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IDIOPATHIC PULMONARY FIBROSIS

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INTRODUCTION

Patients presenting with dyspnea and the radiographic appearance of diffusely dispersed pulmonary disease immediately capture the interest of the clinician, radiologist, and physiologist. The patient is percussed, auscultated, x-rayed, skin tested, sputum cultured and functionally tested-all at no small expense. Frequently, in an effort to obtain a specific diagnosis, a pulmonary biopsy is performed. Often, however, the pathologist sees only diffusely thickened alveolar walls with collagen deposition, metaplastic changes of the lining cells, sparce cellular reaction and variable degrees of pulmonary arterial wall thickening. A diagnosis of diffuse idiopathic pulmonary fibrosis is made, specialty interest fades and the practitioner is left with a most difficult therapeutic problem with little help from his consultants.

Although there are earlier references to a similar clinical syndrome in the German literature (1-3), most authors have cited the reports of Hamman and Rich (4) as being the genesis of appreciation of this disease. In 1933, these investigators presented a clinical-pathologic conference of a 47 yr old black man who presented on December 16, 1931, complaining of cough, shortness of breath, and swelling of the ankles of three weeks duration. The patients symptoms rapidly worsened and he died on March 22, 1932, with extreme cyanosis, dyspnea, and right ventricular failure. At autopsy the patient showed marked pulmonary fibrosis with cor pulmonale. In 1935, these authors reported three, and possibly a fourth, patient with a similar syndrome (5). Confidently expecting to see more such cases the authors delayed a full report of their findings until 1944 (6) at which time they were able to add a confirmed fourth case. The clinical picture of their patients was that of rapid onset of severe dyspnea progressing to dyspnea at rest associated with cyanosis. The patients died from 31 days to approximately 6 months after the first onset of symptoms. Hamman and Rich considered the pathological findings in the lungs to be specific and to be unlike any previously reported cases. The authors termed this new syndrome acute diffuse interstitial fibrosis of the lungs. Subsequently, throughout much of the literature the terms Hamman-Rich Syndrome, and diffuse interstitial fibrosis are used interchangeably. Clinicians soon began to diagnose this illness anti-mortem and by 1957, more than 50 cases had appeared in the literature under the heading "Hamman-Rich Syndrome". As more cases were described, it became apparent that the fulminating course of the original patients of Hamman and Rich manifested only part of the spectrum of the disorder now known as idiopathic pulmonary fibrosis (7-38).

DIFFERENTIAL DIAGNOSIS OF RETICULONODULAR INFILTRATES

The physician faced with a patient complaining of unexplained dyspnea usually obtains a chest x-ray early in the course of the evaluation. The finding of a diffuse reticular, nodular, or honey-combed infiltrate enters one on a lengthy diagnostic path which may ultimately result in a diagnosis of idiopathic pulmonary fibrosis. A reticular infiltrate consists of a network of linear shadows which may be conceived as a series of rings surrounding spaces of air density giving a fine hairnet appearance. Some of the linear densities run at right angles to the normal vascular pattern of the lung which radiates in a branching but not crossing manner from the hilar areas. The purely nodular interstitial diseases

of the lung consist of discreet, punctate shadows which range from tiny nodules 1 mm in diameter which are barely visible roentgenographically to 5 mm shadows. Frequently, there will be a mixture of the reticulation and the nodularity and this pattern is termed reticulo-nodular infiltrates. A honeycomb pattern refers to a very coarse reticulation in which the air spaces in the mesh of the net measure not less than 5-6 mm in diameter. In addition to a reticulo-nodular pattern, these patients may also present with discreet or confluent fluffy densities termed alveolar infiltrates mixed in with the background of a reticular infiltrate. While Fraser and Pare' (39) have suggested that the coexistence of alveolar infiltrates alters the differential diagnostic possiblities, most clinicians and radiographers are not able to make such a fine differentiation and thus the occurrence of alveolar infiltrates does not alter the differential diagnosis.

Having determined that the patient has an interstitial pulmonary disease process, the differential diagnosis is extremely broad. Several classifications of interstitial lung disorders have been proposed, but the most useful involves grouping according to known or unknown etiology as shown in Table I and Table II.

TABLE 1

INTERSTITIAL LUNG DISEASES OF KNOWN ETIOLOGY

Occupational and environmental inhalants
- Inorganic dusts
- Organic dusts
- Gases, fumes, vapors, aerosols

Drugs

Poisons

Radiation

Infectious agents

Interstitial disease caused by disorders of organs other than lung
- Chronic pulmonary edema
- Chronic uremia

In all, there are approximately 150 specific or semi-specific diseases which have been defined as producing interstitial lung disease. Although the etiology is known in only 25-30 percent of cases, the remaining patients with interstitial disease of unknown etiology, can be characterized into specifically defined disorders. It is clear that a systematic approach to making a diagnosis is indicated, but this approach will vary depending upon the severity and acuteness of the patients process. It is not my purpose to discuss these categories in detail but I would like to indicate a few general guidelines that may be helpful.

TABLE 2

INTERSTITIAL LUNG DISEASES OF UNKNOWN ETIOLOGY

- Idiopathic pulmonary fibrosis
- Chronic interstitial disease associated with the collagen-vascular disorders
  - Rheumatoid arthritis
  - Progressive systemic sclerosis
  - Systemic lupus erythematosus
  - Polymyositis-dermatomyositis
  - Sjögren's syndrome
  - Overlap syndrome
- Sarcoidosis
- Eosinophilic granuloma
- Goodpasture's syndrome
- Idiopathic pulmonary hemosiderosis
- Wegener's granulomatosis
- Lymphocytic infiltrative disorders
  - Lymphomatoid granolumatosis
  - Immunoblastic lymphadenopathy
  - Unclassified
- Churg-Strauss syndrome
- Hypersensitivity angiitis
- Overlap vasculitides
- Inherited disorders
  - Tuberous sclerosis
  - Neurofibromatosis
  - Familial pulmonary fibrosis
- Pulmonary veno-occlusive disease
- Ankylosing spondylitis
- Diffuse amyloidosis of lung
- Chronic eosinophilic pneumonia
- Lymphangioleiomyomatosis

A complete list of diseases included in the differential diagnosis of interstitial pulmonary disease is shown in the Appendix, page 44.

The best data regarding the yield of various diagnostic procedures are found in Gaensler's series of 381 patients with interstitial lung disease collected over a 15 year period. The types of patients with which Gaensler dealt are shown in Table 3 (40).

TABLE 3

381 PATIENTS WITH INTERSTITIAL LUNG DISEASE

		No. Cases
I.	Infections	22
II.	Inhalational	114
III.	Neoplastic	19
IV.	Therapeutic agents	3
V.	Connective tissue diseases	11
VI.	Cardiovascular	35
VII.	Aspirational	0
VIII.	Airways disease	0
IX.	Trauma	0
X.	Miscellaneous or Idiopathic	150
	No diagnosis	27
	Total	381

Gaensler: *Advances In Cardiopulmonary Diseases, Vol III*, 1966

The entire series of patients was collected at Boston City Hospital. Since this area is an area of high industrial exposure, it is likely that his incidence of inhalational diseases is higher than would be seen in the Dallas area. Gaensler reported 54 cases of chronic berylliosis, 22 cases of silicosis, and 22 cases of asbestosis. Conversely, the incidence of inhalational diseases from industrial or work exposure may be markedly under estimated in our clinical population. It is indeed a rarity to find an adequate occupational or exposure history in charts on the pulmonary ward at Parkland Hospital.

Additionally, it should be noted that this series reflects Gaensler's referral practice. He reported no aspirational, airways, or traumatic diseases. He included only 22 cases of atypical pneumonias, markedly under estimating the overall incidence of acute infection as a cause of a diffuse interstitial pattern. While recognizing that this series does not indicate the relative prevalence of each of these diseases, nevertheless, when interpreted in this light, the study does provide useful insight regarding the diagnostic yield of various procedures.

TABLE 4

DIAGNOSIS OF 381 PATIENTS WITH INTERSTITIAL LUNG DISEASE

	No. Patients	Percent
History	121	32
Physical exam	35	9
Routine laboratory exam	4	1
Skin tests	3	1
Sputum culture and cytology	11	3
Special x-rays	9	2
Bronchoscopy	?	0
Prescalene biopsy	25	6
Other non pulmonary biopsy	21	6
Lung biopsy	116	30
Autopsy	13	3

Gaensler: *Advances In Cardiopulmonary Diseases, Vol III,* 1966

The clinical history was clearly the most important diagnostic device available to the physician. The chief complaint was usually quite non-specific including cough or dyspnea in one half of all patients no matter what the ultimate diagnosis. The portion of the history dealing with occupation, recreation activities, and travel was most significant. In 73 patients (20 percent) this led to the presumed diagnosis.

The physical examination of the chest is virtually never diagnostic. Physical examination might be helpful in regard to the heart and in some patients with lymphadenopathy or skin lesions. Routine laboratory examination led to a presumptive diagnosis in only four patients, two with sarcoidosis and one each with leukemia and Loeffler's syndrome. Skin testing was helpful only in three patients with chronic histoplasmosis. Eleven patients with miliary tuberculosis were included in this series. Four of eleven of these patients had a negative second strength PPD skin test and only three of eleven patients with miliary tuberculosis had acid-fast bacilli in the sputum. Special x-ray procedures such as a metastic bone survey, a barium swallow (scleroderma) also yielded few diagnosis.

It is apparent that invasive procedures are frequently required to make the diagnosis. While Gaensler found bronchoscopy to be of no benefit in these diseases, it should be noted that fiberoptic bronchoscopy and transbronchial biopsy were not available at the time of this series. While the interstitial processes do not cause characteristic changes in the bronchial mucosa, several of the interstitial lung diseases have sufficiently characteristic findings to make transbronchial biopsy useful. Diseases in which transbronchial biopsy has been shown to be useful include miliary tuberculosis, histoplasmosis, coccidiodomycosis, measles, cytomegalovirus, pneumocystis carinii, neoplastic diseases, and sarcoidosis.

It is apparent from this series that the correct diagnosis will be made only by a lung biopsy in many patients with interstitial pulmonary disease. The relative merits of an open lung biopsy for the diagnosis of idiopathic pulmonary fibrosis will be discussed later in this protocol. While it seems reasonable to believe that some patients can be diagnosed by needle biopsy or by transbronchial biopsy when specific findings are obtained, the physician should be prepared to proceed with an open lung biopsy if a specific diagnosis is not made.

Having outlined the general approach to patients with reticular or reticulo-nodular pulmonary infiltrates, I want to spend the remainder of my time considering the entity of idiopathic pulmonary fibrosis.

CLINICAL PRESENTATION OF IDIOPATHIC PULMONARY FIBROSIS

The chief complaint in idiopathic pulmonary fibrosis is usually breathlessness found in 91 percent of patients (41,9,20). This complaint was found in 100 percent of the patients reported by Crystal (41). The dyspnea develops rapidly with minimal exertion and, even at rest, the patient may note an apparent "air hunger". A dryness of the mouth and throat associated with over-breathing are also frequent complaints. Most patients also note a non-productive cough early in the course of the disease. Joint pain and fatigue are noted in approximately 5 percent of patients. Chest pain, if present, is often of a deep aching nature although pleuritic pain is sometimes reported. Occasional patients with cor pulmonale presented primarily because of substernal, exertional chest pain. Hemoptysis and edema were uncommon presenting complaints being seen in approximately 3 percent of cases.

