appears that IPF is increasingly considered to be a clinical diagnosis by medical practitioners. Remarkably, as many as half of all cryptogenic fibrosing alveolitis patients in the United Kingdom die without even seeing a pulmonary specialist.

Very few support the notion that all patients with suspected pulmonary fibrosis must have a lung biopsy.[40] However, it is particularly important to secure an accurate diagnosis in patients who are younger, have normal, atypical or rapidly evolving radiographs, constitutional symptoms or hemoptysis. An adequate tissue sample is useful in several ways.[41] First, a surgical biopsy will indicate a specific diagnosis in the large majority of cases. Several conditions (i.e., chronic hypersensitivity pneumonitis, BOOP, eosinophilic granuloma, vasculitides, and rarely infectious or neoplastic processes) can mimic IPF clinically and radiographically.[2,15] Second, a lung biopsy allows one to discriminate between the different histologic subsets of IPF. This has important implications regarding long-term prognosis and the likelihood of a favorable treatment response.[6,15,27,28,29] Such information may, in certain circumstances, be crucial in a patient's informed decision about whether or not to accept the risks inherent in currently available treatment regimens. Third, optimally secured and interpreted surgical specimens provide a valuable assessment of disease activity. The relative degrees of cellularity (inflammation), granulation connective tissue, fibrosis and honeycomb change may further influence predictions of treatment responsiveness and mortality.[1,6,8,42,43,44,45] Indeed, certain histologic patterns may even suggest a need to explore the patient's suitability for lung transplantation earlier rather than later.

Only about 15 to 30 percent of patients objectively respond to current anti-inflammatory or anti-fibrotic therapies.[1,6,8,12] An informed decision regarding biopsy must therefore be made giving full consideration to the associated costs, risks and benefits. An open biopsy procedure is not appropriate for every patient suspected of having IPF.[40,41] If patients have had a transbronchial biopsy to exclude granulomatous disease, infection, and malignancy, and their HRCT strongly suggests UIP, then a surgical biopsy can reasonably be averted. Patients with extensive honeycombing are unlikely to benefit from a biopsy. In general, patients over 65 to 70 years of age are much less likely to be referred for VATS, but age alone does not represent a valid reason to forgo tissue confirmation or treatment in a patient with interstitial lung disease. That being said, these patients commonly have major comorbidities, more advanced disease, or other contraindications to biopsy or treatment.

The Idiopathic Interstitial Pneumonias

In the 1970's, Liebow created the first comprehensive histologic classification system for the idiopathic interstitial pneumonias.[46] He divided them into five groups: usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), lymphoid interstitial pneumonia (LIP), bronchiolitis obliterans interstitial pneumonia (BIP), and giant cell interstitial pneumonia (GIP). Over the years, certain modifications to Liebow's system have been required. LIP is now considered to be a lymphoproliferative disorder with ties to autoimmune disease, HIV and Epstein-Barr virus infection.[47,48,49,50] GIP is also missing from the current classification system. This is believed to be a form of hard metal pneumoconiosis.[51,52] BIP has been renamed bronchiolitis obliterans with organizing pneumonia (BOOP), and is also called cryptogenic organizing pneumonia (COP).[30,53,54] BOOP mainly consists of the intraluminal deposition of granulation connective tissue within conducting airways and alveoli. Because the associated interstitial process is generally modest and limited to the immediate regions involved by the organizing air space disease, it is probably best considered separate from the interstitial pneumonias.[27,28]

While the current nomenclature has not improved much, the system is more reproducible with clearly defined pathologic criteria. There are now four subsets to consider: usual interstitial pneumonia (UIP), desquamative interstitial pneumonia/respiratory bronchiolitis-associated interstitial lung disease (DIP/RB-ILD), nonspecific interstitial pneumonia (NSIP), and acute interstitial pneumonia (AIP) or Hamman-Rich

disease.[27,28,29,30] The latter was previously thought to represent an accelerated form of UIP, but is now recognized to be a distinct clinicopathologic entity which is rarely confused with IPF.[46,55,56] On the other hand, considerable clinical and radiologic overlap is noted between UIP, NSIP and DIP/RB-ILD with each accounting for a fraction of IPF cases. UIP is clearly the most prevalent of the idiopathic interstitial pneumonias. It accounts for 62 to 90 percent of IPF cases.[15,30,31] NSIP may be seen in up to 14 percent of patients, and DIP in up to 8 percent.[15] The major pathologic features of the idiopathic interstitial pneumonias are contrasted in Table 3.

Table 3
Contrasting Pathologic Features of the Idiopathic Interstitial Pneumonias

Features	UIP	DIP/RBILD	AIP	NSIP
Temporal appearance	Variegated	Uniform	Uniform	Uniform
Interstitial inflammation	Scant	Scant	Scant	Usually prominent
Collagen fibrosis	Yes, patchy	Variable, diffuse (DIP) or focal, mild (RBILD)	No	Variable, diffuse
Fibroblast proliferation	Fibroblast foci prominent	No	Diffuse	Occasional, diffuse, or rare fibroblast foci
BOOP	No	No	No	Occasional, focal
Microscopic honeycomb change	Yes	No	No	Rare
Intraalveolar macrophage accumulation	Occasional, focal	Yes, diffuse (DIP) or peribronchiolar (RBILD)	No	Occasional, patchy
Hyaline membranes	No	No	Occasional, focal	No

Definition of abbreviations: AIP = acute interstitial pneumonia; DIP/RBILD = desquamative interstitial pneumonia/respiratory bronchiolitis interstitial lung disease; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia; BOOP = bronchiolitis obliterans organizing pneumonia.

From: Katzenstein and Myers. AJRCCM 1998; 157: 1301

Usual Interstitial Pneumonia

Most usual interstitial pneumonia cases are sporadic (IPF), but about 30 percent are associated with collagen-vascular diseases, especially progressive systemic sclerosis and rheumatoid arthritis.[1,5,16,17,46,57,58,59] Other pulmonary disorders which may produce a UIP-like pattern include asbestosis, chronic aspiration, chronic hypersensitivity pneumonitis, chronic radiation pneumonitis, chronic eosinophilic pneumonia, and others. One report suggests that the prognosis of UIP is better in the setting of a related connective tissue disorder, but unless vasculitis in present concomitantly, the lesions are histologically indistinguishable.[58] For idiopathic cases, the mean survival is three to six years after diagnosis.[1,6,17]

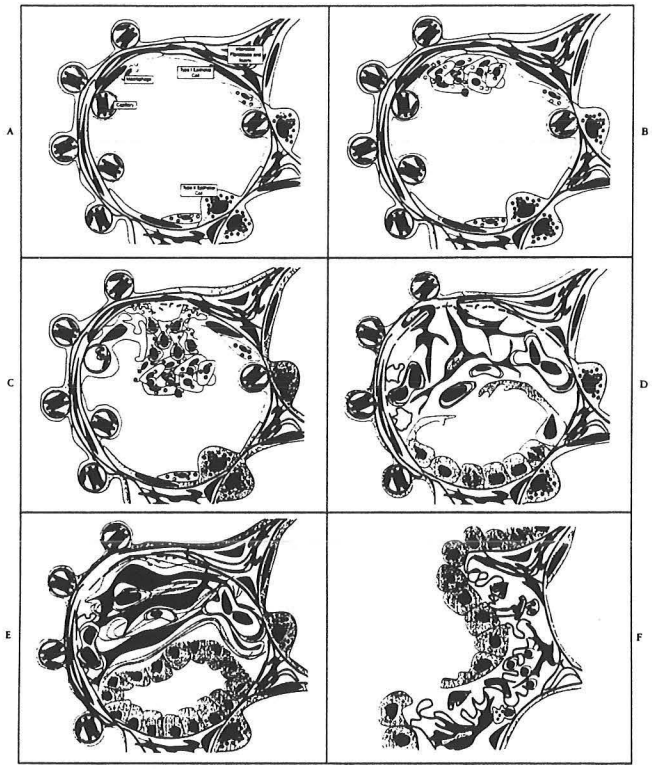
Although the event or agent that initiates the cascade of lung injury and repair in UIP remains unknown, the sequence of histologic changes has been fairly well established (figure 2).[27,28,30,60,61,62,63,64] Injury to the alveolar wall, results in the extrusion of proteinaceous exudates into the alveolar space. Activated macrophages accumulate in these damaged alveoli and elaborate a variety of substances which facilitate the recruitment and activation of other inflammatory cells and fibroblasts. Fibroblasts move through gaps in the damaged basement membrane and ulcerated epithelium, and may undergo certain phenotypic changes within the airspace to become "myofibroblasts" which stain strongly for actin. These cells proliferate and, along with other cell types, elaborate various components of the extracellular matrix (ECM) including fibronectin, proteoglycans and collagen.[60,65]

As these intraalveolar exudates become organized, the so-called fibroblastic foci are produced. These are bundles of spindle-shaped fibroblasts in a loose connective tissue matrix within the airspace (see appendix 1).[27,28,29,66,67] Subsequently, hyperplastic type II cells proliferate over the surface of these fibrous and inflammatory elements to reestablish epithelial continuity including the generation of a new basement membrane. In doing so, the fibroblastic foci within alveolar lumens become incorporated into the interstitial space ("mural incorporation"). When these zones of "active fibrosis" mature and contract, dense bands of relatively acellular, eosinophilic staining collagen appear in the interstitial space. This is often the most

conspicuous light microscopic feature noted in UIP patients. As more and more parenchymal elements are involved over time, irreparable architectural distortion and functional impairment occurs.[60]

It was previously thought that there was an "early" phase of the disease where interstitial inflammation was prominent, but there is little evidence to support this concept. Katzenstein and Myers have noted variable numbers of lymphocytes along with occasional plasma cells, neutrophils, eosinophils, and mesenchymal cells in the interstitium of UIP patients, but cellularity is rarely prominent and mostly seen adjacent to areas with already significant collagen deposition or honeycombing.[28] In fact, they indicate that if a specimen features prominent interstitial cellularity, the diagnosis of UIP should be questioned.[28] Rather, disorders like NSIP and LIP would be suggested by such an appearance.

Figure 2
Evolution of Fibrosis and Alveolar Collapse in IPF



A, normal alveolus. B, formation of intraalveolar inflammatory exudate. C, alveolar ulceration and possible focal basal lamina disruption. D, alveolar organization. Fibroblasts migrate through gaps in the basal lamina into the alveolar exudate. E, alveolar fibrosis. Fibroblasts deposit collagen matrix within the airspace. The previous interstitium is still detectable by virtue of the previous basal lamina (heavy dark line). F, alveolar collapse. Characteristic skeins of folded basal lamina are noted due to juxtaposition of ulcerated alveolar walls. From: McDonald JA. Chest 1991; 99: 87S

Honeycombing is the end stage of the fibrotic process and is seen in virtually all cases of UIP. It refers to the development of enlarged and distorted interconnecting air spaces with thickened walls which are typically lined by a cuboidal epithelium. It is usually not the consequence of primary interstitial thickening and fibrosis. Rather, it is the result of airspace fibrosis and alveolar collapse.[2,60,66,67,68] The contraction of fibrous tissue derived from the mural incorporation of unevenly distributed and organized air space exudates favors the development of severe architectural distortion. Moreover, after epithelial injury, it is common to see apposition of the denuded alveolar walls.[60,67,68] Unlike simple microatelectasis, this may become permanent due to the development of cross-linking fibrous adhesions. Alveolar collapse is often difficult to appreciate on standard sections when the epithelium is missing and no residual airspace is evident, but immunohistochemical staining for basement membrane elements will distinguish regions of collapse from interstitial fibrosis. The traction forces produced by atelectasis and fibrous contraction are transmitted to alveolar ducts and bronchioles; and the honeycomb appearance is actually formed as a result of this traction bronchiolectasis with the migration of bronchiolar-type epithelium into these distorted airspaces.[27,60]

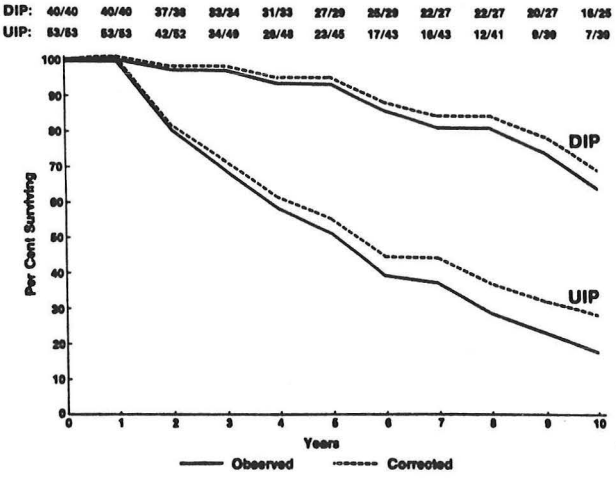
Perhaps the most striking feature of UIP is that it is entirely lacking in uniformity from one region of the lung to the next. It appears that only small and spatially detached areas of the lung are affected at any one time. This produces one of the histologic hallmarks of UIP called temporal heterogeneity.[27,28] This refers to the juxtaposition of zones featuring normal alveoli, inflammation, fibrosis, and honeycomb change sometimes within a single low power microscopic field (see appendix 1). This pattern is derived from repeated focal injury and repair to small portions of lung parenchyma over an extended period of time. This feature is essential for the diagnosis of UIP, along with the identification of fibroblastic foci, which represent islands of active injury and repair.[27,28] High resolution CT may reveal predominantly ground glass attenuation (GGA) early on, but UIP cases tend to demonstrate mostly subpleural irregular linear opacities and honeycombing.

Desquamative Interstitial Pneumonia and Respiratory Bronchiolitis

Desquamative interstitial pneumonia (DIP) is a relatively rare form of interstitial lung disease. The bulk of the existing clinical and pathologic evidence suggests that DIP is not an early "cellular" form of UIP as many have suggested, but rather a distinct form of interstitial lung disease which occurs predominantly in cigarette smokers (90 percent in Carrington's series of 42 patients).[6,28,69] Unlike UIP, this lesion is uncommonly linked to clinical or serological evidence of collagen vascular diseases.[70]

Histologically, DIP is characterized by the often striking and diffuse accumulation of macrophages within alveolar lumens (see appendix 1).[27,28,71,72] Originally, these cells were thought to represent sloughed alveolar epithelial cells, hence the term "desquamative" interstitial pneumonia.[69] Interstitial fibrosis is seen in varying amounts, but this is usually not a dominant feature.[27,28,30] Unlike UIP, the lesion is temporally homogeneous with one microscopic field closely resembling the next. Liebow noted that the "monotonously uniform features (of DIP) are quite in contrast with the variegation typical of other interstitial pneumonias."[69] This pattern suggests a diffuse injury to the lung at one point in time resulting in a similar histologic reaction from zone to zone. Also unlike UIP, fibroblastic foci are not seen, and significant honeycombing develops in only a small minority of DIP patients.[27,28] As detailed previously, the natural history of this disorder is quite different from UIP (figure 3).[6,73] In Carrington's series, the mortality in DIP was only 28 percent over an extended follow-up period with a mean survival of 12.2 years. In the group which did not receive treatment, 22 percent of patients with DIP improved, while no UIP patients spontaneously improved. Sixty-three percent and 85 percent worsened, respectively. With corticosteroids, however, 62 percent of DIP patients improved compared to only 12 percent with UIP, while 27 and 69 percent respectively, experienced progression.[6] Nearly one third of the treated DIP patients fully recovered from their disease.

Figure 3
Comparison of Survival Curves for UIP and DIP



Relative survival curves for UIP and DIP. Dashed lines are corrected for expected survival given the age difference between the two groups (mean age of DIP group 42 years at diagnosis vs. 51 years for UIP group) From: Carrington et al. N Engl J Med 1978; 298: 801

Smoking cessation is also believed to be essential in DIP, and could be responsible for the occasional cases which remit without specific pharmacologic intervention. DIP has been linked morphologically to the lesion known as respiratory bronchiolitis (RB). RB is characterized by the accumulation of pigmented macrophages within respiratory bronchioles, alveolar ducts, and adjacent air spaces.[27,28] This lesion is commonly identified cigarette smokers undergoing lung resection or biopsy for unrelated reasons, and is a common incidental finding in autopsy specimens from smokers.[27,74] RB is believed to be responsible for the "dirty lung" appearance commonly identified on chest radiographs from patients who smoke. Occasionally, patients with a more advanced RB lesion develop signs and symptoms, as well as radiographic evidence, of true interstitial lung disease (RB-ILD).[28,75,76] The major difference between RB-ILD and DIP is that DIP involves the lung diffusely, whereas RB is limited to the small airways and related structures. DIP, however, is also strongly linked to tobacco abuse, and peribronchiolar accentuation of the histologic changes is common in DIP.[27,28] Some authors have suggested that DIP and RB are simply two ends of the spectrum of the same smoking, or occasionally other inhalant-related lung injuries.[28] Since DIP is itself a misnomer, the term RB-ILD may soon replace it entirely.