TABLE 5

PRESENTING SYMPTOMS OF IPF

Symptom	% Of Patients
Breathlessness	91
Cough	86
Joint pain	5
Fatigue	5
Chest pain, pleuritic or other	5
Hemoptysis	3
Edema	2

Crystal: Ann. Intern. Med. 85:769, 1976
Marks: Med. Clin. North Amer. 51:439, 1967
Scadding: Brit. Med. J. 1:443, 1960

Clubbing of the digits is the most common physical finding associated with idiopathic pulmonary fibrosis appearing in 72 percent of the patients. In contrast to other pulmonary disorders associated with clubbing (42), patients with idiopathic pulmonary fibrosis with clubbing

rarely have hypertrophic osteoarthropathy. Excluding clubbing, all of the important clinical manifestations of idiopathic pulmonary fibrosis are limited to the chest. Early in the course of the disease, the chest examination may be normal. Later, in mid course, the typical patient with idiopathic pulmonary fibrosis will have harsh dry râles at both bases (65 percent), tachypnea (46 percent), and findings consistent with pulmonary hypertension (70 percent). Occasionally, patients will have only diffuse broncho-vesicular breath sounds or rhonchi or both. Although cardiac examination findings can be normal for years, the usual progression includes the development of a right ventricular heave and eventual right sided failure (16). Approximately 20 percent of patients with idiopathic pulmonary fibrosis eventually die from a cardiovascular disorder but most succomb to primary respiratory failure often precipitated by infection (29). Cyanosis is rarely present at rest but may develop to a striking degree with exercise. Chest movement may appear restricted with decreased diaphragmatic excursion. The lungs fields are resonant to percussion and on auscultation, air exchange is good with loud, harsh breath sounds. Wheezing and prolongation of the expiratory phase are not present.

TABLE 6

PRESENTING SIGN OF IPF

Sign	% Of Patients
Systemic findings	
Clubbing	72
Chest findings	
Râles	65
Tachypnea	46
Rhonchi	21
Normal	14
Cardiac findings	
Augmented P_2	70

Crystal: Ann. Intern. Med. 85:769, 1976
Marks: Med. Clin. North Amer. 51:439, 1967
Scadding: Brit. Med. J. 1:443, 1960

Most patients with idiopathic pulmonary fibrosis have an elevated sedimentation rate (94 percent). Additionally, idiopathic pulmonary fibrosis is associated with abnormalities of the immune system (43-46), however, none of the abnormalities are specific for this disorder. The most commonly noted abnormality was the presence of circulating cryoimmunoglobulins (36). Specific immunoglobulins involved have not been characterized as yet. Abnormalities in antinuclear antibodies, rheumatoid factor, and gamma-globulin levels were noted in from 7-41 percent of patients. Earlier studies (45-46) have reported a higher incidence of serological abnormalities in idiopathic fibrosis than the more recent series from which these figures are drawn, but many of these studies did not exclude patients with obvious collagen vascular disease. Serum complement levels are usually normal with depression of the CH_{50} level being noted in only 6 percent of patients. While most patients with idiopathic

pulmonary fibrosis have resting arterial hypoxemia that worsens with exercise, polycythemia is almost never seen in marked contrast to other hypoxic states such as chronic obstructive lung disease or congenital heart disease where polycythemia is common.

TABLE 7

LABORATORY FINDING IN IPF

Study	% Of Patients
Elevated sedimentation rate	94
Cryoimmunoglobulins	41
Antinuclear antibodies	7
Rheumatoid factor	14
Abnormal protein electrophoresis	
Elevated $\alpha 2$ macroglobulins	22
Elevated γ globulins	17
Depressed complement (CH_{50})	6
Polycythemic	3

Crystal: Ann. Intern. Med. 85:769, 1976

PULMONARY PHYSIOLOGY IN IDIOPATHIC PULMONARY FIBROSIS

Over the years, many testing procedures have been developed to characterize the physiological disturbances in lung function which accompany interstitial reactions in the lung. An outstanding physiologic feature of tissue reactions in the distal portions of the lungs beyond the terminal bronchioles is a reduction in the air containing volume of the lung (47). As a consequence, vital capacity and total lung capacity are reduced below values predicted according to the height of the patient. The average values for patients with idiopathic pulmonary fibrosis were a vital capacity of 62 percent of predicted and a total lung capacity of 63 percent of predicted (41). The functional residual capacity and the residual volume are also reduced below predicted values but not usually to the same extent as the vital capacity so that the ratio of residual volume to total lung capacity, which is normally 30 percent or less depending on age, is usually elevated (34 percent, 115 percent of predicted). Therefore, instead of indicating hyperinflation or emphysematous changes in the lung, the high RV/TLC ratio in this group of disorders reflects severe restriction of the vital capacity. As a corollary of the fact that the residual volume usually changes less than the vital capacity, the vital capacity is often a useful guide to a change in the air containing volume of the lung in idiopathic pulmonary fibrosis. The dynamic pulmonary functions, such as the FEV_1, peak expiratory flow rate, and the maximal ventilatory volume are usually well maintained (41, 48). The high Maximal Ventilatory Volume is secondary to the stiffened lungs and the increase in the retractive force that they exert on large airways. The result of these effects is that airways are dilated, their patency is maintained throughout the vigorous breathing efforts and airway resistance decreases.

TABLE 8

PULMONARY PHYSIOLOGIC STUDIES IN IPF - VENTILATION

Study	Mean % Of Predicted
Vital capacity	62
Total lung capacity	63
Residual volume/Total lung capacity	115
Forced expiratory volume - 1 second	98
Maximal ventilatory volume	100

Crystal: Ann. Intern. Med. 85:769, 1976

While conventional tests of airway obstruction, i.e., for large airways, are normal, recent data suggests that small airways disease, undetectable by FEV_1 and plethysmographic methods, is present in idiopathic pulmonary fibrosis. The small airways may be narrowed as a consequence of peribronchiolar fibrosis and/or inflammation and even bronchiolitis (48). When tests of small airway function are performed, dynamic compliance is abnormal in 70 percent, maximal expiratory flow volume curves are abnormal in 45 percent, particularly at low lung volumes, and maximal flow-static recoil curves are abnormal in 31 percent. Closing volume values in interstitial fibrosis have been so variable that at present, they have no clinical meaning (41). This physiologic evidence of small airways disease correlates well with morphological observations of small airways in idiopathic pulmonary fibrosis. Seventy percent of the patients with this disease show narrowed airways with evidence of peribronchiolar fibrosis and inflammation (48). The clear association of abnormal physiologic function of small airways with the morphologic evidence of disease of these airways suggests that at least part of the ventilation abnormalities and hence part of the hypoxemia, of idiopathic pulmonary fibrosis may be due to small airways disease.

TABLE 9

PULMONARY PHYSIOLOGIC STUDIES IN IPF - AIRWAYS

Study	% Of Patients With Abnormal Results
FEV_1	0
Airway resistance by body plethysmography	0
Dynamic compliance	70
Maximal expiratory flow-volume curves	45
Maximal flow-static recoil curve	31
Closing volume	Variable

Fulmer: J. Clin. Invest. 60:595, 1977

Historically the diseases now categorized as interstitial pulmonary fibrosis achieved clinical distinction as the syndrome of "alveolar capillary block" (49). This designation, suggested by Austrian and his associates, had the advantage of readily comprehensible conceptual basis for relating abnormalities in arterial blood gas composition to the anatomic abnormalities in the lung parenchyma. Implicit in this concept was both an increase in the tissue barrier to O_2 diffusion from alveolar gas to pulmonary capillary blood and a reduction in the total area available for gaseous diffusion. This term was popular in the literature until 1962, when Finley, et al. (50), presented data suggesting that the major cause of hypoxemia in these patients was not a diffusion barrier to oxygen but rather was secondary to ventilation perfusion mismatching. Using sophisticated methods, Wagner and associates (51) have recently shown that most of the hypoxemia in idiopathic pulmonary fibrosis is indeed secondary to ventilation perfusion imbalance. In patients with idiopathic pulmonary fibrosis the arterial PO_2 at rest is below normal, but not markedly so, usually in the range of 58-75 mm Hg. Thus, the oxygen content of arterial blood, while the patient is resting, is not markedly abnormal. On the other hand, alveolar-arterial differences in PO_2 of the order of 20-30 mm Hg are quite common in these patients (15, 41). Because the O_2 diffusivity in water membranes and the diffusion distances across the alveolar capillary membranes would not account for the differences in PO_2, it is reasonable to suspect that ventilation perfusion disproportions would be involved in the pathogenesis of the mild arterial hypoxemia and in the widening of the alveolar arterial difference in PO_2. Physiologic shunt at rest as measured by 100 percent O_2 breathing can be significant in idiopathic pulmonary fibrosis but usually develops late in the course of the disease (49, 50). Patients with early idiopathic pulmonary fibrosis usually have physiologic shunts of less than 6 percent, whereas, patients with advanced disease often have shunts as great as 30 percent. Thus, although physiologic shunt is generally not a significant cause of hypoxemia early in the disease, it becomes a major problem in the care of patients very late in their course. Physiologic dead space was found to be elevated in 60 percent of the patients with idiopathic pulmonary fibrosis (10, 15). Normal persons waste less than one third of their total ventilation, while patients with idiopathic pulmonary fibrosis had an average dead space/tidal volume ratio of 0.4.

Probably the most characteristic physiological abnormality in idiopathic pulmonary fibrosis is the impairment in the diffusion of oxygen across the air blood interface. The diffusing capacity of the lungs for carbon monoxide is a sensitive test of pulmonary dysfunction in interstitial fibrosis. A reduction in diffusing capacity for carbon monoxide is widely accepted as one of the earliest physiologic abnormalities in interstitial disease of the lungs and this abnormality may occur when other conventional tests of lung function are still within the normal range. As stated earlier, this abnormality in the transfer of CO probably reflects loss of alveolar gas exchanging units as a result of cellular and tissue encroachment on alveolar spaces, capillaries or both. A recent series reported mean value for diffusion capacity of 10.5 which is 46 percent of predicted. It is possible to divide the diffusing capacity of the lung into two compartments: the pulmonary membrane (Dm) and the pulmonary capillary blood (θVc). In patients with idiopathic pulmonary fibrosis, both Dm and θVc are reduced, however, the Dm decreases some what more than θVc (52). These observations suggest the changes in the alveolar

capillary membrane predominate over destruction of capillaries in reducing the diffusion capacity of the lungs even though both changes take place.

TABLE 10

PULMONARY PHYSIOLOGIC STUDIES IN IPF - GAS EXCHANGE

Study	Mean Value
P_AO_2	69 mm Hg
$(A\text{-}a)O_2$	30 mm Hg
Shunt	6 - 30%
V_D/V_T	40%
Diffusing capacity	10.5

Crystal: Ann. Intern. Med. 85:769, 1976
Scadding: Thorax 29:271, 1974

While diffusion abnormalities are not the predominant cause of hypoxemia at rest, most investigators agree that, during exercise, the total diffusing capacity is an important factor in causing hypoxemia. During exercise, the arterial PO_2 decreases sharply, while PCO_2 usually remains normal or even low. The reasons for this change are illustrated in Figures 1 A and 1 B. Figure 1 A shows the rate of increase in pulmonary capillary PO_2 and alveolar-capillary PO_2 differences in a normal subject while Figure 1 B illustrates the same information in a patient with diffuse interstitial fibrosis. In both panels, the time spent by blood in the pulmonary capillary is shown on the x axis and the PO_2 of blood is shown on the y axis. The upper line labeled P_AO_2 indicates the partial pressure of oxygen in the alveolus in each instance. In Figure 1 A, the normal lung, equilibration of pulmonary capillary blood with alveolar PO_2 occurs early in the course of a red cell transit through the normal pulmonary capillary bed if the subject is at rest. At rest, the time a red blood cell spends traversing the pulmonary capillary bed is approximately 0.75 seconds. In a normal patient with exercise, the time spent by blood in pulmonary capillary decreases to approximately 0.5 seconds as indicated by the heavy arrow. In spite of this, even with exercise, there is virtually no alveolar capillary difference in PO_2 at the end of the capillary because of the rapidity with which arterial PO_2 equilibrates with alveolar PO_2. In Figure 1 B, the findings in interstitial fibrosis are outlined. The alveolar oxygen tension is shown to be lower than normal, about 90 torr, on the assumption that diseased regions of lung are under ventilated. Even though thickening of the alveolar capillary membrane decreased the rate of diffusion of oxygen from alveolar gas to pulmonary capillary blood at the end of the capillary (indicated by the lesser slope of the dotted line) the alveolar-capillary oxygen gradient is still only a few torr at the end of the capillary. However, during exercise, the reduced rate of diffusion of oxygen across the diseased alveolar capillary membrane, and the more rapid circulation of blood through the reduced capillary bed (resulting in a much shorter time in the capillary) results in a much larger alveolar capillary difference in PO_2. Additionally, it should be noted that points A and B, the mixed venous PO_2, are decreased in the

patient with diffuse interstitial fibrosis. It can be seen then that there are three reasons for the increased hypoxemia seen in idiopathic pulmonary fibrosis patients during exercise: 1) lowering of the mixed venous O_2 content during exercise augments the contribution of ventilation perfusion imbalances and shunting to arterial hypoxemia, 2) lowering of mixed venous PO_2 leads to a decrease in mean pulmonary capillary PO_2 because of a diffusion limitation imposed by the diseased alveolar capillary membrane, and 3) the time spent by red blood cells in the pulmonary capillaries is shorter during exercise so that time for equilibration of PO_2 between capillary blood and alveolar gas is abbreviated.