Focal areas of DIP-like change are commonly seen in other interstitial pneumonias including UIP, NSIP, eosinophilic granuloma, and a variety of other unrelated conditions.[27,77] This underscores the need for generous surgical specimens and attention to strict diagnostic criteria before confirming DIP.[27]

Acute Interstitial Pneumonia

In 1944, Hamman and Rich described a series of patients with a rapidly progressive interstitial pneumonia associated with marked fibrosis.[56] It is the least common and most fulminant of the idiopathic interstitial pneumonias. Until recently, this disorder was felt to represent an accelerated form of UIP and was included under the clinicopathologic umbrella of idiopathic pulmonary fibrosis. This is no longer the case.[78,79] Histologically, these cases represent organizing diffuse alveolar damage (DAD), the pathologic diagnosis associated with the fibroproliferative phase of the adult respiratory distress syndrome (ARDS).[27,28,29,30] The principle distinguishing feature is the lack of an identifiable cause for the acute lung injury in AIP. These patients typically give a history of fever, cough and dyspnea that progresses over days or weeks to respiratory failure.[78] Although a viral prodrome is common, cultures and ultrastructural studies reveal no evidence of infection.[78] Patients ultimately need ventilatory support. The mortality rate is high with about 60 percent dying within two months of diagnosis.[28] Chest radiographs indicate diffuse alveolar infiltrates similar to other cases of ARDS.[79,80] By HRCT, ground glass opacities are commonly seen in conjunction with extensive and usually dependent air space consolidation.[80] Empiric treatment with antibiotics, antiviral therapies and corticosteroids have not demonstrated clear benefit, but anecdotal experience suggests that aggressive "pulse" steroids are helpful in some cases. [79] If the patient survives, the radiograph may clear completely over time. Interestingly, though, some cases of idiopathic diffuse alveolar damage are recurrent, and multiple episodes may ultimately lead to end-stage fibrosis in patients who survive the acute phase of the illness.

Light microscopic findings include marked thickening of the interstitial space by proliferating fibroblasts, edematous stroma, and a variable mixture of mostly mononuclear inflammatory cells (see appendix 1).[27,28,30,78,79] Collagen deposition is not substantial except in very protracted cases. Severe architectural distortion can occur, however, as a result of widespread alveolar collapse and the overdistention of adjacent air spaces.[28,81] Excessive distention of functioning alveoli may partly result from the high-pressure, high-volume ventilatory strategies that are often utilized in these patients.[82,83] Unlike true honeycomb cysts, the walls of these dilated acini are lined by alveolar epithelium.[28] As expected from the abrupt onset of this disease, temporal uniformity is characteristic within the histologic specimen. Other features of acute lung injury are also commonly present including hyaline membrane remnants, type II cell hyperplasia and atypia, and organizing thrombi in small to medium sized vessels due to accompanying endothelial damage.[27,28,78,79]

Nonspecific Interstitial Pneumonia

Nonspecific interstitial pneumonia is a term coined by Katzenstein and Fiorelli to describe those interstitial pneumonias which cannot be classified as UIP, DIP/RB-ILD, AIP or BOOP.[84] It is not simply a "wastebasket diagnosis" since consistent histologic features are present from case to case. It is, however, a

nonspecific reaction to a variety of parenchymal insults. Three different patterns may be seen by light microscopy, and while involvement can be patchy, all affected areas demonstrate temporal homogeneity (see appendix 1). Most frequently, a prominent lymphoplasmacytic infiltrate is identified with minimal fibrosis (31 of 64 patients in the largest series).[84] The second largest group of NSIP patients has a more balanced mixture of fibrosis and inflammation (24 of 64 cases).[84] The fibrosis in NSIP features mostly mature collagen, but a few of these patients have prominent fibroblastic proliferation. The third and smallest subset exhibits dense interstitial collagen deposition and architectural distortion (9 of 64 cases).[84] Honeycombing was seen in only four patients in this series and was strictly microscopic in two. In cases that have significant fibrosis, the finding of temporally uniformity throughout the lesion is critical in separating NSIP from UIP.[27,28,29,30,84] Intraluminal alveolar macrophage accumulation may be seen, but unlike DIP, these areas are patchy and associated with much more prominent interstitial widening with inflammation and/or fibrosis.[27,28,30,84] Fibroblastic foci, a hallmark of UIP, are noted in only about 20 percent of NSIP patients. It is possible, of course, that some of these cases actually represent poorly sampled UIP.[84] Scattered areas of BOOP and lymphoid hyperplasia are also quite common.[84] The "cellular" form of NSIP may be confused with lymphocytic interstitial pneumonitis which demonstrates monotonous sheets of lymphocytes in the interstitial space, but LIP lacks regions of BOOP, DIP-like change and fibroblastic foci.[28]

Several disorders have been linked to NSIP including a variety of collagen vascular diseases and other autoimmune conditions like Hashimoto's thyroiditis, primary biliary cirrhosis, and acute glomerulonephritis.[27,28,84] Hypersensitivity pneumonitis can show this pattern while lacking other concomitant "diagnostic" features like ill-formed granulomas and bronchiolitis in the available specimen. Other potential but unproven exposures have also been noted in NSIP. Among Katzenstein and Fiorelli's patients were two garment factory workers, a paper factory worker, a coal handler, a brewer, a farmer and a veterinarian.[84] The lesion has also been seen following toxic fume exposure, severe pneumonia, slowly recovering acute lung injury, and as a manifestation of drug toxicity. Nevertheless, most cases are idiopathic and part of the clinical spectrum of IPF.[84]

The clinical presentation of NSIP is not particularly distinctive compared to other forms of pulmonary fibrosis. Gradually progressive dyspnea and a dry cough are the most common reasons for seeking medical attention. A minority experience fever, chest pain, hemoptysis or constitutional symptoms.[84] There appears to be a slight female predominance in this disease.[84]

Chest radiographs in NSIP may show interstitial, alveolar or mixed disease, and rarely will be normal.[84,85] The most reliable finding on HRCT scanning in NSIP is bilateral patchy ground glass attenuation (GGA) with no particular zonal predominance.[85] Park and colleagues noted that areas of basilar predominant consolidation were also seen in the majority of their patients with random linear opacities noted in less than one third.[85]

The most striking difference from UIP is the superior prognosis of NSIP. Most of the patients in Katzenstein's series were treated with corticosteroids, and 45 percent of the patients with follow-up recovered completely.[84] Many others showed improvement with treatment, and only 11 percent died of their disease. Thus, the natural history of this disease more closely parallels that of DIP/RB-ILD. Patients with a cellular infiltrate and little fibrosis had a greater likelihood of response than patients with mixed disease; and patients with mixed disease had a better prognosis than those with "pure" fibrosis.[84] However, complete recovery was even shown be possible in one patient with isolated fibrosis.[84]

Cellular and Molecular Events in the Idiopathic Interstitial Pneumonias

Much has been learned in recent years about the various cell types, cytokines, and growth factors involved in the genesis of pulmonary fibrosis.[60,64,86] The nature of the initial injury, however, remains a mystery. The trigger for IPF could be environmental, infectious or immunologic, and may vary from case to case. There may also be an undefined genetic predisposition to this disorder perhaps involving regulation of inflammatory or fibrotic events.

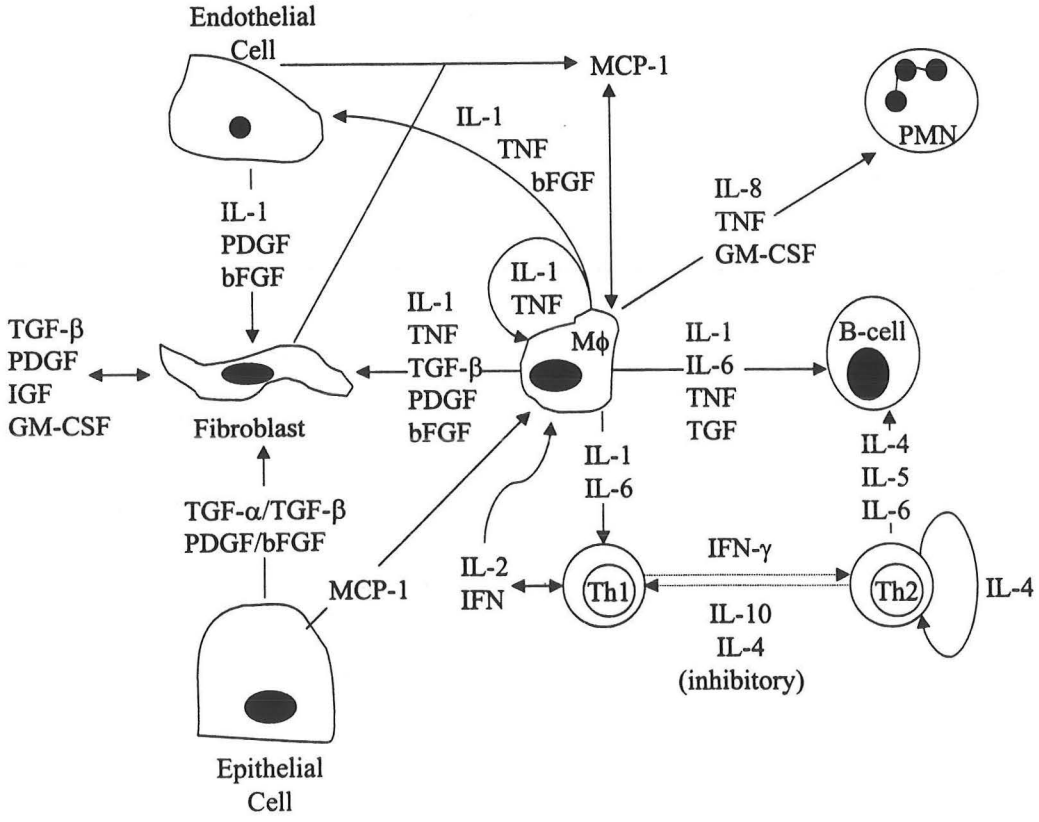
To produce such a chronic and progressive condition, either the primary injurious agent must persist in the lung, or a self-perpetuating cascade of biologic events is triggered which drives the tissue reaction toward fibrogenesis. Although there is no good animal model which mimics IPF, much relevant data has been gathered from the bleomycin-induced pulmonary fibrosis model, transgenic models, simple wound healing experiments, and cell culture studies.

Damage to the alveolar epithelium (and possibly the capillary endothelium) is the first step in this complex process of lung injury and repair. Vascular permeability is altered and plasma proteins exude into injured tissues. An inflammatory response is born as various substances released from dead and dying cells lead to the recruitment and activation of peripheral blood monocytes and resident alveolar macrophages.[13,87] This inflammatory exudate within the alveolar space represents the earliest histologic finding in IPF. Activated macrophages release "proximal" cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) which recruit additional immune effector cells to the area.[88,89] Many cell types participate in the events which follow including lymphocytes, monocytes, macrophages, mast cells, epithelial and endothelial cells, fibroblasts, and perhaps neutrophils and eosinophils.[2,60,86] When activated, these cells express message for a number of additional proinflammatory and profibrotic cytokines, chemokines, growth factors, adhesion molecules and matrix elements.[60,86,90] Moreover, they may elaborate toxic oxygen species, proteases and complement components which further fuel the repeating cycle of injury and repair.[60,91,92]

An imbalance exists in pulmonary fibrosis on at least three critical planes: oxidants are prevalent while antioxidant defenses are depleted, procoagulant activity exceeds fibrinolytic activity, and matrix production outweighs matrix degradation.[92,93,94,95,96,97,98,99] These factors contribute heavily to the formation and delayed clearance of alveolar exudates leading to organization and fibrosis.[60]

The cytokine networks which are active in interstitial lung disease are extremely complex (figure 4).[100] The molecules involved may exert autocrine, paracrine, and even endocrine effects.[86,100] The biologic effect of a given cytokine also depends on the current phenotypic state of the target cell and its surrounding milieu.[86,90,100] A given cytokine may either augment or antagonize the activity of another when present in the same microenvironment. For example, the production of both IL-1 and TNF-α by macrophages is known to be enhanced in patients with IPF.[88] Either molecule alone will stimulate fibroblast proliferation via platelet derived growth factor (PDGF) and upregulate the synthesis of collagen and fibronectin.[88,101,102] However, the combination of IL-1 and TNF-α leads to a marked inhibition of fibroblast proliferation, in part through the elaboration of prostaglandin E2.[103]

Figure 4
Simplified Schematic of Active Cytokine Networks in Interstitial Lung Disease



The most important growth factors in the development of pulmonary fibrosis are transforming growth factor-beta (TGF-β), platelet derived growth factor (PDGF) and basic fibroblast growth factor (bFGF).[2,61,86,90,101,104,105,106,107,108,109,110,111] Hepatocyte growth factor and macrophage derived insulin-like growth factor have also been implicated in lung fibrogenesis.[112,113] Still another protein with an emerging role in fibrosing alveolitis is endothelin-1. In addition to its vasoconstrictive properties, endothelin-1 exhibits potent mitogenic activity on fibroblasts and smooth muscle cells and is increased in some patients with IPF.[114,115] The increased expression in several cell types may be induced by proinflammatory cytokines like IL-1 and TNF which are prevalent in the lungs of IPF patients.[116] Increased endothelin-1 levels have been shown to precede the rise in lung collagen content which occurs after bleomycin injury.[117] Moreover, increased staining for endothelin-1 is noted in regions of developing fibrosis.[117]

TGF-β has received particular attention as a key "proximal" modulator of disease activity in the idiopathic interstitial pneumonias. It is derived from several cell sources in the lung including lymphocytes, macrophages, fibroblasts, epithelial and endothelial cells.[86,105,118] TGF-β is essential in pulmonary embryogenesis and normal wound healing, but dysregulated production of this cytokine has been tightly linked to the development of pulmonary fibrosis.[104,105,106,119,120,121,122] TGF-β is a potent chemotactic agent for mononuclear phagocytes, and its expression is increased in IPF.[104,105,106,123] It also stimulates fibronectin and collagen production directly and indirectly.[124] TGF-β induces target cells to elaborate IL-1 and TNF-α in addition to other growth factors like PDGF and bFGF.[125] In turn, fibroblast recruitment and proliferation occurs and collagen synthesis and contraction increases.[105,126,127,128] TGF-β also inhibits the expression of matrix degrading enzymes.[118,129]

Interestingly, administration of anti-TGF-β antibodies decreases the accumulation of collagen in the lungs of bleomycin treated mice.[130] Furthermore, when the active TGF-β1 gene is transferred to rat lung, a mononuclear predominant inflammatory cell infiltrate develops accompanied by the rapid onset of pulmonary fibrosis characterized by the differentiation and proliferation of myofibroblasts.[131] Even though significant transgene expression did not occur after day 14 in these experiments, the fibrotic process continued to evolve. The authors suggest that this may have been due to synthesis of "downstream" cytokines and growth factors released by activated inflammatory cells, epithelial cells and fibroblasts.[131] This sort of self-perpetuating cascade of proinflammatory and profibrotic events may also be responsible for the persistent "repair" response associated with UIP (if the initiating injury does not persist over long periods in that disease). Actually, several transgenic models of pulmonary fibrosis have recently been established which result in either more or less inflammation, and predominantly fibroblastic or collagenous fibrosis. These other models involve overexpression of TNF-α, TGF-α, IL-6 or PDGF and will further help to define the specific roles of these biological agents in normal repair and disease.[132,133,134]

Lymphocytes are present to some degree in all of the idiopathic interstitial pneumonias and may be especially prominent in some disorders like NSIP. It appears that a Th2-like pattern of cytokine production predominates in the lymphocyte response associated with IPF.[135,136] Th2 lymphocytes typically elaborate a profile including IL-4, IL-5, IL-6 and IL-10, and are associated with the development of a humoral immune response. In mice, a subset of pulmonary fibroblasts have been shown to proliferate and release extracellular matrix proteins including collagen after exposure to IL-4.[137] Wallace and colleagues confirmed that most mononuclear cells in the interstitium of IPF patients stain positively for IL-4 and IL-5, and few (less than 10 percent) stain for interferon gamma (IFN-γ) which is the major Th1 cytokine.[135] In Th2 dominant responses, IL-4 is the main T cell mitogen. It also suppresses cytokine production in Th1 cells.[138] Since IFN-γ is an important anti-fibrogenic cytokine, the consequences of this pattern of expression are clear.[139] In one study, IPF patients with the lowest circulating IFN-γ levels demonstrated the worst decrement in lung function at follow-up.[140]

It appears, then, that several cytokines and growth factors are both chemotactic and mitogenic for effector cells involved in the inflammatory and fibrotic arms of the interstitial pneumonias. Other important leukocyte and fibroblast chemoattractants include fibronectin, complement components, and chemokines like monocyte chemoattractant protein-1α (MCP-1α) and macrophage inflammatory protein-1α (MIP-1α).[60,141,142,143,144] MIP-1α expression, for instance, increases in response to TNF-α. Interestingly, passive immunization with anti-MIP-1α attenuates the fibrotic response following experimental bleomycin injury.[145] Other chemokines such as IL-8 and IFN-γ inducible protein (IP-10) appear to regulate angiogenesis in IPF.[146] The process of neovascularization is thought to be important in supporting fibroblast proliferation and matrix

deposition, and an apparent imbalance exists between these angiogenic (IL-8) and angiostatic (IP-10) factors.[146]

Recent evidence suggests that leukotrienes may also play a role in the pathogenesis of IPF. Wilborn and colleagues demonstrated constitutive activation of 5-lipoxygenase in the lungs of patients with idiopathic pulmonary fibrosis.[147] This is associated with a several fold rise in synthesis of leukotriene B4 and C4 which may directly or indirectly facilitate inflammatory and proliferative events in IPF.[147,148,149,150,151]

The presence of cytokines and other chemoattractant gradients is not the only factor promoting large scale leukocyte migration into areas of injury in IPF. Endothelial expression of various leukocyte selective cell adhesion molecules is also important.[152,153,154] Intercellular adhesion molecule-1 (ICAM-1) expression, for instance, is increased in IPF and represents an important surface ligand for circulating lymphocytes, directing them to the interstitial space.[154] ICAM-1 also provides an important co-stimulatory signal needed for activation of resting T cells, and plays a role in antigen presentation.[155,156] Interestingly, the Nagoya University group has demonstrated that ICAM-1 and MHC class II antigens are strongly expressed by regenerating type 2 pneumocytes and alveolar macrophages in IPF, suggesting that both cell types may function in antigen presentation in this disease.[154,157]

Following the initial injury to the alveolar wall in IPF, plasma derived fluid filters into the air space where the coagulation cascade is activated and fibrinogen is converted to cross-linked fibrin. This entraps plasma proteins like fibronectin in the solid phase.[158] Fibronectin is a key component of the extracellular matrix. It appears to regulate cell adhesion, migration, proliferation, matrix assembly, and cytoskeletal organization.[159,160] This and other elements within the fibrin provisional matrix provide the scaffolding on which fibroblasts and endothelial cells invade the alveolus to form granulation connective tissue.[161] Specifically, fibroblast migration through the extracellular matrix relies on CD44 mediated adhesion to fibrin, fibronectin and hyaluronic acid.[161,162,163,164] CD44 is a transmembrane glycoprotein which functions as a cell surface matrix receptor.[165] It is densely distributed on filopodia and lamellipodia which are involved in cell migration. Monoclonal blocking antibodies to CD44 will inhibit fibroblast invasion into a fibrin matrix.[161]

Interestingly, procoagulant activity appears to be increased in the lungs of IPF patients, while antifibrinolytic activity is reduced.[166,167,168] This results in excessive fibrin deposition and an attractive environment for fibroblast adherence and proliferation. This imbalance is partly created by increased tissue factor (TF) expression in IPF.[167] TF is both a receptor and cofactor for factor VII which initiates the extrinsic coagulation cascade leading to fibrin deposition.[169] Imokawa and colleagues showed that most of the TF message and protein localizes to type II cells covering fibroblastic foci and diseased alveolar septae.[167]

After this amalgam of phagocytic, inflammatory and mesenchymal cells is recruited to the zone of injury by chemotactic, cell adhesion and matrix-dependent mechanisms, certain harmful events may occur including the elaboration of excessive amounts of toxic oxygen species. The role of substances like hydrogen peroxide, superoxide, peroxynitrite and oxygen radicals in IPF may be underappreciated.[92,170,171] Persistent exposure of affected areas to high levels of oxidative stress depletes the antioxidant barrier in the epithelial lining fluid and exposes parenchymal cells to direct injury.[172,173] Furthermore, an increasing role for intracellular oxidant species in signal transduction and gene regulation is becoming apparent.[174,175,176,177] Indeed, these molecules may act as second messengers for transcription factor activation, chemotaxis, cell proliferation and apoptosis.[176] Superoxide exposure, for instance, has been linked to CD11/CD18 adhesion molecule expression on alveolar macrophages, and anti-CD11 antibodies will inhibit bleomycin-induced pulmonary fibrosis in mice.[93,178,179]

Finally, consideration must be given to the role of programmed cell death in the termination of inflammatory and fibrotic events, and the restoration of a functional gas-exchanging unit. Reestablishment of a normal alveolar-capillary interface requires that the infiltrating and locally proliferating cells be eliminated without inducing an inflammatory response in the process.[180,181,182] When cells undergo programmed cell death, they are recognized and ingested by phagocytes before they can release proinflammatory intracellular contents into the local milieu. Apoptosis of mesenchymal cells is likely a crucial step in turning off the repair response after lung injury, thereby permitting the regression of airspace and interstitial granulation tissue. If this mechanism were defective, and dying cells were allowed to release their toxic components, it could contribute to a chronic inflammatory response and excessive scarring.

On the other hand, excessive programmed cell death may also play a role in the development of pulmonary fibrosis.[183] Fas is a cell surface antigen which mediates apoptosis after joining with Fas ligand (FasL), another cell surface protein. In the bleomycin model, Fas expression is increased in epithelial cells rather than mesenchymal cells.[183] Infiltrating T lymphocytes simultaneously overexpress FasL.

Consequently, epithelial cell apoptosis occurs. Presumably, this represents a means of clearing unwanted cells during the early response to injury so that orderly repair may occur. However, since the epithelium normally exercises tight control over mesenchymal proliferation, prolonged epithelial disruption by excessive apoptosis could contribute to increased scarring.[183] Interestingly, Hagimoto and coworkers found that glucocorticoid treatment inhibits Fas/FasL expression and epithelial apoptosis while preventing fibrosis. In a separate study, this group showed that repeated inhalation of anti-Fas antibody will cause epithelial apoptosis followed by a lymphoplasmacytic alveolitis and pulmonary fibrosis.[184] Another line of evidence supporting this concept of dysregulated apoptosis comes from a study of polycystic kidney disease (PKD).[185] Epithelial apoptosis is a known feature of this disorder as well, and PKD is associated with a secondary interstitial fibrosis histologically. Cyclosporine A nephropathy is also characterized by accelerated apoptosis and interstitial fibrosis.[186] Indeed, many disease states in other organ systems (some involving fibrotic reactions) are linked to abnormal apoptosis.[187,188]

Possible Etiologies in Idiopathic Pulmonary Fibrosis

Although the cellular and molecular events associated with IPF are becoming clear, the root cause of the disease remains a mystery. It is generally thought to be triggered by an immune response in genetically susceptible persons to an exogenous or endogenous antigen, which may vary from case to case. Various environmental associations have been noted, but causality has not been established. In the UK, patients with IPF were found to be more likely to have had exposure to metal dusts, to have worked with cattle, or to have lived in a house heated by a wood fire.[14] Also, a general association was found with "dirty" occupations including craftsman, machinest, miner, textile worker, etc. No link to tobacco use was found in this study, but certainly this is important in DIP/RB-ILD. In a large autopsy series from Japan, over 1300 IPF cases were reviewed.[7] The incidence of IPF among individuals whose jobs exposed them to dust or organic solvents was more than double that of other subjects. Occupations with significantly ($p<0.01$) higher rates of disease included laundry workers, barbers, beauticians, metal workers, woodworkers and painters. A live case control study was simultaneously conducted by Iwai and colleagues in which they also demonstrated a significantly higher rate of IPF in workers exposed to metallic dusts.[7] Of course, inhalation of organic and inorganic dusts has long been known to result in fibrosing lung disorders like hypersensitivity pneumonitis, asbestosis and silicosis. Exposure to solvents has been linked to both pulmonary fibrosis and systemic sclerosis.[7,189,190,191] Kennedy and Chan-Yeung point out a useful analogy to occupational asthma.[192] Over 200 compounds in the working environment have been shown to induce asthma in susceptible individuals; and once the disease is firmly established, the inflammatory process may not resolve even though the patient is removed from the proximate source of the problem.[193]

Viral infections are considered another possible link in the development of IPF.[194] In one study, 14 of 20 patients showed evidence of *in vivo* Epstein-Barr virus replication within type II alveolar epithelial cells compared to two of 21 controls with a variety of other inflammatory or neoplastic pulmonary disorders.[195] Most of these patients had not received immunosuppressive treatment which might be expected to reactivate a latent viral infection. Nevertheless, the lower respiratory tract has been shown to be a reservoir for EBV, and this virus has been linked to the development of LIP.[196,197] Egan and colleagues suggest that particularly in older patients, senescent immunologic responses could favor reactivation of latent viral infections like EBV and predispose these patients to the development of IPF.[195] Such infections could alter class II MHC expression or trigger the development of crossreactive autoantibodies.[194,198,199] Viral genes could also function as transactivating factors regulating a variety of transcriptional events in the lung.[194] Adenoviral transformation of type II cells, for instance, has been associated with stimulation of type I collagen genes.[200]

A potential association with autoimmune phenomena cannot be overlooked. Various interstitial pneumonias (UIP, NSIP and BOOP) have been clearly associated with disorders like systemic lupus erythematosis, rheumatoid arthritis, progressive systemic sclerosis, polymyositis/dermatomyositis and Sjogren's syndrome. Moreover, the frequent association of IPF with increased levels of antinuclear antibodies or rheumatoid factor is well established, despite the lack of clinical evidence indicating an associated systemic disease.[2,4,8,20,201]

Most studies have focused on the role of dysregulated cellular immunity in IPF, but there may also be a role for humoral activation in this disease.[20,202,203,204] A number of investigators have identified circulating immune complexes, as well as immunoglobulin and complement deposition in the lungs of IPF

patients.[5,19,20,202,204,205] Wallace and colleagues have even described circulating IgG autoantibodies in IPF patients which recognize a yet unidentified 70-90 kDa lung antigen associated with alveolar epithelial cells.[203] The authors indicate that this protein appears to be cytoplasmic in origin, and may be released following an unrelated initial injury. Still, subsequent immune complex formation and complement activation could foster a persisting local inflammatory response within the alveolus.[203] Humoral activation in IPF may be favored by the Th2-dominant response among infiltrating lymphocytes.[136]

The role of genetics in the development of the idiopathic interstitial pneumonias remains unclear. A familial form of IPF exists, but few answers have yet been garnered from these rare subjects.[206,207] Thus far, no linkage to any specific HLA haplotypes among sporadic cases has been identified, but small numbers of available subjects in any one area have hindered this work.[208,209] The existence of animal models of inherited interstitial lung disease and strain-specific susceptibilities to agents like bleomycin suggest that genetic influences may be important in lung fibrosis.[60,210,211,212] Unquestionably, altered gene expression could play a major role in some patients. Innumerable defects might be relevant to the generation or perpetuation of this sort of disease process. These might include genes involved in immunoglobulin production, programmed cell death, growth factor and cytokine expression, MHC class II expression, oxidant-antioxidant production, collagen polymorphisms, adhesion molecule expression, and so on.

Utility of High Resolution Computed Tomography in IPF

It is clear that pulmonary function testing cannot distinguish "inflammatory" from fibrotic change. With regard to noninvasive tests, high resolution computed tomography (HRCT) seems to offer the most information regarding differential diagnosis and the "stage" of disease. HRCT patterns have been shown to correlate better than plain roentgenographic features with histopathologic findings.[31,33,213,214,215] HRCT can also reliably diagnose typical cases of certain diffuse parenchymal lung diseases including sarcoidosis, eosinophilic granuloma, lymphangioleiomyomatosis, silicosis, asbestosis, and lymphangitic carcinomatosis.[35] It is therefore indicated to narrow the differential diagnosis when patients present with a chest radiograph showing a diffuse infiltrative pattern.

UIP often exhibits a fairly "classical" appearance on HRCT. However, while UIP may be favored by a particular constellation of findings, HRCT cannot reliably separate the pathologic variants of IPF. See table 4 for a list of typical HRCT findings in patients with IPF. HRCT also cannot distinguish IPF from fibrosis associated with the collagen vascular diseases.[216] Furthermore, some cases of chronic hypersensitivity pneumonitis (and other disorders) can mimic IPF exactly on computed tomography scans.

Table 4
HRCT Findings in IPF

Findings of Fibrosis
Intralobular interstitial thickening
Visible intralobular bronchioles
Traction bronchiectasis
Honeycombing
Irregular interlobular septal thickening
Ground glass opacity
Subpleural predominance
Lower zone and posterior predominance

From: Webb et al. *High Resolution CT of the Lung*, 2nd edition

In IPF, varying proportions of ground glass attenuation (GGA), irregular linear opacities, consolidation, and honeycombing may be seen depending on the histologic subtype and stage of disease.[217] Linear or reticular change on HRCT generally corresponds to fibrosis, while ground glass attenuation has been suggested to represent areas of active inflammation which are potentially more amenable to immunosuppressive treatment.[33, 85,213,217,218,219,220,221] In one study of 76 patients, 43 percent of those with predominant GGA experienced a greater than 15 percent improvement in lung function at one year compared to 33 percent with a mixed pattern, and 9 percent with mostly irregular linear opacities (figure

5).[213] Interestingly, though, no difference was noted between the actuarial survival curves of patients with mixed disease or mainly reticular changes, but the patients with predominant GGA did much better (figure 6). All of these patients were alive 4 years after diagnosis versus only 45 percent of those with more reticular disease. Other studies have suggested that areas of GGA usually progress to fibrosis and honeycomb change. This definitely occurs, but most of the patients in these series had extensive fibrosis to begin with.[222,223]

Figure 5

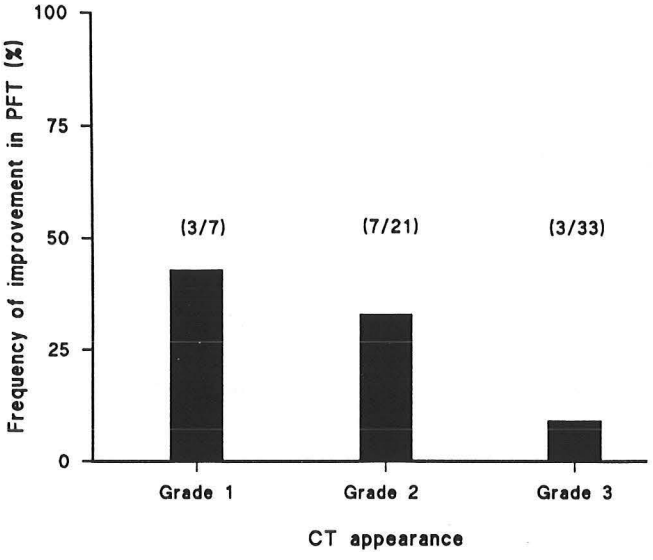


Figure 6

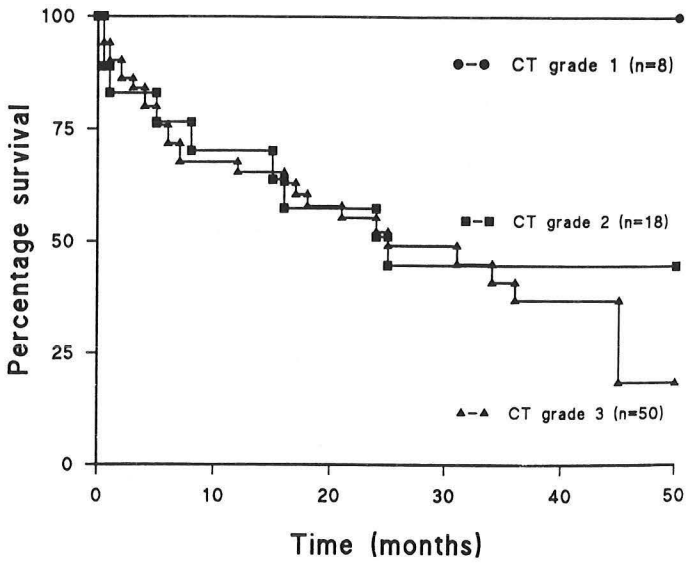


Figure 5. Frequency of improvement in pulmonary function in treated patients at 1 year in relation to initial CT appearance. Patients with predominantly ground glass disease (Grade 1) improved more frequently than those with more equivalent amounts of ground glass and reticular disease (Grade 2). Patients with grade 2 CT scans responded more frequently than subjects with predominantly reticular disease (Grade 3).