FIGURE 1 A

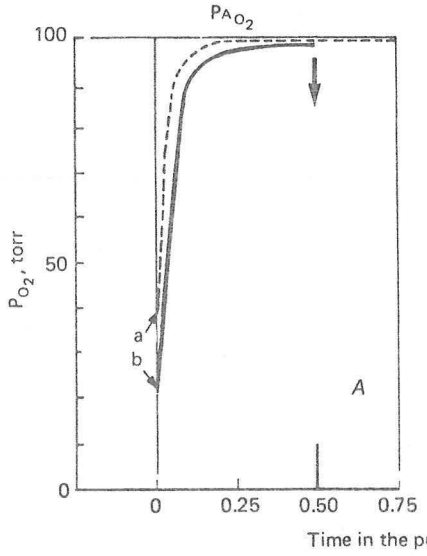
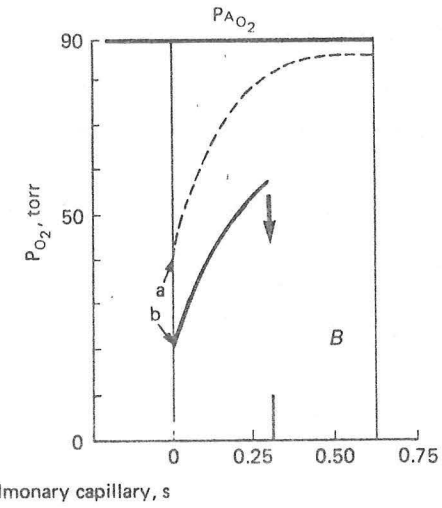


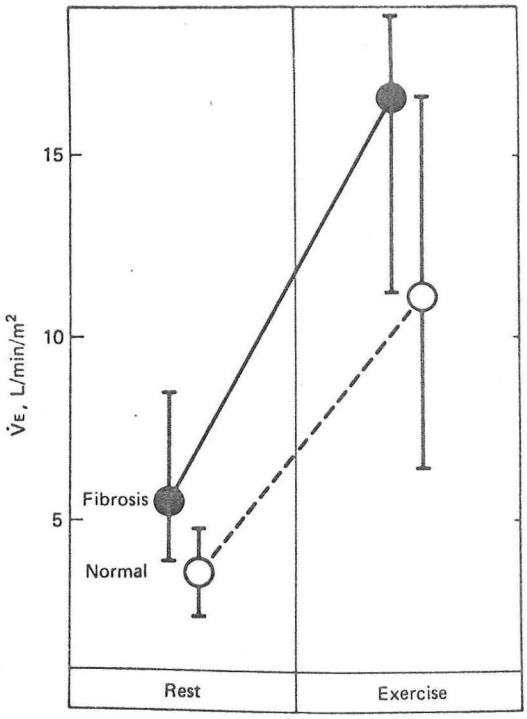
FIGURE 1 B



Time in the pulmonary capillary, s

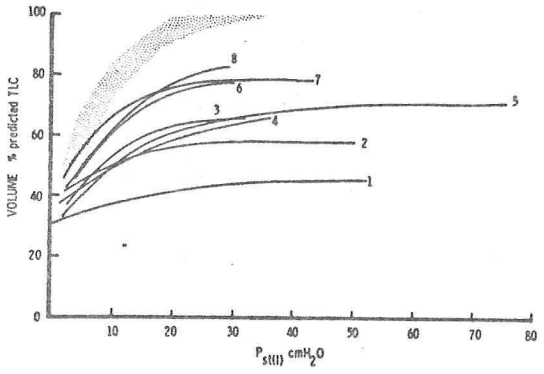
Most patients with pulmonary interstitial fibrosis have marked increases in the minute ventilation both at rest and at given levels of exercise as shown in Figure 2. Patients with interstitial pulmonary fibrosis may have such a high minute ventilation at rest that they not only overcome their high physiological dead space but, in addition, maintain hyperventilation resulting in the low arterial PCO_2. Lourenco, et al., (53) have shown that the abnormally high minute ventilation is accomplished by increases in respiratory frequency rather than increases in tidal volume; the mean respiratory frequency in patients with idiopathic pulmonary fibrosis being 34.6/min. The heightened minute ventilation in these patients could arise from either an excessive amount of work performed by the respiratory muscles in response to a normal number of stimuli from the respiratory center or from an abnormally large number of nervous stimuli to the respiratory muscles from the respiratory center. The later mechanism seems more likely in light of the fact that no circumstances (e.g. unusual stretch) exists which should cause respiratory muscles to function more efficiently.

FIGURE 2



The abnormally large output of nervous stimuli from the respiratory center to the respiratory muscles could arise from two mechanisms: 1) an increased rate of discharge from the respiratory center in response to normal afferent stimulation, and 2) an abnormally large afferent stimulation to the respiratory center. The first mechanism might be operative in two circumstances: 1) an abnormal setting of the respiratory controlling system, or 2) a decrease in intracellular buffering capacity of the cells of the respiratory center. Neither of these circumstances are likely in idiopathic pulmonary fibrosis in that most patients with diffuse fibrosis have normal carbon dioxide tension making the first circumstance unlikely and the latter circumstance is unlikely because most patients have normal blood buffering capacities, and the slopes of the ventilatory response curve to carbon dioxide breathing of patients is not significantly different from those with normal subjects. Hypoxemic stimulation is also an unlikely inciting stimulus in that breathing of an enriched oxygen mixture does not decrease minute ventilation in any of these patients. For the reasons cited, most observers have favored an abnormally large afferent stimulation to the respiratory center as an explanation for the high minute ventilation in these patients. The origin of these nervous stimuli remains unknown, but are felt by most to arise from alteration in mechano-receptors in the diseased interstitium. Evidence for the importance of pulmonary mechano-receptors has been obtained in a few patients with interstitial disease in whom blockade of the vagi has produced prolonged breath-holding time, decreased minute ventilation and has relieved dyspnea (54).

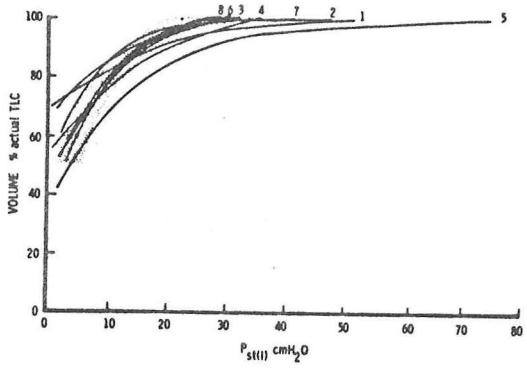
FIGURE 3



The compliance of the lungs is characteristically low in interstitial fibrosis. As shown in Figure 3 , the expiratory pressure volume curve of patients with interstitial pulmonary fibrosis falls to the right and below the curve of a normal subject. In Figure 3 the pressure volume curves have been plotted with the ordinate expressed as "percent of predicted TLC" to allow for differences in size between patients. In general, there is a good correlation between the reduction in compliance and the reduction in either vital capacity or total lung capacity. While compliance curves such as those shown above are usually interpreted as indicating stiffening of peripheral lung units, the need to take into account the decreased lung volumes seen in this disease has long been recognized (55, 56). If one expresses volume as percent of measured TLC rather than as percent predicted TLC, the result is a pressure volume curve that, as a first approximation, reflects the elastic properties of the surviving, ventilated alveoli. When data from these same patients are replotted in this way, (57) Figure 4 , Pst (L) close to full inflation remains abnormally high in most patients, but at lower volumes it is normal. The values of static compliance in relation to actual TLC, however, remain subnormal in most patients. Pst (L) at TLC showed a considerable decrease during breath holding, but, as shown previously (58), the proportional decrease in pressure with time was similar to that seen in normal patients. In only four patients in this series was the slope ($\Delta V/\Delta P$) in the mid-volume range definitely low. Even this correction does not remove all of the abnormalities produced by an acquired loss of lung volume in adult life. In the shrunken lung there will be a tendency to retain the chest cage, respiratory muscles, and airways appropriate for the original size of the lungs, the precise extent of preservation of respiratory muscle and airway function depending on the distribution of disease. Because of the interactions with chest wall and airways, a decrease in lung compliance that was disproportionate to the change in lung volume, high values of lung recoil pressure close to full inflation and an enhanced rate of lung emptying could all be found in a "shrunken lung" in which the number of functional units was decreased but the surviving units were mechanically normal. Therefore, a true decrease in distensibility of functioning alveoli cannot be deduced solely from a decrease in volume corrected compliance or accelerated lung emptying as is seen in this disease. It is probable, however,

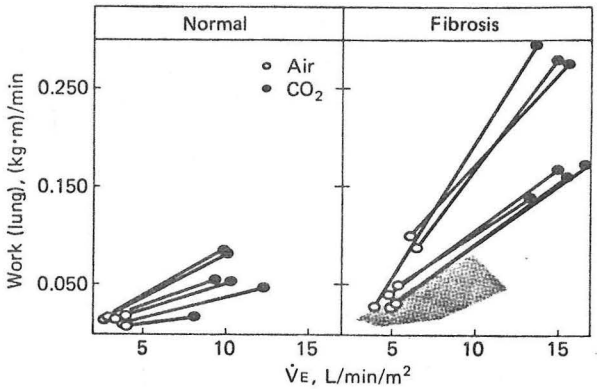
that abnormalities in distensibility are present when these changes are severe. As a summary of the mechanical data, it would seem that in most patients there are two parallel populations of alveoli in pulmonary fibrosis. It is likely that there are only a small number of stiffened but functioning alveoli when compared to the larger subpopulation of either normal or unventilated alveoli with normal distensibility for their lung volume.

FIGURE 4



An important consequence of these mechanical changes, whatever they may be, is an increase in work and energy cost of breathing which results from the more negative intrapleural pressures that have to be generated to overcome the increase in elastic recoil of the lungs. As illustrated in Figure 5 , the work of breathing is often increased two-three-fold in these patients and this abnormality may be critically related to the common clinical presentation of dyspnea (59).

FIGURE 5



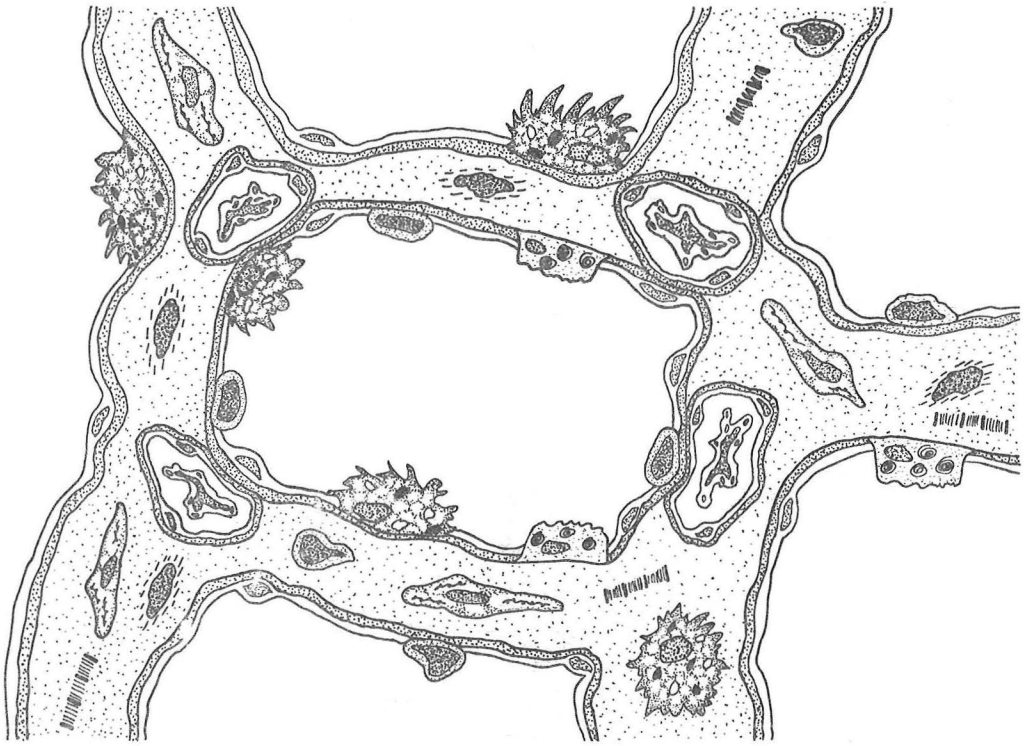
STRUCTURE AND MAINTENANCE OF THE NORMAL ALVEOLUS

Most of the recent literature on idiopathic fibrosis is concerned with the etiology, pathogenesis and clinical approach to this disorder. Since a significant amount of new information in idiopathic pulmonary fibrosis deals with alterations of the cellular and non-cellular constituent of the lower respiratory tract, a consideration of the current concepts of the structure and maintenance of the normal alveolus would seem germaine. With this foundation, the emerging concepts of pathogenesis classification, diagnosis, and staging will be discussed.

Structure Of The Normal Alveolus:

FIGURE 6

NORMAL ALVEOLUS



The major function of the lung is to exchange gases between the atmosphere and the blood. The alveolus is the critical structure of the lung where air and blood are brought into close approximation to make efficient gas exchange possible. The alveolar unit is composed of cells and non-cellular components, each performing specific functions that contribute to overall alveolar function (60). The air surface is bordered by

Type I and Type II epithelial cells. While Type I cells are numerically in the minority, the vast majority of the alveolar surface is lined by these cells (60). The blood surface is bordered by capillary endothelial cells. Together the epithelial and endothelial cells form the boundries of the structure known as the alveolar interstitium. In addition to containing mesenchymal fibroblast-like cells, macrophages, and lymphocytes, the interstitium is composed primarily of non-cellular connective tissue components.

Collagen is the most abundant constituent of this matrix, comprising 60-65 percent of the total extra-cellular mass. The remainder consists of elastic fibers (elastin and micro-fibrils, 35-40 percent) and ground substance (proteins and glycosaminoglycans, less than 5 percent) (61, 62). The functions of the alveolar interstitium are to: provide a frame work that helps maintain alveolar structure; provide a scaffolding that defines the growth patterns of alveolar epithelial and endothelial cells; partially control the mechanical properties of the lung during the respiratory cycle; protect the integrity of the alveolar space by preventing leakage of fluid from the vascular space; provide a secondary line of defense against inhaled injurious materials; and regulate local air and blood flow by controlling alveolar and capillary dimensions.

Most of these functions result from the inherent properties of interstitial connective tissue. The major roles of the cells of the interstitium are to maintain the connective tissue (mesenchymal cells), defend the interstitial and intra-alveolar spaces (macrophage, lymphocytes), and partially regulate local ventilation and perfusion (the contractile cell, a subclass of interstitial mesenchymal cells).

The final class of cells present in the normal alveolus are circulating blood cells. It is not clear at this time whether the circulating blood cells are important in the minute to minute maintenance of lung parenchyma. Polymorphonuclear leukocytes are sequestered in the lung under certain circumstances (63), so the possibility exists that they could influence structure from the capillary lumen. The normal alveolar septum has rare polymorphonuclear leukocytes and the normal alveolar lumen has none, so it is doubtful these cells are critically important in the normal lung. These cells are, however, of great importance in both alveolar defense and alveolar injury.

A constant interchange between blood and lung lymphocytes likely exists. Thus, the circulating lymphocyte replenishes the lung lymphocyte and vice versa (64) but it is not clear how important this process is in the maintenance of normal lung structure or in the production of alveolar disease. The circulating blood monocyte is accepted as the progenitor of the pulmonary alveolar macrophage (65) but the exact timing in control of this change in monocyte differentiation is unknown (66).

Collagen:

Collagen exists in the interstitium of the lung in at least three forms: Type I, Type III, and basement membrane collagens (61, 62). The fundamental unit of collagen is the tropocollagen molecule, which, by its

capacity to copolymerize with other tropocollagen molecules and to interact with a variety of other connective tissue elements, is capable of forming structures such as cartilage, basement membrane, and various fibrils that form the pleura and skeleton of the lung parenchyma.

Tropocollagen is composed of three alpha (α) chains in a right-handed helical arrangement (67). Tropocollagen is heterogeneous; the four types found in the body being distinguishable by the α chains composing them. Type I tropocollagen contains two $\alpha 1$ (I) chains and one $\alpha 2$ chain and thus has the structure $[\alpha 1\ (I)]_2\ \alpha 2$. Each of the other tropocollagens, Type III and basement membrane collagen, is composed of three identical α chains of the appropriate type; the structures are $[\alpha 1\ (III)]_3$, and $[\alpha 1\ (IV)]_3$, respectively.

TABLE 11

TYPE I COLLAGEN

65% of total interstitial collagen

Easily visible with Masson-Trichrome

Highly organized cross-banded fibers

Non-compliant

Although they share certain properties, each of these collagens is a distinct macromolecule with a characteristic amino acid sequence. The most abundant is Type I, representing 60-70 percent of the total interstitial collagen (68). This material is best visualized by light microscopy with a Masson-Trichrome stain (Type I collagen stains blue). By electron microscopy, Type I collagen is seen as cross-banded fibers, usually 50-1000 nm in diameter, running parallel to the basement membrane. Most studies suggest that Type I collagen is the most highly organized, least compliant form of interstitial collagen and that it plays a critical role in maintaining normal alveolar structure and function.

TABLE 12

TYPE III COLLAGEN

30% of total interstitial collagen

Not well visualized with light microscopy

Randomly dispersed fibrils

Influences Type I fibril formation

Type III collagen represents 30-40 percent of the total interstitial collagen (69). Unlike Type I collagen it is not well visualized by light microscopy. In the electron micrographs, it appears to be predominently in the form of 150-250-nm, randomly dispersed fibrils. Type III collagen fibrils probably contribute to alveolar structure and function via their influence on the way in which Type I collagen forms fibrils. Thus, while the function of these two collagen types is not definitively known, there is growing evidence that the mechanical properties of tissues are significantly controlled by the relatively stiff Type I collagen, the

form of which appears to be significantly influenced by the relative amounts of Type III collagen present (70). Thus, the contribution of collagen to lung function is modulated, at least in part, by the ratio of Type I to Type III collagen within the alveolar interstitium.

TABLE 13

BASEMENT MEMBRANE COLLAGEN

5% of total interstitial collagen

Structure unknown

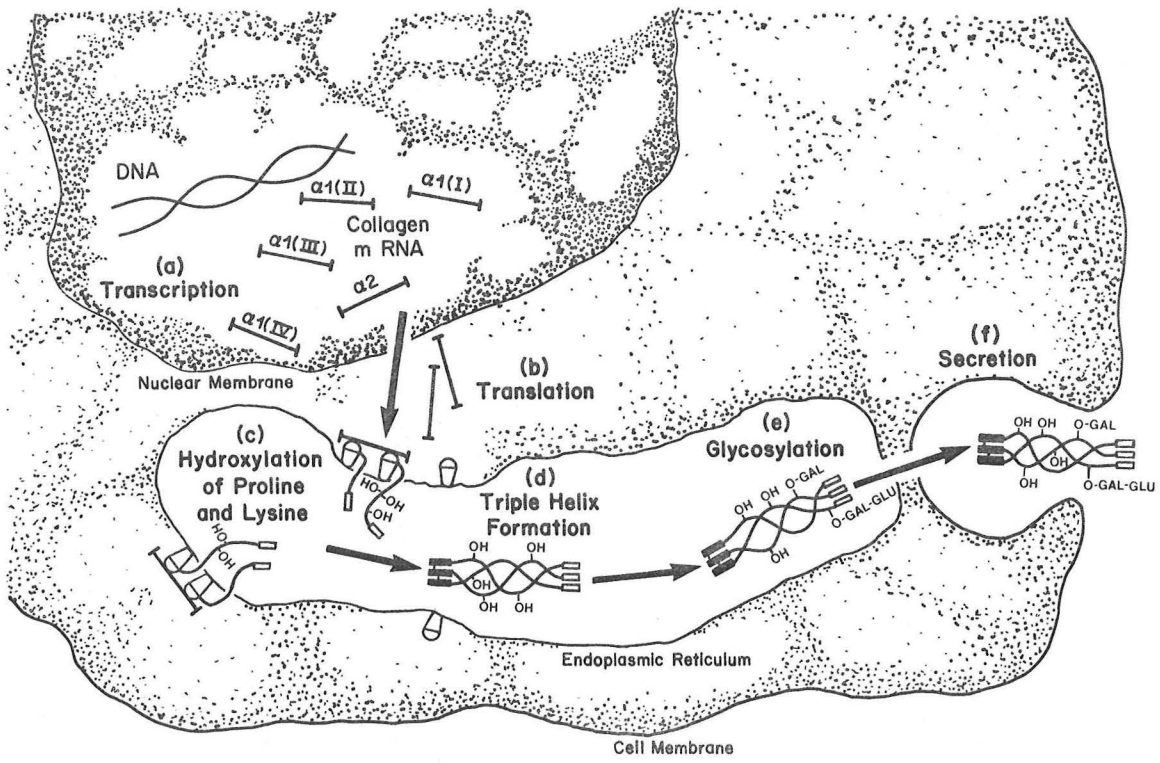
Defines growth patterns of epithelial and endothelial cells

Integrity determines reversibility of process

Basement membrane is found beneath the alveolar epithelial and beneath the capillary endothelial cells (61). The composition of lung basement membrane is not well described, but evidence from other tissue suggests that at least 50 percent of basement membrane is made up of collagen. Besides providing anatomic barriers, basement membrane appears to play a critical role in defining the growth patterns of epithelial and endothelial cells following injury (71). It is suspected but not proved, that part of the irreversibility of some interstitial disorders depends on whether the basement has remained intact. When basement membrane is intact the remaining lung cells may be able to rebuild the injured alveolus. If, however, the basement membrane is significantly disrupted, the alveolar structures remain irrevocably disordered.