Figure 6. Survival curves for IPF based on the initial CT appearance. CT Grade 1 indicates predominance of ground glass disease. CT Grade 2 indicates equally extensive ground glass and reticular disease. CT Grade 3 indicates predominant reticular opacities. No difference was noted in survival of patients with mixed or predominantly reticular disease, but patients with mostly ground glass attenuation had significantly decreased mortality rates.

From: Wells et al. ARRD 1993; 148: 1076

One study suggested that the fate of GGA is largely dependent on the type of interstitial pneumonia with which it is associated.[224] Serial HRCT scans indicated that nine of 12 patients with UIP had either worsening of their GGA, or conversion to irregular lines or honeycombing at follow-up. Eleven of these patients were receiving steroids or cytotoxic therapy at the time. In contrast, only one patient each out of 11 with DIP showed progression to reticular or honeycomb change. Nine subjects demonstrated improvement or stability in the radiographic extent of disease. In UIP, GGA is almost always accompanied by irregular linear opacities and usually honeycombing unless it is detected very early. In DIP, ground glass may be the only abnormality noted and honeycombing is uncommon. Irregular linear opacities accompanied GGA in less than half of the DIP patients in this series.[224] In NSIP, GGA is again the dominant feature, often accompanied by patchy areas of consolidation.[85] Irregular lines and honeycombing are much less frequent than in UIP. In the only serial HRCT study of NSIP patients, three of seven showed improvement in their scans, and another three demonstrated complete resolution in these opacities after treatment.[85]

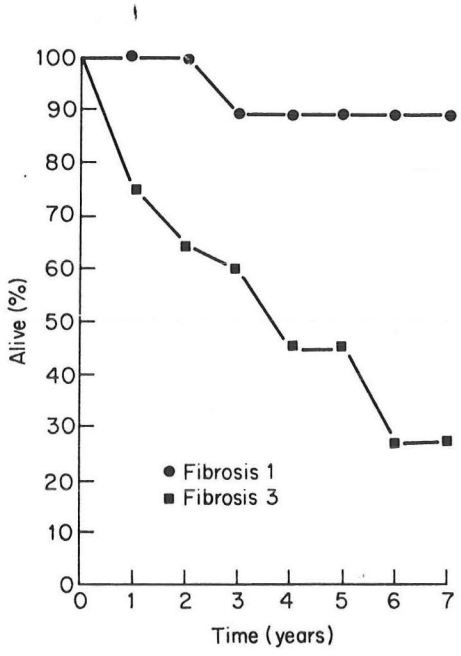
As a general rule, patients who have GGA in association with extensive fibrosis will predictably progress in regions of GGA; and patients with predominant GGA without architectural distortion have a better chance of improving or stabilizing on treatment. The resolution of presently available scanners does not permit a distinction between cellular disease and fine fibrosis. In one study, GGA corresponded to

inflammation in 65 percent and fibrosis in 54 percent of patients with various diffuse infiltrative lung diseases.[218] When GGA is seen in association with prominent linear opacities, traction bronchiolectasis or honeycombing, however, it very likely represents fibrosis.[217,218]

Predicting Outcome in Idiopathic Pulmonary Fibrosis

The rate and pattern of disease progression in individuals with IPF are notoriously unpredictable. Many attempts have been made to correlate various clinical, physiologic, pathologic and radiologic indices with disease activity and the likelihood of progression. In general, a higher risk of progression has been associated with the following: male gender, older age, worse dyspnea scores, a longer symptomatic period prior to treatment (greater than one year), former smoking, a marked reduction in vital capacity, BAL neutrophilia or eosinophilia, a reticular-predominant or honeycomb pattern on HRCT, and an initial poor response to steroids.[1,12,22,24,213,220,225,226,227] Still, optimally secured and interpreted surgical biopsy specimens which distinguish UIP from other interstitial pneumonias provide the most reliable predictions of long term outcome. It was previously thought that the only certain indicator of "active" disease was the presence of a predominantly cellular lesion (alveolitis) on a biopsy specimen.[1,6,42] In the early 1980's, Wright and co-workers showed that patients with predominantly inflammation and less fibrosis had a much better actuarial survival compared to those with mostly fibrosis and less inflammation (figure 7).[42] This is a generally well accepted notion, but a recent prospective analysis of 94 UIP patients evaluated at the National Jewish Hospital failed to confirm this (unpublished data). In this group, the morphologic assessment of extent of fibrosis and cellularity did not significantly correlate with survival. This may, however, have been due to the fact that fibrosis was already significant in almost all of the subjects when they presented to this referral center, and no patients with DIP/RB-ILD or NSIP were included in the study. The key histologic finding which correlated with mortality in this series, rather, was the prevalence of immature granulation connective tissue. Patients who had higher scores for fibroblastic foci died earlier.

Figure 7
Dependence of IPF Survival on Histologic Scores for Fibrosis



Survival curves for IPF patients based on the identification of predominant inflammation with minimal fibrosis (fibrosis 1) versus predominant fibrosis (fibrosis 3). From: Wright et al. Br J Dis Chest 1981; 75: 61

Experience suggests that individual clinical, radiologic and physiologic parameters are not reliable indicators for assessing disease activity, prognosis or treatment responsiveness.[1,5,24,228,229,230,231] It is not uncommon for some of these variables to improve during therapy while other seemingly related variables simultaneously worsen. Consequently, the Denver group devised a composite clinical-radiographic-physiologic (CRP) scoring system to allow a quantitative assessment of overall patient impairment over time.[232] This is a weighted system which encompasses symptom scores, type and severity of radiographic abnormalities, and several pulmonary function variables into an overall CRP score. The CRP score has been shown to correlate better than any individual test with histologic indices of disease activity.[232] Worse degrees of impairment are associated with higher CRP scores.

Gay and colleagues recently published an important prospective study designed to determine the efficacy of steroid treatment in IPF.[45] Thirty-eight previously untreated patients with biopsy proven IPF (37 UIP, 1 DIP) were each treated with three months of high dose steroids. CRP scores were utilized to determine whether patients improved (>10 point fall in CRP), remained stable (change ≤10 in either direction) or progressed (>10 point rise in CRP). Responders were tapered over the next 18 months, while nonresponders were quickly tapered and placed on cyclophosphamide. The CRP scores of 10 patients (26%) improved with treatment, 14 (37%) remained stable, and another 14 (37%) worsened. Half of the nonresponders died of respiratory failure while receiving high dose steroids. Interestingly, a higher CRP score (worse severity) was evident in the responders compared to either of the other groups. More severe physiologic impairment at presentation did not predict long term mortality. As other investigators have found, responders in this study were younger (45.1 ± 4.3 yr) compared to those who remained stable (53.1 ± 3.3 yr) or worsened (61.4 ± 3.5 yr). Also, the pretreatment ground glass score on HRCT was significantly higher in the responder group than in the nonresponder or stable groups, but the overall radiographic score was higher in those who did not respond. In fact, pretreatment HRCT represented the best noninvasive method for identifying patients likely to respond to therapy (higher ground glass scores) and live longer (lower fibrosis scores). Not unexpectedly, a higher fibrosis score on lung biopsy was also noted in the nonresponder group. Importantly, a significant survival benefit was noted for patients who either improved or remained stable on treatment compared to those who worsened.

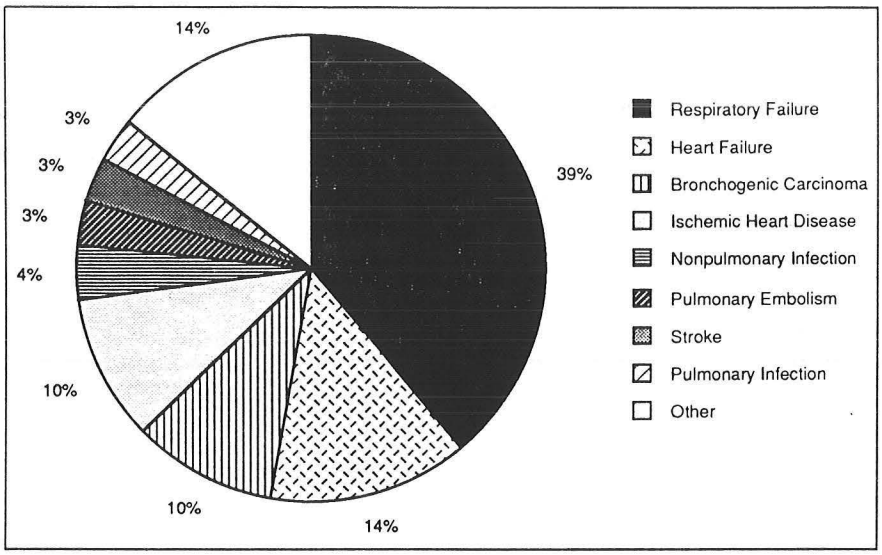
Assessing Clinical Deterioration in IPF

During the course of the illness, essentially all patients with IPF will experience periods of clinical deterioration. When this happens, it is essential to determine whether the increased symptoms or declining function is due to disease progression, complications of the disease, comorbid conditions, or untoward effects of therapy.[25] Many different medical problems may be obscured by the underlying chronic respiratory disease including infection, thromboembolism, cardiac disease, bronchogenic carcinoma, pneumothorax or steroid myopathy.[25,233,234,235,236,237,238,239] Most often, it is due to worsening of the underlying disease.

The most common primary cause of death in IPF is respiratory failure related to progression of the interstitial disease. However, when Panos and coworkers analyzed the mortality data from six large series of IPF patients, respiratory failure accounted for only 39 percent of deaths (figure 8).[25] Cardiovascular complications including heart failure, ischemic heart disease and stroke combined for 27 percent of the deaths. Lung cancer caused 10 percent, and infection or pulmonary embolism combined for another 10 percent.[25]

Occasionally, patients with IPF develop the rapid onset of respiratory failure, fever, and leukocytosis with no evidence of infection.[26,240] The clinical presentation is similar to that of acute lung injury or AIP. By HRCT, new areas of peripheral, multifocal or diffuse consolidation are observed.[240] Histology indicates organizing diffuse alveolar damage and abundant fibroblastic foci superimposed on the baseline changes.[26,240] The prognosis of patients who enter this accelerated phase of the disease is poor, but patients may respond to pulse corticosteroids.

Figure 8
Cause of Death in Idiopathic Pulmonary Fibrosis



From: Panos et al. Am J Med 1990; 88: 396

Treatment of the Idiopathic Interstitial Pneumonias

It seems clear that there is a general skepticism regarding the efficacy of medical therapy in IPF. Indeed, some have suggested that the only truly favorable responses occur in subjects who have been mistakenly diagnosed with IPF when they really have disorders like BOOP, hypersensitivity pneumonitis, chronic eosinophilic pneumonia, pulmonary capillaritis, and so on.[241] Certainly, there are interstitial disorders which may mimic IPF and respond better to treatment, but some true subsets of IPF (DIP/RB-ILD and NSIP) clearly show a positive response to therapy as well.[6,15,28,84] Unfortunately, most patients with IPF demonstrate a UIP lesion histologically. It is true that no randomized, placebo-controlled trials exist to prove that treatment is effective (or ineffective) in patients with UIP. Still, as many as 25 percent of patients with UIP will objectively improve on treatment, and the condition of many others appears to stabilize.[1,6,12,45] It is simply not certain that this is a result of the pharmacologic intervention.

One glaring difference between the more responsive disorders listed above and UIP is that the former lesions are all temporally homogeneous. This suggests that the initiating factor more or less uniformly injured involved portions of the lung over a relatively brief time period. Because of this, these patients tend to present earlier in their disease course. This is different from UIP where the temporal variegation suggests a patchy, ongoing injury which affects the lungs piecemeal.

If treatment is to be successful in a patient with UIP, early intervention is a must. Unfortunately, symptoms like dyspnea are frequently dismissed as "normal" in aging and deconditioned individuals, and this promotes a delay in appropriate diagnostic testing. Another major problem in IPF is the practice of witholding treatment until clear evidence of disease progression is noted.[242,243] Mildly symptomatic patients with interstitial disease on chest films are commonly observed for months or years as deficits slowly accumulate. Moreover, some patients may not even consider themselves "limited" until their lung capacity is 60 to 70 percent of predicted or less, by which time the fibrotic process is well established. If the diagnosis is correct, it is safe to assume that the process will worsen in almost everyone without treatment. Disease progression is insidious in most (especially in UIP), and apparent stability in symptoms, radiographs and pulmonary function studies may belie real worsening of parenchymal involvement. Since mature fibrosis and architectural distortion are not reversible, and cellularity is not typically prominent in UIP patients, stabilization of the disease process has to be considered the primary treatment goal. Put another way, if someone has severe deficits related to UIP when treatment is initiated, that person will likely have severe

deficits after treatment is complete. Unfortunately, this is commonly interpreted as a lack of response to the prescribed therapy. It is this misunderstanding which feeds the already prevalent nihilism among physicians regarding the institution of potentially hazardous treatments in IPF.[244]

Corticosteroids are by far the most commonly prescribed agents in the treatment of IPF.[2,4] The mechanisms of action are complex and incompletely understood. Alveolar macrophages express steroid receptors, for example, but glucocorticoid therapy does not modulate their release of fibronectin or alveolar macrophage derived growth factor.[245] On the other hand, steroids are believed to inhibit the effects of TGF-β on the type I collagen promoter.[87] Steroids inhibit the synthesis of virtually all known cytokines and decrease immune complex formation while affecting leukocyte and fibroblast function and trafficking.[246,247] Many of these effects may be mediated by inhibition of nuclear factor kappa B (NF-kappa B) expression through induction of the I kappa B alpha inhibitory protein.[248,249,250] NF-kappa B is an activator of numerous cytokine genes and helps mediate the proinflammatory effects of IL-1 and TNF.

The standard protocol for IPF treatment consists of initially high dose prednisone (1-1.5 mg/kg/d, not to exceed 100 mg/d) for 8 to 12 weeks. This is then tapered by half for an additional 12 weeks before the dosage is reduced to 0.25 mg/kg/d. If no response is obtained by three to six months, or if side effects are limiting, the treatment may be discontinued or changed. However, it requires at least three months to determine whether a patient will have objective improvement. Certain interstitial pneumonias like NSIP, DIP/RB-ILD, BOOP and hypersensitivity pneumonitis tend to be steroid responsive, and it is uncommon to require second-line agents in these disorders. This is not true for UIP, however, and untoward effects are frequent. These may include impaired glycemic control, hypertension, weight gain, bone demineralization, cushingoid appearance, psychiatric disturbances, cataracts and glaucoma.[251,252,253]

When patients progress on steroids or the treatment is poorly tolerated, a cytotoxic drug is often added.[3,43,254,255,256,257,258] These include cyclophosphamide and azathioprine. More and more, in fact, these agents are being used as first line drugs in combination with low dose steroids to avoid the severe side effect profile of high dose steroids. Cyclophosphamide is an alkylating agent that lowers lymphocyte counts and affects lymphocyte function. This is typically initiated at 25-50 mg/d and increased by 25 mg increments every one to two weeks (maximum dose 150-200 mg/d) provided that the total leukocyte count remains above 3500 cells/mm^3 and gastrointestinal tolerance is acceptable. The medication should be taken in the morning, and generous intake of fluids with frequent bladder emptying is encouraged to avoid hemorrhagic cystitis. Azathioprine is a purine analog that affects RNA and DNA synthesis. It has effects on both the cellular and humoral limbs of the immune system. It tends to be well tolerated by most patients and is dosed similarly to cyclophosphamide (target 2-2.5 mg/kg/d, not to exceed 200 mg).