FIGURE 7

BIOSYNTHESIS OF COLLAGEN

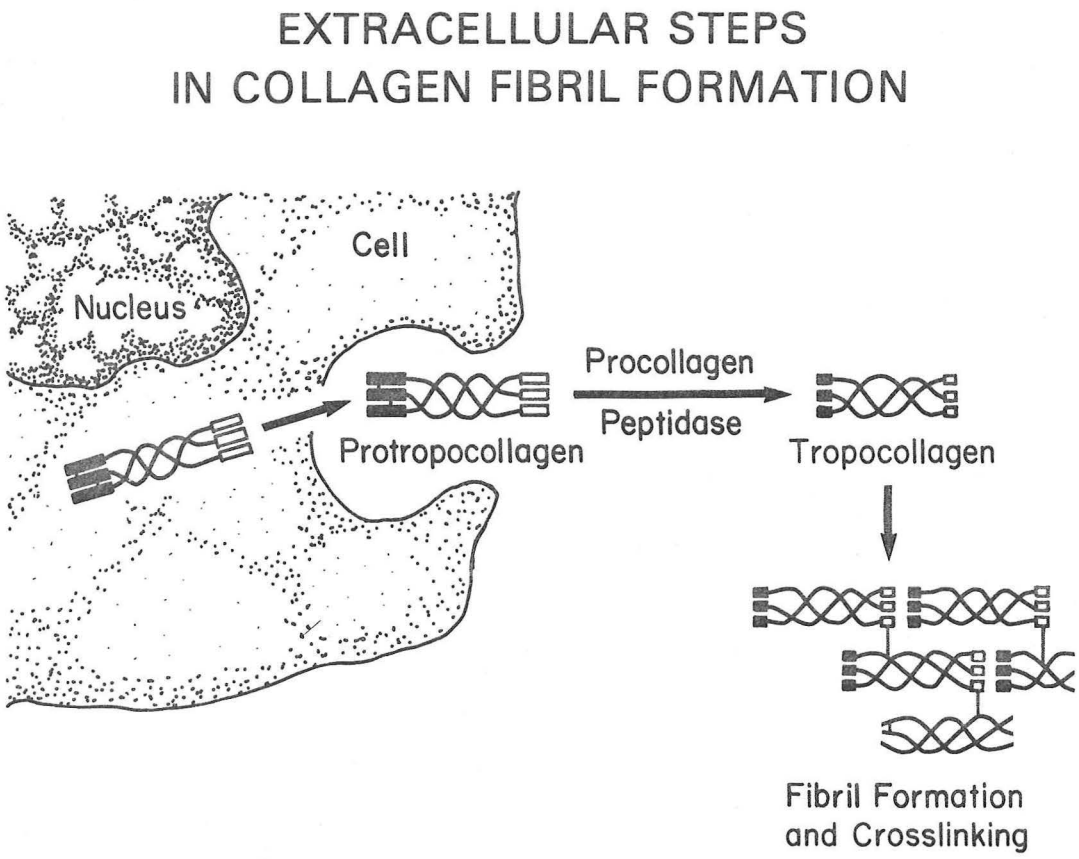


Because of the abundance and wide distribution of collagen, its biochemistry has received considerable attention. A schematic representation of the biosynthesis of collagen is shown in Figure 7 . The five known α chains have different primary amino acid sequences and are the products of different structural genes. While very little is known concerning the transcription of collagen mRNA or the mechanism of its transcriptional control, this process results in a distinct mRNA for each of the α chain types. It is assumed, but not proved, that each differentiated cell transcribes only the collagen mRNAs specific for the collagen type characteristic for that cell. Collagen mRNAs are then transported from the nucleus to the ribosomes lining the rough endoplasmic reticulum. Collagen mRNA is known to be translated on these ribosomes in a fashion typical to that for other proteins destined for secretion (72-75). The large collagen mRNA (MW>1.6 x ^{6}daltons) (76) is capable of accomodating many ribosomes and therefore the polysomes directing its synthesis are large (77). The translation product of collagen mRNA is not the α chain but rather a large precursor (MW:150,000 daltons) called the pro-α chain (78). Translation time for an intact pro-α chain is probably 7-8 min *in vivo*. The pro-α chain contains three regions: an N- terminal non-collagenous region (MW:20,000 daltons) (); a middle α chain region (MW:95,000 daltons) (), and a C-terminal non-collagenous region (MW:35,000 daltons) (). As the precursor pro-α chains are synthesized, they move into the cisternae of the endoplasmic reticulum, where some of the proline and lysine molecules are hydroxylated enzymatically (79). Additionally, some of the hydroxylysyl residues are glycosylated by enzymatic addition of the monosaccharide, galactose (GAL), or the disaccharide, glucosylgalactose (GLU-GAL) (80). Glycosylation takes place both before pro-α chains are released from the ribosome and after helix formation (81). The final important step before secretion is the formation of the triple helix. The importance of the N- and C- terminal non-collagenous pro-regions of the pro-α chain is just beginning to be understood. Near the time of release of the newly synthesized pro-α chains from the ribosome but before helix formation, three pro-α chains of the appropriate type are aligned, probably through interaction of the non-collagenous regions. This association is stabilized by disulfide bonds in the C-terminal region (78). Subsequent triple helix formation of the middle α chain "collagenous" regions results in the formation of protropocollagen, the form in which collagen is secreted from the cells (78). In addition to its role in stabilizing the association of the pro-α chains, other functions suggested for the "pro" regions include: 1) ensuring solubility of collagen during cellular and extra-cellular transport (82); 2) facilitating proper orientation of tropocollagen during fibrillogenesis (83); and 3) inhibiting premature crosslink formation (84). Following the formation of the triple helix, the molecule is then secreted by the cell. While it is known that optimal secretion requires protropocollagen to be in the triple helical configuration (78), the mechanism by which the newly synthesized protropocollagen is secreted remains uncertain. It has been suggested that protropocollagen moves from the smooth endoplasmic reticulum to the Golgi apparatus, to Golgi-derived vascules, and eventually to the extra-cellular space.

The ultimate ability of collagen to serve its supportive function requires the formation of strong collagen fibrils, which, together with the associated non-collagen connective tissue glycoproteins forms the matrix for individual tissues. The extra-cellular biochemical steps which

are necessary for collagen fibril formation are shown in Figure 8 . Newly secreted protropocollagen consists of three coiled collagen α chains plus N-terminal and C-terminal non-collagenous peptides. The proteolytic action of procollagen peptidase cleaves the N- terminal non-collagen peptides producing the intermediate p-tropocollagen. Further proteolytic activity removes the C- terminal non-collagen peptides, leaving tropocollagen composed of a helical region of three α chains with short, non-helical peptides at either end (85, 86). Tropocollagens then polymerize to form the collagen fibril which is reinforced by crosslinks shown as heavy lines (67). While crosslinking is not necessary for fibril formation, it undoubtedly is of great importance in determining lung structure. Without crosslinking, the fibrils lack high tensile strength. The location, amount, and stability of lung collagen crosslinks has not been explored directly, but almost certainly plays an important role in the molecular basis of normal development, aging, and many lung diseases.

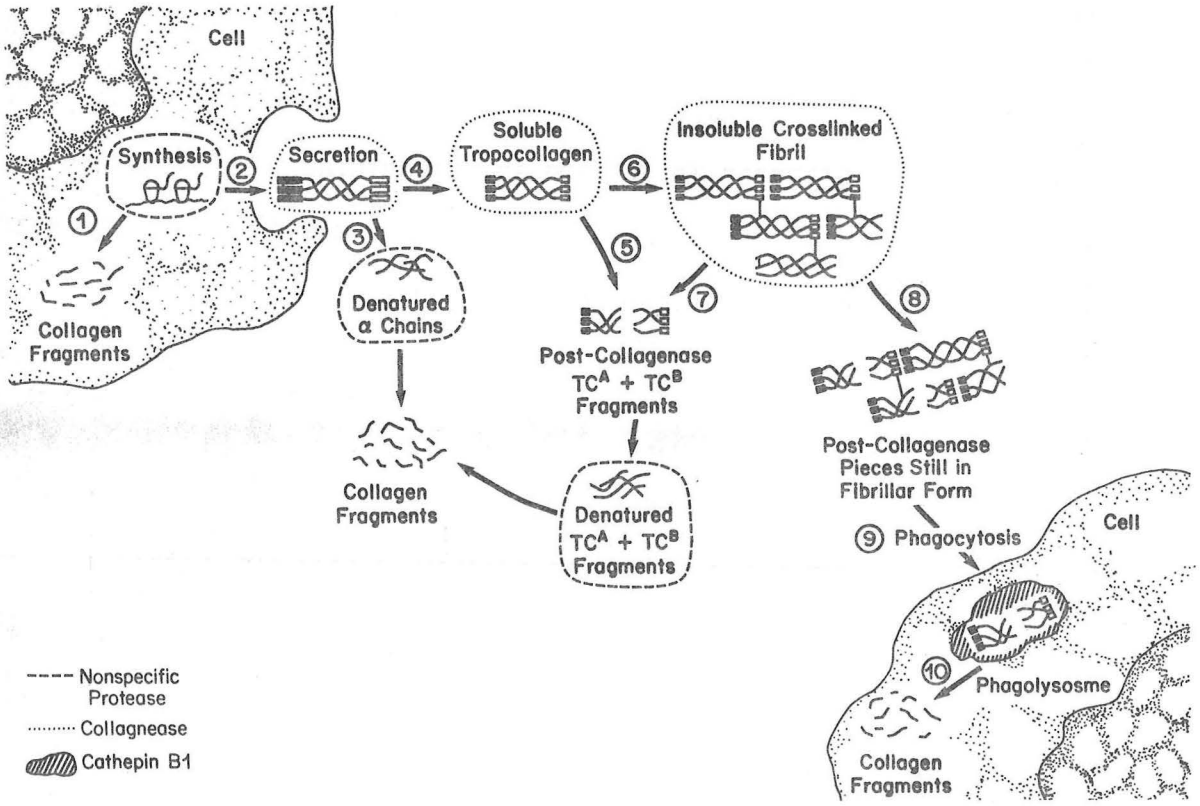
FIGURE 8



The normal adult lung continually synthesizes collagen by the processes just described; yet, on the average, the concentration of collagen in the normal adult lung does not change (87). To preserve the constancy of collagen per unit lung mass, there must be a continual normal destruction of collagen at a rate that matches the synthetic rate. The mechanisms by which this takes place are just beginning to be understood and are shown in Figure 9 .

FIGURE 9

COLLAGEN DEGRADATION



In the triple helical form, collagen is very resistant to proteolytic attack, thus placing considerable restrictions on possible mechanisms of collagen degradation (88, 89). However, before collagen is in the helical form, intra-cellular degradation can occur (90). This process does not require collagenase; and numerous non-specific proteases can hydrolyze collagen in this form (90). Once the α chains are in the triple helical form, that is after secretion has occurred, the α chains can be degraded only by vertebrate collagenase or microorganism collagenase (91). Presumably, the latter is not normally present in the alveolar milieu. If the triple helix is denatured, which occurs if under-hydroxylated collagen is formed, then the α chains can be attacked once again by non-specific proteases. However, with the conversion of protropocollagen to soluble tropocollagen, the molecule now consists of three α chains in helical form which can be degraded only by collagenase. Collagenase secretion has been demonstrated from explants of rabbit lung parenchyma and cultured rabbit alveolar macrophages (61). Both polymorphonuclear leukocytes and alveolar macrophages are known to be sources of vertebrate collagenase (61). While it is unknown which cell is responsible for the production of the enzyme secreted by rabbit parenchyma, these two cells are likely candidates. It is also probable that lung mesenchymal cells synthesize and secrete collagenase. Regardless of its source, the

results of vertebrate collagenase proteolysis is the formation of a tropocollagen molecule in two helical fragments and an N- terminal and C- terminal fragment. These fragments then denature and can be attacked by non-specific proteases. The final mechanism of collagen degradation that is known to occur requires phagocytosis. If the intermolecular crosslinks leave the postcollagenase pieces still in fibrillar form, the partially degraded fibril can be phagocytized and in the resulting phagolysosome, enzymes such as cathepsin B1 can degrade the fibril at an acid pH (92).

PATHOGENESIS OF INTERSTITIAL PULMONARY FIBROSIS: CELLS, COLLAGEN AND FIBROSIS

The original light microscopic descriptions of interstitial pulmonary fibrosis suggested that the "fibrosis" was simply an accumulation of interstitial collagen mediated by activated fibroblasts responding to injury (23).

It was predicted, therefore, that quantitation of the concentration of collagen in biopsy specimens of interstitial pulmonary fibrosis would reveal increased amounts of collagen and that quantitation of the rates of collagen synthesis by the lung cell would show elevated rates compared to normal. Thus, it was surprising to find that both collagen concentration and rates of synthesis are normal in this disease (93, 94). Initially these findings were difficult to reconcile with the light microscopic observations in idiopathic pulmonary fibrosis. However, as information has accrued using ultrastructural and biochemical techniques, it has become apparent that the fibrosis of idiopathic pulmonary fibrosis is much more complex and includes the following abnormalities.

TABLE 14

BIOCHEMICAL AND MORPHOLOGICAL CHARACTERISTICS
OF IPF - COLLAGEN

Normal collagen concentration and rates of synthesis

Localized accumulations of collagen

Type I/III ratio markedly increased

Abnormalities of collagen fibers

Basement membrane thickening

Although collagen is evenly distributed throughout the normal interstitium, in idiopathic pulmonary fibrosis there are localized accumulations such that some septa are markedly thickened, whereas, others are not. On the average, the interstitial pulmonary fibrosis interstitium contains relatively more Type I and less Type III collagen than is found in the normal alveolus. Whereas, the normal alveolus contains collagen Type I and III in a ratio of 2.5-1, the idiopathic pulmonary fibrosis alveolus contains far more Type I collagen, a ratio Type I to Type III of 5-1 (95). Since Type I, and not Type III, stains with the usual light microscopy connective tissue stains, a shift towards Type I collagen would be perceived as increased amounts of total collagen while the total (Type I plus III) is actually unchanged. Since Type I is the less compliant of the collagen types (70), this finding could help to explain the restrictive physiological findings which are present in this disease. Not only does the interstitium contain relatively more Type I

fibers, but the fiber bundles seen in idiopathic pulmonary fibrosis are thickened, twisted, frayed and randomly oriented, while the Type I fibers in the normal interstitium are contained in sharply defined, relatively thin bundles running parallel to the basement membrane. Finally, the basement membranes in idiopathic pulmonary fibrosis lung are thickened, but in some areas they are thinned and occasionally disrupted particularly on the epithelial surface. This information, together with the knowledge that maintenance of the interstitial collagen in the normal lung requires the balance of synthetic and degradative processes by a variety of cells, suggests that the fibrosis of idiopathic pulmonary fibrosis is not simply secondary to increased synthesis by activated fibroblasts. Rather, the deranged collagen of the idiopathic pulmonary fibrosis interstitium must result from a number of processes involving multiple cell types in which the coordinated control of collagen synthesis and degradation is lost.

TABLE 15

MORPHOLOGICAL CHARACTERISTICS OF IPF - CELLS

Decreased numbers of Type I cells

Increased numbers of Type II and mesenchymal cells

Abnormal cell locations

Increased numbers of inflammatory and immune effector cells

While interstitial fibrosis is a prominent feature pathologically, evaluation of the parenchymal populations in idiopathic pulmonary fibrosis also reveals marked changes in both cell types and location of cells. Most importantly there are decreased numbers of Type I epithelial cells, but increased numbers of Type II cells and mesenchymal cells (96, 97). In addition, there appear to be changes in the clonal populations of mesenchymal cells present. The normal interstitium contains few smooth muscle cells, while idiopathic pulmonary fibrosis is characterized by islands of these cells scattered throughout the parenchyma. This finding led to the coining of the pathological term "muscular cirrhosis of the lung". Not only are the parenchymal populations changed in idiopathic pulmonary fibrosis, but they are also found in abnormal locations and topological arrangements. Since many of these cells normally synthesize the interstitial collagens, alteration in the number, type and location of these cells could have profound effects on the type and location of collagen that is newly synthesized (96). Thus, it is quite possible that interstitial collagen could become significantly altered even though the rates of collagen synthesis remain unchanged.

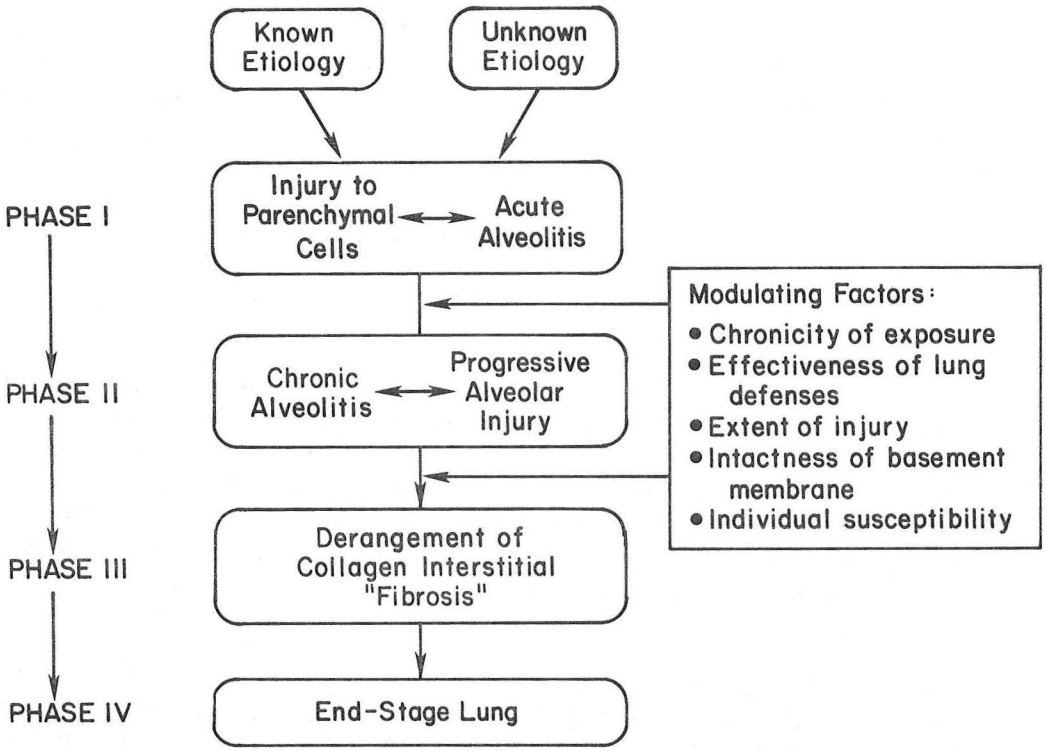
The key to understanding the pathogenesis of the fibrosis of idiopathic pulmonary fibrosis is an appreciation that in addition to the above mentioned classic findings, idiopathic pulmonary fibrosis is importantly associated with profound alterations in the inflammatory and immune effector cells that are present within the alveolar structures (98).

The current concept of the pathogenesis of idiopathic pulmonary fibrosis is that there is a progression of the disease through at least four phases (99). Phase I represents the initial injury to lung parenchyma and the

associated alteration in cell types. Parenchymal injury could result from direct toxicity to existing parenchymal cells or from indirect injury mediated through inflammatory and immune reactions. Regardless of the mechanism, Phase I is associated with significant alterations in parenchymal cell types and with an acute alveolitis characterized by the proliferation, recruitment and activation of inflammatory and immune effector cells. Throughout this discussion, the term alveolitis will be used repeatedly. This morphologic term, which characterizes one of the alterations of alveolar structures found in this disease, refers to the inflammatory and immune effector cells that accumulate in the interstitium or in the alveolar air spaces. While the terms pneumonitis and pneumonia have also been used in reference to the accumulation of these inflammatory and immune effector cells, the term alveolitis would seem preferable to emphasize the non-infectious nature of idiopathic pulmonary fibrosis.

FIGURE 10

PATHOGENESIS OF THE INTERSTITIAL LUNG DISORDERS



Phase II is characterized by development of chronic alveolitis and progressive injury to the non-cellular and cellular constituents of the alveolus including alterations in parenchymal cell numbers, types, locations and/or differentiated properties. There is usually evidence of damage to Type I epithelial cells and proliferation of Type II epithelial cells during this phase. As will be seen in the following sections, a large portion of the current literature has been concerned with characterizing the chronic alveolitis of Phase II and with understanding the

mechanisms by which it effects progressive injury to alveolar structures. The transition from Phase I to Phase II can occur within days or years. This transition may in fact take place long after the initial inciting agent is removed. Because of the alterations in alveolar structures that take place in Phase II the transition from Phase I to Phase II marks the time when the disease becomes less reversible. A recurrent theme of the current literature is that a number of factors appear to modulate whether the disease process will progress from earlier to later phases or will revert towards normal. Of these modulating factors, the most important are chronicity of exposure to the causative agent, effectiveness of lung defense mechanisms, extent of injury, intactness of the basement membranes, and individual susceptibility.

Phase III is characterized by a derangement in interstitial collagen. recognized with light microscopy as fibrosis. It is apparent from the previous section, that interstitial fibrosis is not simply a build up of collagen resulting from activation of fibroblast, but is a result of a complex series of events involving collagen synthesis and destruction by several cell types. As was previously discussed in the section on the maintenance of normal alveolar structure, interstitial collagen is maintained in its normal state by epithelial, endothelial, and interstitial cells. It is not surprising, therefore, that alterations in parenchymal cell-types which occur in Phase II result in a significant derangement of collagen in Phase III. As we will see in a subsequent section, the mechanisms of collagen derangement are just beginning to be understood, but it clearly can change in type, form, and location, and in some areas it can be so disrupted that alveolar septi are destroyed and cystic spaces are formed. As with the transition from Phase I to II, the transition of the interstitial disorders from Phase II to III is modulated by a number of factors that seem to regulate whether the disease stabilizes, progresses or reverses. However, by the time Phase III is reached, the structures of the affected alveoli are deranged sufficiently to make complete reversibility less likely.

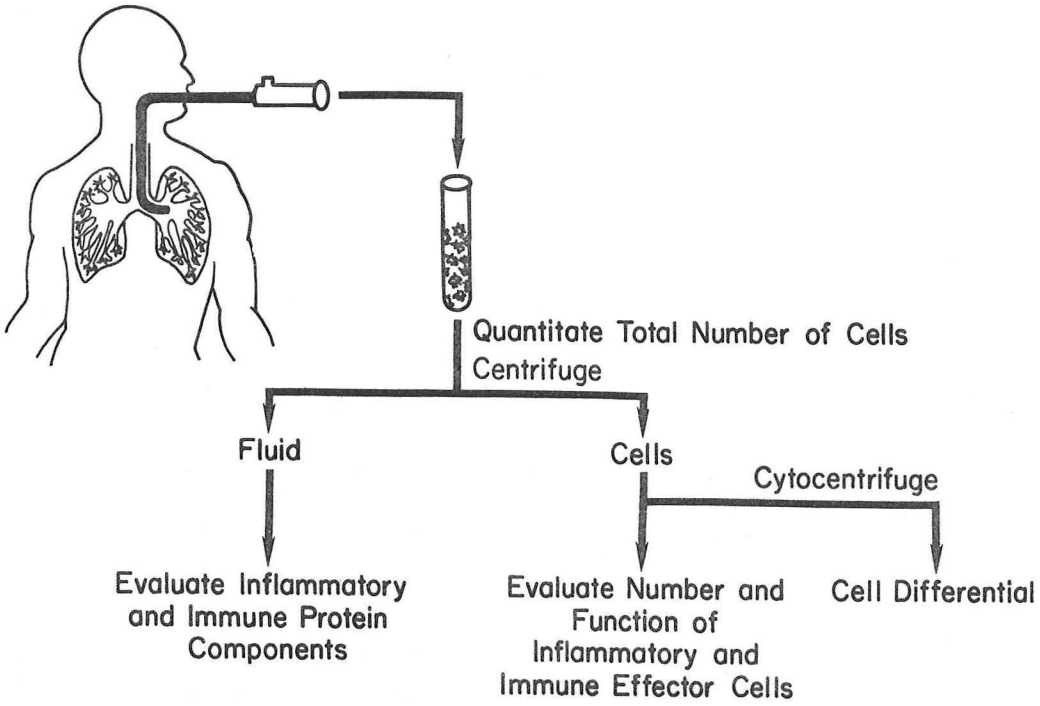
Phase IV, or end stage lung, is characterized by complete loss of alveolar structure and by the wide spread formation of non-functioning cystic spaces. This phase is the final common pathway for almost all of the interstitial disorders. In the presence of severe fibrosis and destruction, few features of the typical alveolitis or other morphological characteristics (e.g. granuloma) are present, and once this phase has been reached it is often impossible to discern the underlying type of interstitial disease.