Only two controlled treatment trials have ever been performed in IPF.[3,255] One compared prednisolone alone versus a combination of cyclophosphamide and low dose prednisolone, while the other compared prednisone plus placebo versus full dose prednisone and azathioprine. All things considered, there were no statistically significant differences in survival or lung function noted between the different study groups.

Colchicine is a more recent addition to the IPF treatment armamentarium.[259,260] It possesses a broad range of antifibrotic and antiinflammatory properties which may prove useful in this disease.[261] Colchicine inhibits fibroblast proliferation and total collagen secretion at concentrations that are readily obtainable *in vivo*.[261] Unlike steroids, colchicine has also been shown to suppress alveolar macrophage derived growth factor and fibronectin release.[262,263] Colchicine inhibited bFGF-stimulated collagen synthesis in a human lung fibroblast cell line as well.[261] It has even been noted to increase collagenase production, and to protect against bleomycin induced fibrosis when given concurrent to the injury.[264,265] It inhibits lymphocyte proliferation *in vitro*, and has well established effects on neutrophil migration and phagocytosis.[263]

Peters and coworkers retrospectively evaluated 23 patients who had mostly received steroids previously, but either progressed or suffered significant side effects.[259] Five (22%) improved, nine (39%) remained stable, and nine (39%) worsened over an average follow-up period of 22 months. Douglas and colleagues conducted another retrospective study comparing colchicine to a historical control group treated with prednisone.[260] No statistically significant difference was noted in the rate of progression of physiologic restriction or diffusion abnormalities, although there was a trend toward more rapid decline in the steroid treated patients. Colchicine was well tolerated, while significant complications were noted in 12 of 22 patients treated with prednisone. The most serious complication of colchicine therapy, a drug-induced myopathy, is fortunately quite rare. It seems to be more common, though, in individuals with renal insufficiency.[266]

Novel Approaches to the Treatment of IPF

A better appreciation of the pathobiology of pulmonary fibrosis has produced great interest in the development and application of new treatment strategies for IPF.[87,243,267,268,269] Ultimately, control of this disease may require combinations of drugs which address the multifaceted aspects of lung injury, inflammation and repair (Table 5). Perhaps interfering with key cytokines or adhesion molecules will assuage inflammatory cell trafficking in the lung. Soluble receptors or receptor antagonists to proinflammatory cytokines like IL-1 or TNF-α could be administered, or direct antiinflammatory and antifibrotic cytokines (e.g., IFN-γ, IFN-β) could be tried. Without question, more attention will be focused on measures to control fibroblast proliferation, matrix deposition and matrix remodelling. Perfenidone, for instance, blocks the *in vitro* effects of profibrotic cytokines and growth factors on human lung fibroblasts, and reduces bleomycin-induced pulmonary fibrosis in hamsters.[267,270,271] Studies in humans are currently underway. It has also been shown that antibodies to TGF-β will decrease scar formation after dermal incisions without impairing wound healing, and reduce connective tissue accumulation after bleomycin injury.[130,272] Of potential interest also is a natural matrix proteoglycan called decorin which binds to and inactivates TGF-β.[87] Decorin has been shown to protect against scarring and impaired kidney function in experimental glomerulonephritis, and could possibly be delivered locally in IPF patients.[273] Alternatively, other TGF-β inhibitors or receptor antagonists could be developed, or its signal transduction pathway could be attacked.[87]

Table 5
Novel Treatment Strategies in IPF

Blockade of proinflammatory/profibrotic cytokines
Soluble receptors
Receptor antagonists
Perfenidone
Administration of antifibrotic cytokines
Interferon-β, interferon-γ
Inhibition of collagen synthesis, deposition, cross-linking
Lysyl oxidase inhibitors
Modification of arachidonic acid metabolites
PGE2
5-lipoxygenase inhibitors
Leukotriene receptor antagonists
Antioxidant administration
Glutathione
N-acetylcysteine
Adhesion molecule interference
CD44 blockade

Directly inhibiting collagen synthesis, deposition or cross-linking offers additional possibilities.[87,274] Lysyl oxidase is an important enzyme which catalyzes the formation of intermolecular bridges between collagen fibers making them resistant to degradation by proteases.[275,276] D-penicillamine is a lysyl oxidase inhibitor, but its use is limited by frequent toxicity.[277] Other inhibitors with better risk-benefit profiles might prove to be useful in IPF.

With regard to arachidonic acid metabolites, PGE2 has demonstrated potentially important anti-fibrogenic effects *in vitro*.[278,279] Also, a potential role exists for the use of 5-lipoxygenase inhibitors or

leukotriene receptor antagonists in IPF, since certain leukotrienes may mediate some of the inflammatory and fibrotic events in this disease.[147]

Therapies designed to reduce oxidative stress in the lungs may be an important adjunctive consideration in a more global approach to minimizing tissue injury in pulmonary fibrosis. Glutathione, which is depleted in IPF, is largely responsible for protecting the lung against oxidant injury.[280,281] It may, however, be possible to restore the antioxidant balance via oral, intravenous or aerosolized replacement of glutathione or N-acetylcysteine.[282,283,284,285]

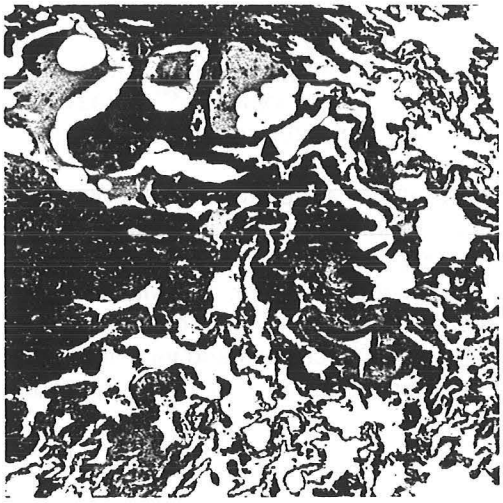
Fibroblastic proliferation in IPF could be approached from other new perspectives. We know from experience with the fibroproliferative stage of ARDS that extensive, organized alveolar exudates can resolve without substantial long term pulmonary dysfunction.[286,287] The cell surface adhesion molecule CD44 is known to mediate fibroblast migration and invasion of the provisional fibrin matrix within the alveolar space.[288] Interrupting CD44 function with a monoclonal antibody has been shown *in vitro* not simply to inhibit motility, but to induce apoptosis in fibroblasts.[289] Further insight into CD44 activities and inhibition may afford new methods of controlling an excessive fibrotic response that threatens to produce organ dysfunction.

Summary

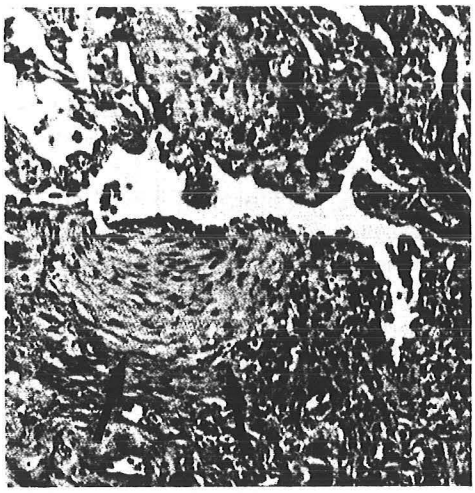
Idiopathic pulmonary fibrosis is a complex and heterogeneous disease. Practice trends indicate that IPF is largely considered to be a clinical diagnosis that can be established on the basis of symptoms, physical exam, plain chest films and HRCT. In some cases an empirical diagnosis utilizing these data is appropriate, and in others it is not. Much information can be gained from a skillfully interpreted surgical lung biopsy. The most common histologic manifestation of IPF is usual interstitial pneumonia. Of all the IPF variants, UIP is the least likely to respond to treatment. Still, more than half of these patients will improve or stabilize when appropriate therapy is initiated. The potential toxicities associated with currently recommended protocols and the lack of impressive improvement in most subjects on therapy has led to fewer patients being treated once the disease is recognized. Furthermore, treatment is commonly withheld until the patient becomes "sufficiently impaired" to warrant intervention with immunosuppressive agents. By the time this occurs, it is usually too late for antiinflammatory drugs to produce significant regression of the parenchymal disease. The earlier treatment is initiated, the better the long-term outcome is likely to be. Novel treatment strategies are currently being developed which may offer more hope for successful intervention in patients with more advanced fibrotic disease. Small numbers of IPF patients in any one area and the intrinsic heterogeneity of this disease have been the major stumbling blocks in the organization of large-scale treatment protocols to date. However, the first multi-center trials to evaluate the efficacy of new therapies are now underway.

Appendix 1
Pathologic Patterns of the Idiopathic Interstitial Pneumonias

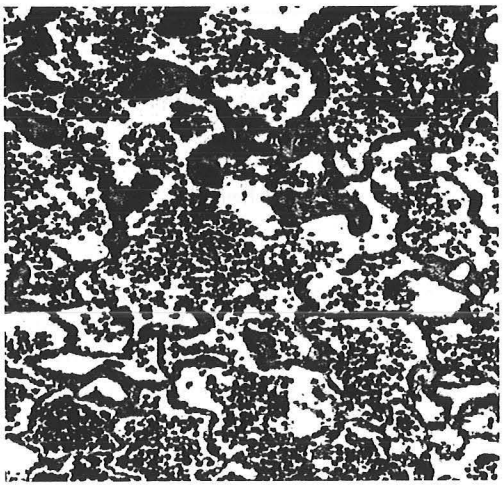
A



B

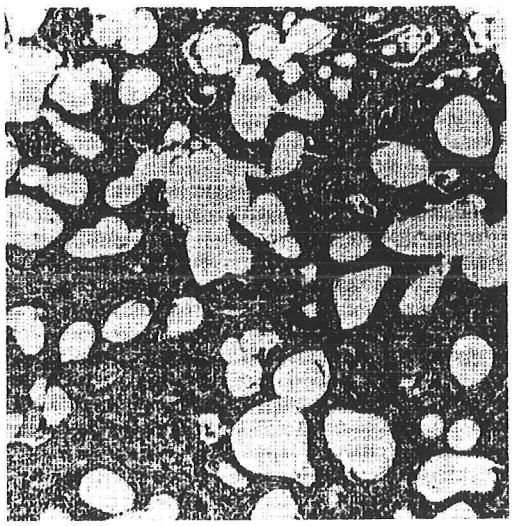


C



D

E



A. Usual interstitial pneumonia with prominent temporal heterogeneity B. Fibroblastic focus in a patient with UIP C. Desquamative interstitial pneumonia. Note uniform interstitial thickening with mild to moderate fibrosis and diffuse intra-alveolar macrophage accumulation
D. Nonspecific interstitial pneumonia. Note uniform thickening of alveolar septae by a predominantly cellular infiltrate consisting mostly of mononuclear cells E. Acute interstitial pneumonia. Marked interstitial thickening due to a temporally uniform influx of fibroblasts with some chronic inflammatory cells. Although the degree of septal thickening and the size of the airspaces varies, the component cellular infiltrate remains constant throughout the specimen

References

[1] Turner-Warwick M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: clinical features and their influence on survival; Thorax 1980; 35: 171-180

[2] King TE, Jr. Idiopathic pulmonary fibrosis; In: *Interstitial Lung Disease*, second edition. Schwarz MI and King TE, Jr., Eds; Mosby Year Book, St. Louis, 1993

[3] Raghu G, Depaso WJ, Cain K, et al. Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial; Am Rev Respir Dis 1991; 144: 291-296

[4] Johnston IDA, Prescott RJ, Chalmers JC, Rudd RM. British Thoracic Society study of cryptogenic fibrosing alveolitis: current presentation and initial management; Thorax 1997; 52: 38-44

[5] Crystal RG, Fulmer JD, Roberts WC, et al. Idiopathic pulmonary fibrosis: clinical, histologic, radiographic, physiologic, scintigraphic, cytologic, and biochemical aspects. Ann Intern Med 1976; 85: 769-788

[6] Carrington CB, Gaensler EA, Coutu RE, et al. Natural history and treated course of usual and desquamative interstitial pneumonia. N Engl J Med 1978; 298: 801-809

[7] Iwai K, Mori T, Yameda N, et al. Idiopathic pulmonary fibrosis: epidemiologic approaches to occupational exposure. Am J Respir Crit Care Med 1994; 150: 670-675

[8] Stack BHR, Choo-Kang YFJ, Heard BE. The prognosis of cryptogenic fibrosing alveolitis. Thorax 1972; 27: 535-542

[9] Johnston I, Britton J, Kinnear W, Logan R. Rising mortality from cryptogenic fibrosing alveolitis. Br Med J 1990; 301: 1017-1021

[10] Mannino DM, Etzel RA, Parrish RG. Pulmonary fibrosis deaths in the United States, 1979-1991. Am J Respir Crit Care Med 1996; 153: 1548-1552

[11] Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. Am J Respir Crit Care Med 1994; 150: 967-972

[12] Schwartz DA, Helmers RA, Galvin JR, et al. Determinants of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1994; 149: 450-454

[13] Crystal RG, Bitterman PB, Rennard AJ, et al. Interstitial lung diseases of unknown cause: disorders characterized by chronic inflammation of the lower respiratory tract. N Engl J Med 1984; 310: 154-166

[14] Scott J, Johnston I, Britton J. What causes cryptogenic fibrosing alveolitis? A case-control study of environmental exposure to dust. Br Med J 1990; 301: 1015-1017

[15] Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998; 157: 199-203

[16] Katzenstein AL, Myers JL, Prophet WD, et al. Bronchiolitis obliterans and usual interstitial pneumonia: a comparative clinicopathologic study; Am J Surg Pathol 1986; 10: 373-381

[17] Guerry-Force ML, Muller NL, Wright JL, et al. A comparison of bronchiolitis obliterans with organizing pneumonia, usual interstitial pneumonia, and small airways disease. Am Rev Respir Dis 1987; 135: 705-712

[18] Gottlieb AJ, Spiera H, Teinstein AS, Siltzbach LE. Serologic factors in idiopathic diffuse interstitial pulmonary fibrosis. Am J Med 1965; 39: 405-410

[19] Martinel Y, Haslam PL, Turner-Warwick M. Clinical significance of circulating immune complexes in "lone" cryptogenic fibrosing alveolitis and those with associated connective tissue disorders. Clin Allergy 1984; 14: 491-497

[20] Driesen RB, Schwarz MI, Theofilopoulos AN, Standford RE. Circulating immune complexes in the idiopathic interstitial pneumonias. N Engl J Med 1978; 298: 353-357

[21] Orens JB, Kazerooni DA, Martinez FJ, et al. The sensitivity of high-resolution CT in detecting idiopathic pulmonary fibrosis proved by open lung biopsy: a prospective study. Chest 1995; 108: 109-113

[22] Erbes R, Schaberg T, Loddenkemper R. Lung function tests in patients with idiopathic pulmonary fibrosis: are they helpful for predicting outcome? Chest 1997; 111: 51-57

[23] Wells AU, Rubens MB, du Bois RM, Hansell DM. Functional impairment in fibrosing alveolitis: relationship to reversible disease on thin section computed tomography. Eur Respir J 1997; 10: 280-285

[24] Cherniack RM, Colby TV, Flint A, et al. Correlation of structure and function in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1995; 151: 1180-1188

[25] Panos RJ, Mortenson RL, Niccoli SA, King TE, Jr. Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment. Am J Med 1990; 88: 396-404

[26] Kondoh Y, Taniguchi H, Kawabat Y, et al. Acute exacerbation in idiopathic pulmonary fibrosis. Chest 1993; 103: 1808-1812

[27] Katzenstein AL. Idiopathic interstitial pneumonia. In: *Katzenstein and Askin's Surgical Pathology of Non-Neoplastic Lung Disease*, 3rd ed; W.B. Saunders Company 1997, Philadelphia

[28] Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. Am J Respir Crit Care Med 1998; 157: 1301-1315

[29] Macadamias HP, Rosado-de-Christenson ML, Wehunt WD, Fishback NF. The alphabet soup revisited: the chronic interstitial pneumonias in the 1990s. RadioGraphics 1996; 16: 1009-1033

[30] Colby TV, Carrington CB. Interstitial lung disease. In: Thurlbeck WM, Churg AM, eds. *Pathology of the Lung*, 2nd edition; Thieme Medical 1995, New York

[31] Muller NL, Colby TV. Idiopathic interstitial pneumonias: high-resolution CT and histologic findings. RadioGraphics 1997; 17: 1016-1022

[32] Rosenow EC III, Myers JL, Swenson SJ, Pisani RJ. Drug induced pulmonary disease, an update. Chest 1992; 102: 239-250