If this hypothesis is correct, in order for us to properly evaluate these disorders, it is important to define the cellular and non-cellular effector components of the alveolitis. The definitive tools for evaluating the alveolitis of these disorders is a lung biopsy. However, besides being an invasive procedure associated with some morbidity, lung biopsy is generally limited to a histological evaluation of the cell population found in the lung parenchyma. Commonly used histologic techniques are not easily adaptable to quantitation to cell types, and these methods give little information about the effector function of cells intimately associated with alveolitis.

Another approach to evaluation of the alveolitis of interstitial disease involves the use of fiberoptic bronchoscopy to sample the fluid lining the epithelial surface of the lower respiratory tract (100). Although this procedure does not give a comprehensive examination of all of the constituents of the lung parenchyma, the cells and non-cellular components present on the epithelial surface of the alveoli are known to be representative of the inflammatory and immune system of the entire lower respiratory tract (100). The tracheo-bronchial tree therefore, is a "window" to the inflammatory and immune system of the alveolar structures and bronchoalveolar lavage allows safe, repetitive sampling of various components of the inflammatory and immune system at the site of their action.

FIGURE 11

BRONCHOALVEOLAR LAVAGE PROCEDURE



Bronchoalveolar lavage is performed using a fiberoptic bronchoscope which allows this evaluation to be carried out with no risk and little discomfort to the patient. After the upper airways and trachea are anesthetized with a xylocaine spray, the fiberoptic bronchoscope is inserted through the nose into the tracheo-bronchial tree. Following routine evaluation of the respiratory tract, the tip of the bronchoscope is wedged into a subsegmental bronchus of the lingula or right middle lobe. Other lobes can be used, but lavage of the upper lobe is more difficult because of the tight bend in the bronchoscope imposed by the anatomy of the upper lobe bronchi, and the amount of fluid recovered from the lower lobes is

slightly less than that from the middle lobes. Once the bronchoscope is wedged, 20 ml of 0.9 sterile saline is inserted into the suction port by the use of a syringe on a three-way stopcock. The fluid is immediately pulled back using 5-100 mm Hg of negative pressure from a usual clinical suction apparatus and the fluid is collected in a 50 ml specimen trap. The process of lavage and suction is then repeated five times and in general, 40-60 percent of the infused volume is recovered. Although, a total of 100 ml of lavage is usually employed, volumes of up to 300 ml may be used if larger numbers of inflammatory or immune cells are desired in a particular subject. Following lavage, the volume of fluid and total number of cells recovered are quantitated and the cells are separated from the fluid by centrifugation. The fluid may be concentrated with the use of an Amicon ultrafiltration membrane prior to evaluation for the presence of various proteins. Cells obtained from the bronchoalveolar lavage are utilized to quantitate the number and function of various inflammatory and immune effector cells. The proportion of bronchoalveolar cells that are alveolar macrophages, lymphocytes or polymorphonuclear leukocytes can than be enumerated on a Wright-Geimsa stain cytocentrifuge preparation of the cells (101-106).

TABLE 16

BRONCHOALVEOLAR LAVAGE CHARACTERISTICS
OF NORMAL SUBJECTS

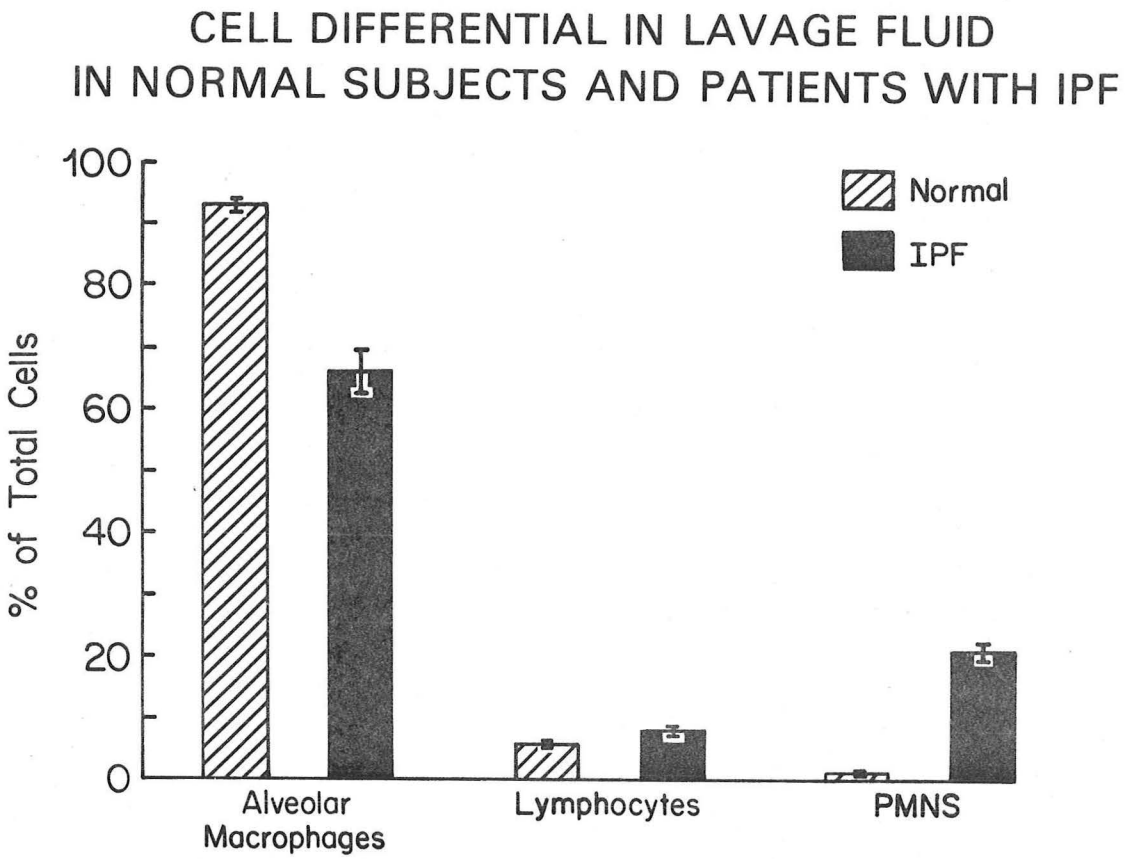
Cell yield	5-10 x 10^6
Differential cell counts	
Alveolar macrophages	93 + 3%
Lymphocytes	7 ± 1%
Neutrophils	<1%
Eosinophils	<1%
Basophils	<1%

Broncho-pulmonary lavage of a normal adult human generally yields 5-10 x 10^6 cells. Differential cell counts of this recovered fluid reveal approximately 93 percent of the cells are alveolar macrophages and 7 percent are lymphocytes. Neutrophils, eosinophils, and basophils each account for an additional 1 percent (104-106).

The bronchoalveolar lavage fluid findings from patients with idiopathic pulmonary fibrosis are shown in Figure 12. Lavage fluid from patients with idiopathic pulmonary fibrosis yielded an average 16.3 million cells while control subjects yielded 6 million cells.

The type of cells recovered in the lavage fluid of patients with interstitial pulmonary fibrosis clearly distinguished these patients from normal controls (104). Patients with interstitial pulmonary fibrosis had a dramatic increase in the number of neutrophils in their lower respiratory tract (21.2 ± 3.4 percent vs 2.1 ± 0.4 percent in control patients). The percentage of lymphocytes was approximately 10 percent in both controls and in patients with idiopathic pulmonary fibrosis, whereas, the number of alveolar macrophages ranged from 82 percent in control patients to 65 percent in patients with idiopathic pulmonary fibrosis.

FIGURE 12



Although the relationship between the effector cells just described and the fibrosis of idiopathic pulmonary fibrosis remains uncertain, convincing data has accumulated implicating certain dominant pathogenic processes. In many instances, the pathogenic processes require interdependence between different effector cells, but for convenience we will discuss each cell separately.

TABLE 17

ROLE OF CELLS IN DERANGEMENT OF INTERSTITIAL COLLAGEN

Lymphocytes:
- a) Subpopulation secrete MIF in response to collagen
- b) Increase macrophage collagenase secretion
- c) Loss of normal suppression of collagen synthesis

Macrophages:
- a) Secrete collagenase
- b) Spontaneously secrete neutrophil chemotactic factor

Neutrophils:
- a) Secrete collagenase which selectively attacks Type I collagen
- b) Secrete neutral proteases
- c) Secrete proteases which alter fibronectin

Lymphocytes:

The relative proportion of lymphocytes in the parenchyma of patients with idiopathic pulmonary fibrosis is normal, but since the number of inflammatory and immune effector cells is increased, the total number of lymphocytes per alveolus is also increased (104). Although direct evaluation of the lymphocyte subpopulations in the idiopathic pulmonary fibrosis parenchyma has demonstrated that the proportion of T and B lymphocytes are normal, it is likely that at least certain lymphocyte subpopulations are different from those in normals. There is evidence that lymphocytes from patients with idiopathic pulmonary fibrosis recognize collagen as "non-self" and produce lymphokines such as macrophage migration inhibition factor (MIF) in response to it (107). The mechanisms by which this occurs are not clear, but the T lymphocyte is required in some fashion, since its removal completely obviates this phenomenon, at least *in vitro*. Two additional roles have been suggested for lymphocytes in relation to the fibrosis of idiopathic pulmonary fibrosis. First, there is evidence that activated lymphocytes can "turn on" macrophages such that they secrete increased quantities of collagenase (108). Second, there is evidence that lymphocytes, in cooperation with mononuclear phagocytic cells, produce factors that suppress mesenchymal cell collagen synthesis by 30-40 percent (109). Thus, it is theoretically possible that one fibrosis-related pathogenic mechanism in idiopathic pulmonary fibrosis is the loss of the suppressive effect and the resultant increased production of collagen by at least some parenchymal cells. This latter hypothesis remains largely untested in idiopathic pulmonary fibrosis patients.

Macrophages:

As with lymphocytes, the relative proportion of macrophages in the idiopathic pulmonary fibrosis lung is not increased but compared to normal lungs the total number of macrophages per alveolus is greatly elevated (104). It is unclear why there are more macrophages present per alveolus but one possibility is that macrophages are induced to stay in the involved alveoli by the influence of MIF produced by lymphocytes in the local area (107). Since alveolar macrophages produce a collagenase capable of attacking Types I and III collagen (110), one consequence of the increase in the numbers of macrophages per alveolus would be an imbalance in the maintenance of interstitial collagen towards collagen destruction.

Recent evaluations of alveolar macrophages recovered from patients with idiopathic pulmonary fibrosis suggest that the macrophage likely plays a critical role in the pathogenesis of idiopathic pulmonary fibrosis by recruiting neutrophils to the alveolar structures. This process is apparently mediated through the secretion by the macrophage of low molecular weight chemotactic factor which selectively attracts neutrophils (111-113). Studies of idiopathic pulmonary fibrosis macrophages have shown that they are spontaneously secreting this neutrophil chemotactic factor possibly mediated by the stimulation of immune complexes present in the lower respiratory tract of these patients (114).