[33] Muller NL, Staples CA, Miller RR, et al. Disease activity in idiopathic pulmonary fibrosis: CT and pathologic correlation. Radiology 1987; 165: 731-734

[34] Staples CA, Muller NL, Vedal S, et al. Usual interstitial pneumonia: correlation of CT with clinical, functional, and radiologic findings. Radiology 1987; 162: 377-381

[35] Swensen SJ, Aughenbaugh GL, Myers JL. Diffuse lung disease: diagnostic accuracy of CT in patients undergoing surgical biopsy of the lung. Radiology 1997; 205: 229-234

[36] Wagner JD, Stahler C, Knox S, et al. Clinical utility of open lung biopsy for undiagnosed pulmonary infiltrates. Am J Surg 1992; 164:104-108
[37] Hartman DL, Mylet D, Gaither JG, et al. Comparison of thoracoscopic lung biopsy with open lung biopsy in diffuse interstitial lung disorders. Am Rev Respir Dis 1992; 145: A750
[38] Venn GE, Kay PH, Midwood CJ, Goldstraw PJ. Open biopsy in patients with diffuse pulmonary shadowing. Thorax 1985; 40: 931-935
[39] Smith CM, Holbrook T. Utilization of the transbronchial biopsy and open lung biopsy for tissue to establish the diagnosis of idiopathic pulmonary fibrosis. Am Rev Respir Dis 1990; 141: A62
[40] Raghu G. Interstitial lung disease: a diagnostic approach. Are CT scan and lung biopsy indicated in every patient? Am J Respir Crit Care Med 1995; 151: 909-914
[41] Raghu G. Idiopathic pulmonary fibrosis: a rational clinical approach. Chest 1987; 92: 148-154
[42] Wright PH, Heard BE, Steel SJ, Turner-Warwick M. Cryptogenic fibrosing alveolitis: assessment by graded trephine lung biopsy histology compared with clinical, radiographic, and physiological features. Br J Dis Chest 1981; 75: 61-70
[43] Winterbauer RH, Hammar SP, Hallman KO, et al. Diffuse interstitial pneumonitis: clinicopathologic correlations in 20 patients treated with prednisone/azathioprine. Am J Med 1978; 65: 661-672
[44] Tukianen P, Taskinen E, Holsti P, et al. Prognosis of cryptogenic fibrosing alveolitis. Thorax 1983; 38: 349-355
[45] Gay SE, Kazerooni EA, Toews GB, et al. Idiopathic pulmonary fibrosis: predicting response to therapy and survival. Am J Respir Crit Care Med 1998; 157: 1063-1072
[46] Liebow AA. Definition and classification of interstitial pneumonias in human pathology. In: *Alveolar Interstitium of the Lung*, Paris FB, Georges R, Eds. Karger, Basel, New York 1975
[47] Katzenstein AL. Primary lymphoid lung lesions. In: *Katzenstein and Askin's Surgical Pathology of Non-Neoplastic Lung Disease*, 3rd edition. W.B. Saunders Company, Philadelphia 1997 pp.223-246
[48] Gibbs AR, Seal RME. Primary lymphoproliferative conditions of the lung. Thorax 1978; 33: 140-152
[49] Koss M, Hochholzer L, Langloss J, et al. Lymphoid interstitial pneumonia: clinicopathological and immunopathological findings in 18 cases. Pathology 1987; 19: 178-185
[50] Travis WD, Fox CH, Devaney KO, et al. Lymphoid pneumonitis in 50 adult patients infected with the human immunodeficiency virus: lymphocytic interstitial pneumonitis versus nonspecific interstitial pneumonitis. Hum Pathol 1992; 23: 529-541
[51] Daroca PJ, George WJ. Giant cell interstitial pneumonia. South Med J 1991; 84: 257-263
[52] Ohori NP, Sciurba FC, Owens GR, et al. Giant-cell interstitial pneumonia and hard-metal pneumoconiosis. A clinicopathologic study of four cases and review of the literature. Am J Surg Pathol 1989; 13: 581-587
[53] Alasaly K, Muller N, Ostrow DN, et al. Cryptogenic organizing pneumonia: a report of 25 cases and a review of the literature. Medicine 1995; 74: 201-211
[54] Lohr RH, Boland BJ, Douglas WW, et al. Organizing pneumonia: features and prognosis of cryptogenic, secondary, and focal variants. Arch Intern Med 1997; 157: 1323-1329
[55] Pratt D, Schwarz M, May J, Dreisin R. Rapidly fatal pulmonary fibrosis: the accelerated variant of interstitial pneumonitis. Thorax 1979; 34: 587-593
[56] Hamman L, Rich AR. Acute diffuse interstitial fibrosis of the lungs. Bull Johns Hopkins Hosp 1944; 74: 177-212
[57] Agusti C, Saubet A, Roca J, et al. Interstitial pulmonary fibrosis with and without associated collagen vascular disease: results of a two-year follow up. Thorax 1992; 47: 1035-1040
[58] Wells AU, Cullinan P, Hansell DM, et al. Fibrosing alveolitis associated with systemic sclerosis has a better prognosis than lone cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 1994; 149: 1583-1590
[59] Yousem SA, Colby TV, Carrington CB. Lung biopsy in rheumatoid arthritis. Am Rev Resp Dis 1985; 131: 770-777
[60] Crouch E. Pathobiology of pulmonary fibrosis. Am J Physiol 1990; 259: L159-L184
[61] McDonald JA, Kuhn C III. Fibroblasts and collagen deposition in interstitial lung disease. In: *Interstitial Lung Disease*, 2nd edition; Schwarz MI, King TE Jr., eds. Mosby Year Book, St. Louis, 1993
[62] Kuhn C and McDonald JA. The role of the myofibroblast in idiopathic pulmonary fibrosis. Am J Pathol 1991; 138: 1257-1265
[63] Hogg JC. Chronic interstitial lung disease of unknown cause: a new classification based on pathogenesis. AJR 1991; 156: 225-233
[64] McDonald JA. Idiopathic pulmonary fibrosis: a paradigm for lung injury and repair. Chest 1991; 99: 87S-93S
[65] Sage H, Farin FM, Striker GE, Fisher AB. Granular pneumocytes in primary culture secrete several major components of the extracellular matrix. Biochemistry 1983; 22: 2148-2155
[66] Kuhn C, Boldt J, King TE Jr., et al. An immunohistochemical study of architectural remodeling and connective tissue synthesis in pulmonary fibrosis. Am Rev Respir Dis 1989; 1693-1703
[67] Myers J, Katzenstein AL. Epithelial necrosis and alveolar collapse in the pathogenesis of usual interstitial pneumonia. Chest 1988; 94: 1309-1311
[68] Burkhardt A. Alveolitis and collapse in the pathogenesis of pulmonary fibrosis. Am Rev Respir Dis 1989; 140: 513-524
[69] Liebow AA, Steer A, Billingsley JG. Desquamative interstitial pneumonia. Am J Med 1965; 39: 369-397
[70] Hunninghake GW, Fauci AS. Pulmonary involvement in the collagen vascular diseases. Am Rev Respir Dis 1979; 119: 471-503
[71] Farr GH, Harley RA, Hennigar GR. Desquamative interstitial pneumonia: an electron microscopic study. Am J Pathol 1970; 60: 347-361
[72] Fromm GB, Dunn LJ, Harris JO. Desquamative interstitial pneumonitis: characterization of free intraalveolar cells. Chest 1980; 77: 552-554
[73] Hartman TE, Primack SL, Swenson SJ, et al. Desquamative interstitial pneumonia: thin-section CT findings in 22 patients. Radiology 1993; 187: 787-790
[74] Niewoehner DE, Kleinerman J, Rice DB. Pathologic changes in the peripheral airways of young cigarette smokers. N Engl J Med 1974; 291: 755-758
[75] Myers JL, Veal CF, Shin MS, Katzenstein AA. Respiratory bronchiolitis causing interstitial lung disease: a clinicopathologic study of six cases. Am Rev Respir Dis 1987; 135: 880-884
[76] Yousem SA, Colby TV, Gaensler EA. Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. Mayo Clin Proc 1989; 64: 1373-1380

[77] Bedrossian CWM, Kuhn C III, Luna MA, et al. Desquamative interstitial pneumonia-like reaction accompanying pulmonary lesions. Chest 1977; 72: 166-169
[78] Katzenstein AA, Myers JL, Mazur MT. Acute interstitial pneumonia: a clinicopathologic, ultrastructural, and cell kinetic study. Am J Surg Pathol 1986; 10: 256-267
[79] Olson J, Colby TV, Elliot CG. Hamman-Rich syndrome revisited. Mayo Clin Proc 1990; 65: 1538-1548
[80] Primack SL, Hartman TE, Ikezoe J, et al. Acute interstitial pneumonia: radiographic and CT findings in nine patients. Radiology 1993; 188: 817-820
[81] Katzenstein AA. Pathogenesis of "fibrosis" in interstitial pneumonia: an electron microscopic study. Hum Pathol 1985; 16: 1015-1024
[82] Amato MBP, Barbas CSV, Medeiros DM, et al. Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome: a prospective randomized study on mechanical ventilation. Am J Respir Crit Care Med 1995; 152: 1835-1846
[83] Marini JJ. Pressure-targeted, lung-protective ventilatory support in acute lung injury. Chest 1994; 105: 109S-115S
[84] Katzenstein AL, Fiorelli RF. Nonspecific interstitial pneumonia/fibrosis: histologic features and clinical significance. Am J Surg Pathol 1994; 18: 136-147
[85] Park JS, Lee KS, Kim JS, et al. Nonspecific interstitial pneumonia with fibrosis: radiographic and CT findings in seven patients. Radiology 1995; 195: 645-648
[86] Rochester CL, Elias JA. Cytokines and cytokine networking in the pathogenesis of interstitial and fibrotic lung disorders. Semin Respir Med 1993; 14: 389-416
[87] Franklin TJ. Current approaches to the therapy of fibrotic diseases. Biochem Pharmacol 1995; 49: 267-273
[88] Zhang Y, Lee TC, Guillemin B, et al. Enhanced IL-1β and Tumor Necrosis Factor-α release and messenger RNA expression in macrophages from idiopathic pulmonary fibrosis or after asbestos exposure. J Immunol 1993; 150: 4188-4196
[89] Shaw RJ. The role of lung macrophages at the interface between chronic inflammation and fibrosis. Respir Med 1991; 85: 267-273
[90] Gauldie J, Jordana M, Cox G. Cytokines and pulmonary fibrosis. Thorax 1993; 48: 931-935
[91] Strunk RC, Eidlen DM, Mason RJ. Pulmonary alveolar type II epithelial cells synthesize and secret proteins of the classical and alternative complement pathways. J Clin Invest 1988; 81: 1419-1426
[92] Cantin AM, North SL, Fells GA, et al. Oxidant-mediated epithelial cell injury in idiopathic pulmonary fibrosis. J Clin Invest 1987; 79: 1665-1673
[93] Borzi RM, Grigolo B, Meliconi R, et al. Elevated serum superoxide dismutase levels correlate with disease severity and neutrophil degranulation in idiopathic pulmonary fibrosis. Clin Sci 1993; 85: 353-359
[94] Idell S, Gonzalez KK, MacArthur CK, et al. Bronchoalveolar lavage procoagulant activity in bleomycin-induced lung injury in marmosets. Am Rev Respir Dis 1987; 136: 124-133
[95] Idell S, James KK, Levin EG, et al. Local abnormalities in coagulation and fibrinolytic pathways predispose to alveolar fibrin deposition in the adult respiratory distress syndrome. J Clin Invest 1989; 84: 695-705
[96] Laiho M, Saksela O, Keski-Oja J. Transforming growth factor-β induction of type-1 plasminogen activator inhibitor. J Biol Chem 1987; 262: 17467-17474
[97] McDonald JA. The yin and yang of fibrin in the airways. N Engl J Med 1990; 322: 929-931
[98] Swiderski RE, Dencoff JE, Floerchinger CS, et al. Differential expression of extracellular matrix remodeling genes in a murine model of bleomycin induced pulmonary fibrosis. Am J Pathol 1998; 152: 821-828
[99] Chapman HA, Allen CL, Stone OL. Abnormalities in pathways of alveolar fibrin turnover among patients with interstitial lung disease. Am Rev Respir Dis 1986; 133: 437-443
[100] Kelley J. Cytokines of the lung. Am Rev Respir Dis 1990; 141: 765-788
[101] Raines EW, Dower SK, Ross R. Interleukin-1 mitogenic activity for fibroblasts and smooth muscle cells is due to PDGF-AA. Science 1989; 243: 393-396
[102] Paulsson Y, Austgulen R, Hofsli E, et al. Tumor necrosis factor-induced expression of platelet-derived growth factor A-chain messenger RNA in fibroblasts. Exp Cell Res 1989; 180: 490-496
[103] Elias JA. Tumor necrosis factor interacts with interleukin-1 and interferons to inhibit fibroblast proliferation via fibroblast prostaglandin-dependent and independent mechanisms. Am Rev Respir Dis 1988; 138: 652-658
[104] Khalil N, O'Connor R, Unruh H, et al. Increased production and immunohistochemical localization of transforming growth factor-beta (TGF-β) in idiopathic pulmonary fibrosis. Am J Respir Cell Mol Biol 1990; 5: 155-162
[105] Khalil N, O'Connor RN, Flanders KC, Unruh H. TGF-β1, but not TGF-β2 or TGF-β3, is differentially present in epithelial cells of advanced pulmonary fibrosis: an immunohistochemical study. Am J Respir Cell Mol Biol 1996; 14: 131-138
[106] Broekelmann TJ, Limper AH, Colby TV, McDonald JA. Transforming growth factor-β1 is present at sites of extracellular matrix gene expression I human pulmonary fibrosis. Proc Natl Acad Sci USA 1991; 88: 6642-6646
[107] Antoniades HN, Bravo MA, Avila RE, et al. Platelet-derived growth factor in idiopathic pulmonary fibrosis. J Clin Invest 1990; 86: 1055-1064
[108] Inoue Y, King TE Jr., Tinkle SS, et al. Human mast cell basic fibroblast growth factor in pulmonary fibrotic disorders. Am J Pathol 1996; 149: 2037-2054
[109] Martinet YW, Rom N, Grotendorst GR, et al. Exaggerated spontaneous release of platelet-derived growth factor by alveolar macrophages of patients with idiopathic pulmonary fibrosis. N Engl J Med 1987; 317: 202-209
[110] Gospodarowicz D, Ferrara N, Schweigerer L, Neufeld G. Structural characterization and biologic functions of fibroblast growth factor. Endocr Rev 1987; 8: 95-114
[111] Shaw RJ, Benedict SH, Clark RAF, King TE Jr. Pathogenesis of pulmonary fibrosis in interstitial lung disease: alveolar macrophage PDGF (B) gene activation and upregulation by interferon gamma. Am Rev Respir Dis 1991; 143: 167-173
[112] Hojo S, Fujita J, Yoshinouchi T, et al. Hepatocyte growth factor and neutrophil elastase in IPF. Respir Med 1997; 91: 511-516
[113] Aston C, Jagirdar J, Lee TC, et al. Enhanced insulin-like growth factor molecules in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1995; 151: 1597-1603
[114] Uguccioni M, Pulsatelli L, Grigolo B, et al. Endothelin-1 in idiopathic pulmonary fibrosis. J Clin Pathol 1995; 48: 330-334
[115] Bobik A, Grooms A, Millar JA, et al. Growth factor activity of endothelin on vascular smooth muscle. Am J Physiol 1990; 258: 408-415

[116] Saleh D, Furukawa K, Tsao M, et al. Elevated expression of endothelin-1 and endothelin-converting enzyme-1 in idiopathic pulmonary fibrosis: possible involvement of proinflammatory cytokines. Am J Respir Cell Mol Biol 1997; 16: 187-193
[117] Mutsaers SE, Foster ML, Chambers RC, et al. Increased endothelin-1 and its localization during the development of bleomycin-induced pulmonary fibrosis in rats. Am J Respir Cell Mol Biol 1998; 18: 611-619
[118] Massauge J. The transforming growth factor family. Annu Rev Cell Biol 1990; 6: 597-641
[119] Raghu G, Masta S, Meyers D, Narayanan AS. Collagen synthesis by normal and fibrotic human lung fibroblasts and the effect of transforming growth factor-β. Am Rev Respir Dis 1989; 140: 95-100
[120] Hoyt DG, Lazo JS. Alterations in pulmonary mRNA encoding procollagens, fibronectin and transforming growth factor-β precede bleomycin-induced pulmonary fibrosis in mice. J Pharmacol Exp Ther 1988; 246: 765-771
[121] Heine UI, Munoz EF, Flanders KC, et al. Colocalization of TGF-β1 and collagen I and III, fibronectin and glycosaminoglycans during lung branching morphogenesis. Development 1990; 109: 29-36
[122] Raghow R. Role of transforming growth factor-β in repair and fibrosis. Chest 1991; 99: 61S-65S
[123] Wahl SM, Hunt DA, Wakefield LM, et al. Transforming growth factor type β induces monocyte chemotaxis and growth factor production. Proc Natl Acad Sci USA 1987; 84: 5788-5792
[124] Fine A, Goldstein RH. The effect of transforming growth factor-β on cell proliferation and collagen formation by lung fibroblasts. J Biol Chem 1987; 262: 3897-3902
[125] McCartney-Francis N, Mizel D, Wong H, et al. TGF-β regulates production of growth factors and TGF-β by human peripheral blood monocytes. Growth Factors 1990; 4: 27-35
[126] Ignotz RA, Massague J. Transforming growth factor-beta stimulates the expression of fibronectin and collagen and their incorporation into the extracellular matrix. J Biol Chem 1986; 261: 4337-4345
[127] Montesano R, Orci L. Transforming growth factor β stimulates collagen-matrix contraction by fibroblasts: implications for wound healing. Proc Natl Acad Sci USA 1988; 85: 4894-4897
[128] Roberts AB, Sporn MB, Assoian RK. Transforming growth factor type beta: rapid induction of fibrosis and angiogenesis in vivo and stimulation of collagen formation in vitro. Proc Natl Acad Sci USA 1986; 83: 4167-4171
[129] Kelley J. Transforming growth factor-β. In: *Cytokines of the Lung.* J Kelley, ed. Marcel Dekker Inc., New York 1993
[130] Giri SN, Hyde DM, Hollinger MA. Effect of antibody to transforming growth factor-β on bleomycin induced accumulation of lung collagen in mice. Thorax 1993; 48: 959-966
[131] Sime PJ, Xing Z, Graham FL, et al. Adenovector-mediated gene transfer of active transforming growth factor-β1 induces prolonged severe fibrosis in rat lung. J Clin Invest 1997; 100: 768-776
[132] Yoshida M, Sakuma J, Hayashi S, et al. A histologically distinctive interstitial pneumonia induced by overexpression of the interleukin 6, transforming growth factor β1, or platelet derived growth factor B gene. Proc Natl Acad Sci 1995; 92: 9570-9574
[133] Korfhagen TR, Swantz RJ, Wert SE, et al. Respiratory epithelial cell expression of human transforming growth factor-α induces lung fibrosis in transgenic mice. J Clin Invest 1994; 93: 1691-1699
[134] Miyazaki Y, Araki K, Vesin C, et al. Expression of a tumor necrosis factor-α transgene in murine lung causes lymphocytic and fibrosing alveolitis. J Clin Invest 1995; 96: 250-259
[135] Wallace WAH, Ramage EA, Lamb D, Howie SEM. A type 2 (Th2-like) pattern of immune response predominates in the pulmonary interstitium of patients with cryptogenic fibrosing alveolitis (CFA). Clin Exp Immunol 1995; 101: 436-441
[136] Furuie H, Yamasaki H, Suga M, Ando M. Altered accessory cell function of alveolar macrophages: a possible mechanism for induction of Th2 secretory profile in idiopathic pulmonary fibrosis. Eur Respir J 1997; 10: 787-794
[137] Sempowski GD, Beckmann MP, Derdak S, Phipps RP. Subsets of murine lung fibroblasts express membrane-bound and soluble IL-4 receptors. J Immunol 1994; 152: 3606-3614
[138] Fiorentino DF, Bond MW, Mosmann TR. Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. J Exp Med 1989; 170: 2081-2095
[139] Duncan MR, Berman B. Gamma-interferon is the lymphokine and β-interferon is the monokine responsible for the inhibition of fibroblast collagen production and late but not early fibroblast proliferation. J Exp Med 1985; 112: 516-527
[140] Prior C, Haslam PL. In vivo and in vitro production of interferon-gamma in fibrosing interstitial lung diseases. Clin Exp Immunol 1992; 88: 280-287
[141] Rennard SI, Hunninghake GW, Bitterman PB, Crystal RG. Production of fibronectin by the human alveolar macrophage: mechanism for the recruitment of fibroblasts to sites of tissue injury in interstitial lung diseases. Proc Natl Acad Sci USA 1981; 78: 7147-7151
[142] Standiford T, Rolfe M, Kunkel S, et al. Altered production and regulation of monocyte chemoattractant protein-1 from pulmonary fibroblasts isolated from patients with idiopathic pulmonary fibrosis. Chest 1993; 103: 121S
[143] Standiford TJ, Rolfe MW, Kunkel SL, et al. Macrophage inflammatory protein-1α expression in interstitial lung disease. J Immunol 1993; 151: 2852-2863
[144] Keane MP, Staniford TJ, Strieter RM. Chemokines are important cytokines in the pathogenesis of interstitial lung disease. Eur Respir J 1997; 10: 1199-1202
[145] Smith RE, Strieter RM, Zhang K, et al. A role for C-C chemokines in fibrotic lung disease. J Leukoc Biol 1995; 57: 782-787
[146] Keane MP, Arenberg DA, Lynch JP III, et al. The CXC chemokines, IL-8 and IP-10, regulate angiogenic activity in idiopathic pulmonary fibrosis. J Immunol 1997; 159: 1437-1443
[147] Wilborn J, Bailie M, Coffey M, et al. Constitutive activation of 5-lipoxygenase in the lungs of patients with idiopathic pulmonary fibrosis. J Clin Invest 1996; 97: 1827-1836
[148] Mensing H, Czarnetzki B. Leukotriene B4 induces in vitro fibroblast chemootaxis. J Invest Dermatol 1984; 82: 9-12
[149] Phan S, McGarry B, Loeffler, Kunkel S. Binding of leukotriene C4 to rat lung fibroblasts and stimulation of collagen synthesis in vitro. Biochemistry 1988; 27: 2846-2853
[150] Baud L, Perez J, Denis M, Ardaillou R. Modulation of fibroblast proliferation by sulfidopeptide leukotrienes: effect of indomethacin. J Immunol 1987; 138: 1190-1195
[151] Phan S, McGarry B, Loeffler K, Kunkel S. Regulation of macrophage-derived fibroblast growth factor release by arachidonate metabolites. J Leukocyte Biol 1987; 42: 106-113
[152] Osborn L. Leukocyte adhesion to endothelium in inflammation. Cell 1990; 62: 3-6

[153] Harlan JM. Leukocyte-endothelial interactions. Blood 1985; 65: 513-525
[154] Nakao A, Hasegawa Y, Tsuchiya Y, Shimodata K. Expression of cell adhesion molecules in the lungs of patients with idiopathic pulmonary fibrosis. Chest 1995; 108: 233-239
[155] Van Seventer GA, Shimizu Y, Horgan KJ, et al. The LFA-1 ligand ICAM-1 provides an important costimulatory signal for T cell receptor-mediated activation of resting T cells. J Immunol 1990; 144: 4579-4586
[156] Springer RA. Adhesion receptors of the immune system. Nature 1990; 346: 425-434
[157] Komatsu T, Yamamoto M, Shimodata K, et al. Phenotypic characterization of alveolar capillary endothelial cells, alveolar epithelial cells and alveolar macrophages in patients with pulmonary fibrosis, with special reference to MHC class II antigens. Virchows Arch A 1989; 415: 79-90
[158] Brown LF, Dvorak AM, Dvorak HF. Leaky vessels, fibrin deposition, and fibrosis: a sequence of events common to solid tumors and to many other types of disease. Am Rev Respir Dis 1989; 140: 1104-1107
[159] Aniyama SK, Yamada SS, Dhen WT, Yamada KM. Analysis of fibronectin receptor function with monoclonal antibodies: roles in cell adhesion, migration, matrix assembly, and cytoskeletal organization. J Cell Biol 1989; 109: 863-875
[160] McDonald JA. Extracellular matrix assembly. Annu Rev Cell Biol 1988; 4: 183-207
[161] Svee K, White J, Vaillant P, et al. Acute lung injury fibroblast migration and invasion of a fibrin matrix is mediated by CD44. J Clin Invest 1996; 98: 1713-1727
[162] McCarthy JB, Hagen ST, Furcht LT. Human fibronectin contains distinct adhesion- and motility-promoting domains for metastatic melanoma cells. J Cell Biol 1986; 103: 179-188
[163] Clark RAF, Lanigan JM, DellaPelle P, et al. Fibronectin and fibrin provide a provisional matrix for epidermal cell migration during wound reepithelialization. J Invest Dermatol 1982; 79: 264-269
[164] Turley EA. Hyaluronan and cell locomotion. Cancer Metastasis Rev 1992; 11: 21-30
[165] Jalkanen S, Jalkanen M. Lymphocyte CD44 binds the COOH-terminal heparin-binding domain of fibronectin. J Cell Biol 1992; 116: 817-825
[166] Kotani I, Sato A, Hayakawa H, et al. Increased procoagulant and antifibrinolytic activities in the lungs of patients with idiopathic pulmonary fibrosis. Thromb Res 1995; 77: 493-504
[167] Imokawa S, Sato A, Hayakawa H, et al. Tissue factor expression and fibrin deposition in the lungs of patients with idiopathic pulmonary fibrosis and systemic sclerosis. Am J Respir Crit Care Med 1997; 156: 631-636
[168] Chapman HA, Allen CL, Stone OL. Abnormalities in pathways of alveolar fibrin turnover among patients with interstitial lung disease. Am Rev Respir Dis 1986; 133: 437-443
[169] Nemerson Y, Bach R. Tissue factor revisited. Prog Hemostasis Thromb 1982; 6: 237-261
[170] Behr J, Maier K, Krombach F, et al. Pathogenetic significance of reactive oxygen species in diffuse fibrosing alveolitis. Am Rev Respir Dis 1991; 144: 146-150
[171] Saleh D, Barnes PJ, Giaid A. Increased production of the potent oxidant peroxynitrite in the lungs of patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1997; 155: 1763-1769
[172] Behr J, Degenkolb B, Maier K, et al. Increased oxidation of extracellular glutathione by bronchoalveolar inflammatory cells in diffuse fibrosing alveolitis. Eur Respir J 1995; 8: 1286-1292
[173] Cantin AM, Hubbard RC, Crystal RG. Glutathione deficiency in the epithelial lining fluid of the lower respiratory tract in idiopathic pulmonary fibrosis. Am Rev Respir Dis 1989; 139: 370-372
[174] Hancock JT. Superoxide, hydrogen peroxide and nitric oxide as signaling molecules: their production and role in disease. Br J Biomed Sci 1997; 54: 38-46
[175] Bulkley GB. Physiology of reactive oxidant-mediated signal transduction: an overview. Biochem Soc Trans 1997; 25: 804-812
[176] Suzuki YJ, Forman HJ, Sevanian A. Oxidants as stimulators of signal transduction. Free Radic Biol Med 1997; 22: 269-285
[177] McAndrew J, Patel RP, Jo H, et al. The interplay of nitric oxide and peroxynitrite with signal transduction pathways: implications for disease. Semin Perinatol 1997; 21: 351-366
[178] Schaberg T, Rau M, Stephan H, et al. Increased number of alveolar macrophages expressing surface molecules of the CD11/CD18 family in sarcoidosis and idiopathic pulmonary fibrosis is related to the production of superoxide anions by these cells. Am Rev Respir Dis 1993; 147: 1507-1513
[179] Piquet PF, Rosen H, Vesin C, et al. Effective treatment of the pulmonary fibrosis elicited in mice by bleomycin or silica with anti-CD-11 antibodies. Am Rev Respir Dis 1993; 147: 435-441
[180] Polnovsky VA, Chen B, Henke C, et al. Role of mesenchymal cell death in lung remodeling after injury. J Clin Invest 1993; 92: 388-397
[181] Cox G, Crossley J, Xing Z. Macrophage engulfment of apoptotic neutrophils contributes to the resolution of acute pulmonary inflammation in vivo. Am J Respir Cell Mol Biol 1995; 12: 232-237
[182] Cohen JJ. Programmed cell death in the immune system. Adv Immunol 1991; 50: 55-85
[183] Hagimoto N, Kuwano K, Nomoto Y, et al. Apoptosis and expression of Fas/Fas ligand mRNA in bleomycin-induced pulmonary fibrosis in mice. Am J Respir Cell Mol Biol 1997; 16: 91-101
[184] Hagimoto N, Kuwano K, Miyazaki H, et al. Induction of apoptosis and pulmonary fibrosis in mice in response to ligation of Fas antigen. Am J Respir Cell Mol Biol 1997; 17: 272-278
[185] Woo D. Apoptosis and loss of renal tissue in polycystic kidney disease. N Engl J Med 1995; 333: 18-25
[186] Thomas SE, Andoh TF, Pichler RH, et al. Accelerated apoptosis characterizes cyclosporine-associated interstitial fibrosis. Kidney Int 1998; 53: 897-908
[187] Nagata S. Fas-induced apoptosis, and diseases caused by its abnormality. Genes to Cells 1996; 1: 873-879
[188] Galle PR. Apoptosis in liver disease. J Hepatol 1997; 27: 405-412
[189] Anonymous. Six workers die in Spanish textiles cover-up. In: *Workers' Health International Newsletter*, No. 34. Sheffield: Hazards Publications, December 1992
[190] Owens GR, Medsger TA. Systemic sclerosis secondary to occupational exposure. Am J Med 1988; 85: 114-116
[191] Billings CG, Howard P. Hypothesis: exposure to solvents may cause fibrosing alveolitis. Eur Respir J 1994; 7: 1172-1176
[192] Kennedy S, Chan-Yeung M. Taking "cryptogenic" out of fibrosing alveolitis. Lancet 1996; 347: 276-277
[193] Chan-Yeung M, Malo J. Etiologic agents in occupational asthma. Eur J Respir Dis 1994; 7: 969-980
[194] Egan JJ, Woodcock AA, Stewart JP. Viruses and idiopathic pulmonary fibrosis. Eur Respir J 1997; 10: 1433-1437

[195] Egan JJ, Stewart JP, Hasleton PS, et al. Epstein-Barr virus replication within pulmonary epithelial cells in cryptogenic fibrosing alveolitis. Thorax 1995; 50: 1234-1239
[196] Lung ML, Lam WK, So SY, et al. Evidence that the respiratory tract is a major reservoir for Epstein-Barr virus. Lancet 1985; 1(8384): 889-892
[197] Barbera JA, Hoyashi S, Hegele RG, Hogg JC. Detection of Epstein-Barr virus in LIP by in situ hybridization. Am Rev Respir Dis 1992; 145: 940-946
[198] Zhang W, Brooks L, Busson P, et al. Epstein-Barr virus latent membrane protein 1 increases HLA class II expression in an EBV-negative B-cell line. Eur J Immunol 1994; 24: 1467-1470
[199] Fujinami RS, Nelson JA, Walker L, Oldstone MA. Sequence homology and immunologic cross-reactivity of human cytomegalovirus and HLA-DR B chain: a means for graft rejection and immunosuppression. J Virol 1988; 62: 100-105
[200] Matsui R, Goldstein RH, Mihal K, et al. Type I collagen formation in rat type II alveolar cells immortalised by viral gene products. Thorax 1994; 49: 201-206
[201] Chapman JR, Charles PJ, Venables PJW, et al. Definition and clinical relevance of antibodies to nuclear ribonucleoprotein and other nuclear antigens in patients with cryptogenic fibrosing alveolitis. Am Rev Respir Dis 1984; 130: 439-443
[202] Schwarz MI, Dreisen RB, Pratt DS, Stanford RE. Immunofluorescent pattern in idiopathic interstitial pneumonia. J Lab Clin Med 1978; 91: 929-935
[203] Wallace WAH, Schofield JA, Lamb D, Howie SEM. Localisation of a pulmonary autoantigen in cryptogenic fibrosing alveolitis. Thorax 1994; 49: 1139-1145
[204] Eisenberg H, Barnett E, Simmons H. Diffuse pulmonary interstitial disease, an immune complex disease. Clin Res 1977; 25: 132A
[205] Gelb AF, Dreisin RB, Epstein JO, et al. Immune complexes, gallium lung scans and bronchoalveolar lavage in idiopathic interstitial pneumonitis-fibrosis, a structure-function clinical study. Chest 1983; 84: 148-153
[206] Watters LC. Genetic aspects of idiopathic pulmonary fibrosis and hypersensitivity pneumonitis. Semin Respir Med 1986; 7: 317-325
[207] Bitterman PB, Rennard SI, Keogh BA, et al. Familial idiopathic pulmonary fibrosis: evidence of lung inflammation in unaffected family members. N Engl J Med 1986; 314: 1343-1347
[208] Fulmer JD, Sposovska MS, vonGal ER,et al. Distribution of HLA antigens in idiopathic pulmonary fibrosis. Am Rev Respir Dis 1978; 118: 141-147
[209] Turton CWG, Morris LM, Lawler SD, Turner-Warwick M. HLA in cryptogenic fibrosing alveolitis. Lancet 1978; 1 (8062): 507-508
[210] Rossi GA, Hunninghake GW, Kawanami O, et al. Motheaten mice: an animal model with an inherited form of interstitial lung disease. Am Rev Respir Dis 1985; 131: 150-158
[211] Harrison JH, Hoyt DG, Lazo JS. Acute pulmonary toxicity of bleomycin: CAN scission and matrix protein mRNA levels in bleomycin-sensitive and resistant strains of mice. Mol Pharmacol 1989; 36: 231-238
[212] Rossi GA, Szapiel S, Ferrans VJ, Crystal RG. Susceptibility to experimental interstitial lung disease is modified by immune- and non-immune-related genes. Am Rev Respir Dis 1987; 135: 448-455
[213] Wells AU, Hansell DM, Rubens MB, et al. The predictive value of appearances on thin section computed tomography in fibrosing alveolitis. Am Rev Respir Dis 1993; 148: 1076-1082
[214] Nishimura K, Kitaichi M, Izumi T, et al. Usual interstitial pneumonia: histologic correlation with high resolution CT. Radiology 1992; 182: 337-342
[215] Muller NL, Miller RR, Webb WR, et al. Fibrosing alveolitis: CT-pathologic correlation. Radiology 1986; 160: 585
[216] Johkoh R, Ikezoe J, Kohno N, et al. High-resolution CT and pulmonary function tests in collagen vascular disease: comparison with idiopathic pulmonary fibrosis. Eur J Radiol 1994; 18: 113-121
[217] Webb WR, Muller NL, Naidich DP. *High-Resolution CT of the Lung*, 2nd edition. Lippincott-Raven, Philadelphia 1996.
[218] Remy-Jardin M, Giraud F, Remy J, et al. Importance of ground glass attenuation in chronic diffuse infiltrative lung disease: pathologic-CT correlation. Radiology 1993; 189: 693-698
[219] Leung AN, Miller RR, Muller NL. Parenchymal opacification in chronic infiltrative lung diseases: CT-pathologic correlation. Radiology 1993; 188: 209-214
[220] Lee JS, Im JG, Ahn JM, et al. Fibrosing alveolitis: prognostic implication of ground glass attenuation at high-resolution CT. Radiology 1992; 184: 451-454
[221] Wells AU, Rubens MB, du Bois RM, et al. Serial CT in fibrosing alveolitis: prognostic significance of the initial pattern. AJR 1993; 161: 1159-1165
[222] Akira M, Sanatani M, Ueda E. Idiopathic pulmonary fibrosis: progression of honeycombing at thin-section CT. Radiology 1993; 189: 687-691
[223] Terriff BA, Kwan SY, Cha-Yeung MM, et al. Fibrosing alveolitis: chest radiography and CT as predictors of clinical and functional impairment at follow-up in 26 patients. Radiology 1992; 184: 445-449
[224] Hartman TE, Primack SL, Kang EY, et al. Disease progression in usual interstitial pneumonia compared with desquamative interstitial pneumonia: assessment with serial CT. Chest 1996; 110: 378-382
[225] Brown K, King TE Jr. Recent advances in interstitial lung disease. In: *1995 Yearbook of Pulmonary Disease*, Bone RC, Petty TL, Eds. Mosby Year Book, St. Louis, 1995
[226] Watters LC, Schwarz MI, Cherniack RM, et al. Idiopathic pulmonary fibrosis: pretreatment bronchoalveolar lavage cellular constituents and their relationships with lung histopathology and clinical response to therapy. Am Rev Respir Dis 1987; 135: 696-704
[227] Van Oortegem K, Wallaert B, Marquette DH, et al. Determinants of response to immunosuppressive therapy in idiopathic pulmonary fibrosis. Eur Respir J 1994; 7: 1950-1957
[228] Robertson H. Clinical application of pulmonary function and exercise tests in the management of patients with interstitial lung disease. Sem Respir Crit Care Med 1994; 5: 1-9
[229] Fulmer J, Roberts W, von Gal E, Crystal R. Morphologic-physiologic correlates of the severity of fibrosis and degree of cellularity in idiopathic pulmonary fibrosis. J Clin Invest 1979; 63: 665-676
[230] Tukininen P, Taskinen E. Holsti P, et al. Prognosis of cryptogenic fibrosing alveolitis. Thorax 1983; 38: 349-355
[231] Jezek V, Fucik J, Michaljanic A, Jezkova L. The prognostic significance of functional tests in cryptogenic fibrosing alveolitis. Bull Europ Physiopath Resp 1980; 16: 711-720

[232] Watters LC, King TE Jr., Schwarz MI, et al. A clinical, radiographic, and physiologic scoring system for the longitudinal assessment of patients with idiopathic pulmonary fibrosis. Am Rev Respir Dis 1986; 133: 97-103
[233] Picadi C, Gomez de Almeida R, Xaubet A, et al. Spontaneous pneumothorax in cryptogenic fibrosing alveolitis. Respiration 1985; 48: 77-80
[234] Jones AW. Alveolar cell carcinoma occurring in idiopathic interstitial pulmonary fibrosis. Br J Dis Chest 1970; 64: 78-84
[235] Turner-Warwick M, Lebowitz M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis and lung cancer. Thorax 1980; 35: 496-499
[236] Snider GL. Interstitial pulmonary fibrosis: clinical features, natural history, and complications. Semin Respir Med 1984; 6: 71-79
[237] Ferguson GT, Irvin CG, Cherniack RM. Effect of corticosteroid treatment on respiratory muscle function and biochemical changes in the diaphragm (abstract). Am Rev Respir Dis 1988; 137: 384
[238] Livingstone JL, Lewis JG, Reid L, Jefferson KE. Diffuse interstitial pulmonary fibrosis: a clinical, radiological, and pathological study based on 45 patients. Q J Med 1964; 33: 71-103
[239] Hampton J, Martinez F, Orens J, et al. Corticosteroids in idiopathic pulmonary fibrosis (IPF): toxicity may outweigh benefits (abstract). Am J Respir Crit Care Med 1994; 149(suppl): A878
[240] Akira M, Hamada H, Sakatani M, et al. CT findings during phase of accelerated deterioration in patients with idiopathic pulmonary fibrosis. AJR 1997; 168: 79-83
[241] Mapel DW, Samet JM, Coultas DB. Corticosteroids and the treatment of idiopathic pulmonary fibrosis. Chest 1996; 110: 1058-1067
[242] du Bois RM. Diffuse lung disease: an approach to management. BMJ 1994; 309: 175-179
[243] Schwarz MI. Treatment of IPF: what does the future hold? Chest 1995; 108: 601-602
[244] Egan JJ, Woodcock AA. Does the treatment of cryptogenic fibrosing alveolitis influence prognosis? Respir Med 1996; 90: 127-130
[245] Lacronique JG, Rennard SI, Bitterman PB, et al. Alveolar macrophages in idiopathic pulmonary fibrosis have glucocorticoid receptors, but glucocorticoid therapy does not suppress alveolar macrophage release of fibronectin and alveolar macrophage derived growth factor. Am Rev Respir Dis 1984; 130: 450-456
[246] Almawi WY, Beyhum HN, Rahme AA, Rieder MJ. Regulation of cytokine and cytokine receptor expression by glucocorticoids. J Leukoc Biol 1996; 60: 563-572
[247] Auphan N, DiDonato JA, Helmberg A, et al. Immunoregulatory genes and immunosuppression by glucocorticoids. Arch Toxicol 1997; 19: 87S-95S
[248] Scheinman RI, Gualberto A, Jewell CM, et al. Characterization of mechanisms involved in transrepression of NF-kappa B by activated glucocorticoid receptors. Mol Cell Biol 1995; 15: 943-953
[249] Scheinman RI, Cogswell PC, Lofquist AK, Baldwin AS Jr. Role of transcriptional activation of I kappa B alpha in mediation of immunosuppression by glucocorticoids. Science 1995; 270: 283-286
[250] Auphan N, DiDonato JA, Rosette C, et al. Immunosuppression by glucocorticoids: inhibition of NF-kB activation through induction of IkBa. Science 1995; 270: 286-290
[251] Frauman AG. An overview of the adverse reactions to adrenal corticosteroids. Adverse Drug React Toxicol Rev 1996; 15: 203-206
[252] Jackson RV, Bowman RV. Corticosteroids. Med J Aust 1995; 162: 663-665
[253] Lamberts SW, Huizenga AT, de Lange P, et al. Clinical aspects of glucocorticoid sensitivity. Steroids 1996; 61: 157-160
[254] Dayton CS, Schwartz DA, Helmers RA, et al. Outcome of subjects with idiopathic pulmonary fibrosis who fail corticosteroid therapy: implications for further studies. Chest 1993; 103: 69-73
[255] Johnson MA, Kwan S, Snell NJC, et al. Randomized controlled trial comparing prednisolone alone with cyclophosphamide and low dose prednisolone in combination in cryptogenic fibrosing alveolitis. Thorax 1989; 44: 280-288
[256] Baughman RP, Lower EE. Use of intermittent, intravenous cyclophosphamide for idiopathic pulmonary fibrosis. Chest 1992; 102: 1090
[257] Silver RM, Warrick JH, Kinsella MB, et al. Cyclophosphamide and low-dose prednisone therapy in patients with systemic sclerosis (scleroderma) with interstitial lung disease. J Rheumatol 1993; 20: 838-844
[258] Meier-Sydow J, Rust M, Kronenbergr H, Srempel S. Survival of patients with idiopathic pulmonary fibrosis following treatment with azathioprine, D-penicillamine or prednisolone: ten year follow-up. Chest 1990; 94: 18S
[259] Peters SG, McDougall JC, Douglas WW, et al. Colchicine in the treatment of pulmonary fibrosis. Chest 1993; 103: 101-104
[260] Douglas WW, Ryu JH, Bjoraker JA, et al. Colchicine versus prednisone as treatment of usual interstitial pneumonia. Mayo Clin Proc 1997; 72: 201-209
[261] Entzian P, Schlaak M, Seitzer U, et al. Antiinflammatory and antifibrotic properties of colchicine: implications for idiopathic pulmonary fibrosis. Lung 1997; 175: 41-51
[262] Rennard SI, Bitterman PB, Ozaki T, et al. Colchicine suppresses the release of fibroblast growth factors from alveolar macrophages in vitro. Am Rev Respir Dis 1988; 137: 181-185
[263] Levy M, Spino M, Read SE. Colchicine: a state-of-the-art review. Pharmacotherapy 1991; 11: 196-211
[264] Harris ED, Krane SM. Effects of colchicine on collagenase in cultures of rheumatoid synovium. Arthritis Rheum 1971; 14: 669-684
[265] Park J-H, Kim I-S, Park R-W, Jo J-S. Inhibition of bleomycin-induced pulmonary fibrogenesis by colchicine. Korean J Biochem 1990; 22: 39-46
[266] Wallace SL, Singer JZ, Duncan GJ, et al. Renal function predicts colchicine toxicity: guidelines for the prophylactic use of colchicine in gout. J Rheumatol 1991; 18: 264-269
[267] Raghu G. Idiopathic pulmonary fibrosis: a need for treatment with drugs other than corticosteroids—a role for antifibrotic agents. Mayo Clin Proc 1997; 72: 285-287
[268] Goldstein RH, Fine A. Potential therapeutic initiatives for fibrogenic lung diseases. Chest 1995; 108: 848-855
[269] Hunninghake GW, Kalica AR. Approaches to the treatment of pulmonary fibrosis. Am J Respir Crit Care Med 1995; 151: 915-918
[270] Lurton JM, Trejo T, Narayanan AS, Raghu G. Pirfenidone inhibits the stimulatory effects of pro-fibrotic cytokines on human lung fibroblasts in vitro. Am J Respir Crit Care Med 1996; 153: A403
[271] Iyer SN, Wild JS, Schiedt MJ, et al. Dietary intake of pirfenidone ameliorates bleomycin-induced lung fibrosis in hamsters. J Lab Clin Med 1995; 1256: 779-785
[272] Shah M, Foreman DM, Ferguson MWJ. Control of scarring in adult wounds by neutralising antibody to traansforming growth factor β. Lancet 1992; Lancet 339: 213-214

[273] Border WA, Noble NA, Yamamoto T, et al. Natural inhibitor of transforming growth factor-β protects against scarring in experimental kidney disease. Nature 1992; 360: 361-364
[274] Riley DJ, Kerr JS, Berg RA, et al. Prevention of bleomycin-induced pulmonary fibrosis in the hamsters by cis-4-hydroxyproline-1-proline. Am Rev Respir Dis 1981; 123: 388-393
[275] Siegel RC. Lysyl oxidase. Int Rev Connect Tissue Res 1979; 8: 73-118
[276] Wakasaki H, Ooshima A. Synthesis of lysyl oxidase in experimental fibrosis. Biochem Biophys Res Commun 1990; 166: 1201-1204
[277] Jimenez SA, Sigal SH. A 15-year prospective study of treatment of rapidly progressive systemic sclerosis with D-penicillamine. J Rheumatol 1991; 18: 1496-1503
[278] Varga J, Diaz-Perez A, Rosenbloom J, et al. PGE_2 causes a coordinate decrease in steady state levels of fibronectin and types I and III procollagens in normal dermal fibroblasts. Biochem Biophy Res Commun 1987; 147: 1282-1288
[279] Fine A, Poliks CF, Donahue LP, et al. The differential effect of prostaglandin E_2 on transforming growth factor-β and insulin-induced collagen formation in lung fibroblasts. J Bio Chem 1989; 264: 16988-16991
[280] Cantin AM, Begin R. Glutathione and inflammatory disorders of the lung. Lung 1991; 169: 123-138
[281] Cantin AM, North SL, Hubbard RC, Crystal RG. Normal alveolar epithelial lining fluid contains high levels of glutathione. J Appl Physiol 1987; 63: 152-157
[282] Borok A, Buhl R, Grimes GJ, et al. Effect of glutathione aerosol on oxidant-anti-oxidant imbalance in idiopathic pulmonary fibrosis. Lancet 1991; 338: 215-216
[283] Meyer A, Buhl R, Magnussen H. The effect of oral N-acetylcysteine on lung glutathione levels in idiopathic pulmonary fibrosis. Eur Respir J 1994; 7: 431-436
[284] Meyer A, Buhl R, Kampf S, Magnussen H. Intravenous N-acetylcysteine and lung glutathione of patients with pulmonary fibrosis and normals. Am J Respir Crit Care Med 1995; 152: 1055-1060
[285] Buhl R, Vogelmeier C, Crittenden M, et al. Augmentation of glutathione in the fluid lining the epithelium of the lower respiratory tract by directly administering glutathione aerosol. Proc Natl Acad Sci USA 1990; 87: 4603-4607
[286] Meduri GU, Belenchia JM, Estes RJ, et al. Fibroproliferative phase of ARDS: clinical findings and effects of corticosteroids. Chest 1991; 100: 943-952
[287] Meduri GU, Chinn AJ, Leeper KV, et al. Corticosteroid rescue treatment of progressive fibroproliferation in late ARDS: patterns of response and predictors of outcome. Chest 1994; 105: 1516-1527
[288] Scee K, Roongta U, Henke C. Cell surface CD44 related chondroitin sulfate proteoglycan mediates acute lung injury fibroblast migration and invasion into a fibrin matrix. Am J Respir Crit Care Med 1995; 151: A592
[289] Henke C, Bitterman P, Roongta U, et al. Induction of fibroblast apoptosis by anti-CD44 antibody: implications for the treatment of fibroproliferative lung disease. Am J Pathol 1996; 149: 1639-1650