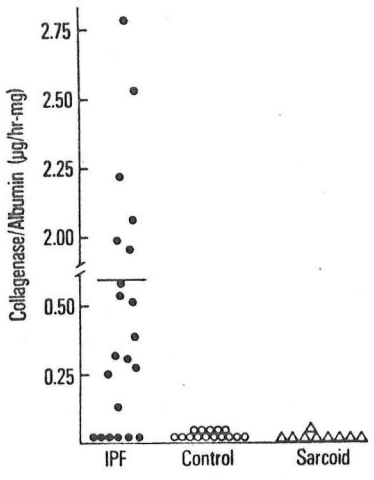
Polymorphonuclear leukocytes:

As described earlier, analysis of the inflammatory and immune effector cells contained in bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis has clearly shown that this disorder is associated with

the chronic accumulation of neutrophils in the alveolar structures (104). These neutrophils are not only on the epithelial surface; analysis of open lung biopsies of these patients have shown that 18 ± 6 percent of the total inflammatory immune effector cells within the biopsy are neutrophils (115) a finding confirmed by morphological evaluation (98). The presence of these cells within the alveolar structure provides a firm basis for understanding the derangements in lung parenchyma that are characteristic of the disease.

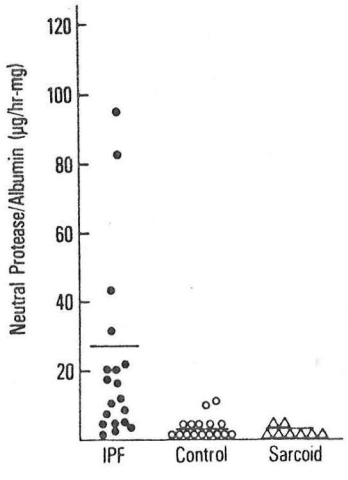
As outlined earlier, the fibrosis of idiopathic pulmonary fibrosis is characterized by the presence of interstitial collagen that is severly disordered (99). According to current thinking this disordering occurs as a result of normal alveolar interstitial collagens being continually disrupted and replaced by collagen that is abnormal in location, amount, type and form (95, 99). Since disruption of normal collagen requires the action of collagenase, validation of this hypothesis requires the demonstration of active collagenase in the lung parenchyma of these patients. Neutrophils carry a variety of preformed proteolytic enzymes that have the potential to cause significant injury to alveolar structures. Most importantly, neutrophils contain the enzymes collagenase and neutral protease both of which are probably important in the deranging of interstitial collagen. Recent studies from the NIH have shown that most patients with idiopathic pulmonary fibrosis have collagenase detectable in their alveolar fluid as shown in Figure 13 A (116). Fifteen of twenty-one patients with idiopathic pulmonary fibrosis showed collagenase activity in their bronchoalveolar lavage fluid, whereas,normal controls and patients with sarcoidosis showed none. In two patients with idiopathic pulmonary fibrosis who were reevaluated after eight to twenty-four months, the collagenase activity was persistent. Further evaluation of the control and sarcoid groups for "latent" or precursor collagenase activity (117) revealed that none was present. As with all mammalian collagenases the collagenase in the lower respiratory tract of patients with idiopathic pulmonary fibrosis specifically cleaved Type I collagen to characteristic A and B fragments (91, 118, 119).

FIGURE 13 A



A

FIGURE 13 B



B

Fluid from patients with idiopathic pulmonary fibrosis also contained elevated levels of a nonspecific neutral protease, Figure 13 B. Although controls and patients with active pulmonary sarcoidosis had low levels of neutral protease activity in their lavage fluid (controls, 4 ± 1μg/hr · mg; sarcoidosis, 3 ± 1μg/hr · mg), nine of nineteen patients with idiopathic pulmonary fibrosis had levels that were in excess of the highest value found in controls or those with sarcoidosis. Mean values for patients with idiopathic pulmonary fibrosis were 25 ± 7μg/hr · mg).

The detection of an active collagenase in a physiological fluid is rare (120,121). When collagenase has been found (such as in snovial fluid from rheumatoid arthritis) it has been suggested that the collagenase was activated because of the concomitant presence of a neutral protease (121). Thus, it is of interest that idiopathic pulmonary fibrosis lavage fluid also contains elevated levels of a neutral protease. Although it is not known whether the neutral protease can account for the activation of latent lung collagenase, it is known that the alveolar macrophage (117) and the neutrophil, the leading candidate as a source of collagenase in the idiopathic pulmonary fibrosis lung secrete collagenase in a latent form that can be activated by a neutral protease with similar specificities as that found in idiopathic pulmonary fibrosis (117).

The consequences of having increased quantities of such enzymes within the interstitium are many, but two are particularly relevant to the disordered collagen that is part of the fibrosis of idiopathic pulmonary fibrosis. First, since neutrophil collagenase selectively attacks Type I collagen over Type II collagen, neutrophil collagenase may be responsible for some of the fraying of the Type I collagen seen on electron micrographs of the idiopathic pulmonary fibrosis interstitium (98,99). Unlike neutrophil elastase, which is inhibited by α1-antiproteinase (an antiprotease plentiful in the lung of patients with idiopathic pulmonary fibrosis), collagenase is inhibited primarily by α2-macroglobulin (an antiprotease not found in alveolar fluid). Second, neutrophil proteases may be the cause of some of the disordering of parenchymal cells noted in this disease. Recent studies by McDonald, et al. (122) have found that fibronectin, a large adhesive glyoprotein found on the surfaces of many cells including lung fibroblasts, is very susceptible to neutrophil proteases. Since fibronectin is thought to mediate cell-cell and cell-connective tissue matrix interactions, destruction of this macromolecule by neutrophil proteases may be an important step in the pathogenesis of idiopathic pulmonary fibrosis.

The fact that the lung in idiopathic pulmonary fibrosis has a substantial collagenolytic burden lasting for months to years helps explain why patients with idiopathic pulmonary fibrosis have a progressive derangement in interstitial collagen of their alveolar structures. In comparison, although acute forms of pneumonitis (e.g., pneumococcal pneumonia) are associated with neutrophils within the alveolar structures, these short lived cells are present for only a few days, and not, apparently, long enough to cause progressive, permanent damage to the interstitial connective tissues. The importance of the persistence of the collagenase in the idiopathic pulmonary fibrosis lung to the pathogenesis of this disease is similar to the pathophysiological importance of active collagenase in the joint fluid of patients with chronic, erosive rheumatoid arthritis (121). Although acute infections of a joint or arthritis

induced by crystals may generate collagenase activity within the joint space, it probably represents only a transient overriding of hemostatic controls. The relevance of collagenase activity to the pathology of articular or alveolar structures probably results from the persistance of the active enzyme and the associated chronic collagen proteolysis during the evolution of these chronic inflammatory disorders.

TABLE 18

ALVEOLAR MACROPHAGE CHEMOTACTIC FACTOR

Low molecular weight, lipid containing substance

Preferentially attracts neutrophils

Activates neutrophils

Immune complexes stimulate secretion

Since neutrophils are so central to the pathogenesis of idiopathic pulmonary fibrosis, it is important to consider the mechanisms that attract these cells to the alveolar structures. As previously mentioned, alveolar macrophages may play a critical role in the recruitment of neutrophils to the alveolar surface. Studies of the alveolar macrophages of patients with idiopathic pulmonary fibrosis have demonstrated that these cells are activated such that they produce alveolar macrophage chemotactic factor (AMCF) for neutrophils (123,124). This low molecular weight chemotactic factor is known to be heterogeneous, made up, at least in part of lipid (112,113). Not only does AMCF attract neutrophils, but it activates them as well (125,126), thus, potentially explaining the elevated levels of collagenase in the alveolar fluid as well as the propensity of these neutrophils to injure parenchymal cells (127). Although the stimulus responsible for the secretion of this chemotactic factor is unknown, recent studies have shown that patients with this disease have both circulating immune complexes and immune complexes within their alveolar structures and bronchoalveolar lavage (123,124,128). In this regard, it is also known that pulmonary B lymphocytes of patients with idiopathic pulmonary fibrosis are activated to the extent of secreting 100 times more immunoglobulin than do normal lung lymphocytes (129). Neither the specificity of these immunoglobulins nor the antigen constituting the immune complexes in these patients are known; however, it is reasonable to hypothesize that they are directed at least in part against alveolar components uncovered by some type of injury.

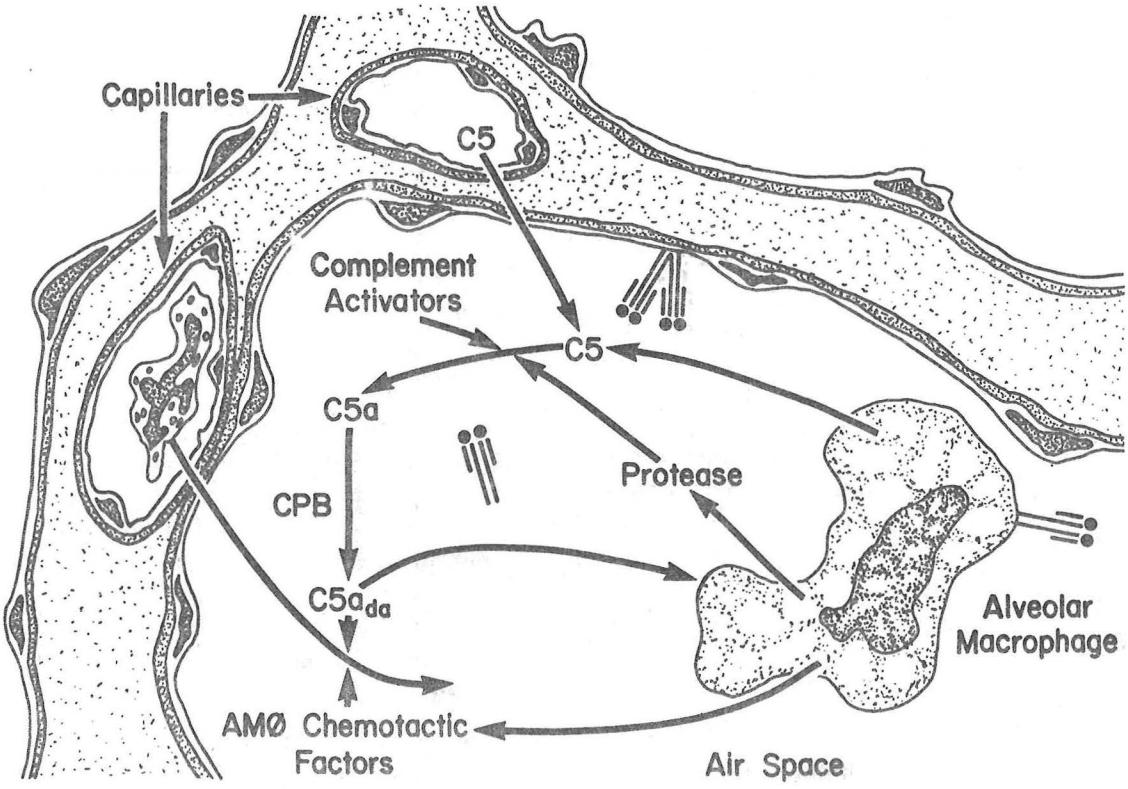
Several observations suggest that the stimulus activating the macrophages in idiopathic pulmonary fibrosis is probably immune complexes (123,124). 1) Normal human alveolar macrophages can be activated by immune complexes; 2) lavage fluid of these patients contains immune complexes and this lavage fluid will activate normal macrophages; 3) macrophages from these patients have immunoglobulin and complement on their surfaces; and 4) there is a strong correlation between the presence of immune complexes in idiopathic pulmonary fibrosis and the proportion of neutrophils found in the lungs of patients with this disease.

Complement fragments, in particular those derived from C5, are also known to be highly potent neutrophil and monocyte attractants. While there is presently no evidence that complement plays a role in the neutrophil recruitment seen in patients with idiopathic pulmonary fibrosis, evidence from animal studies suggest that it might be important in a variety of pulmonary inflammatory disorders including immune complex induced disease (130,131), anti-basement membrane, antibody induced disease (132), oxygen toxicity (133) and following exposure to a wide variety of environmental toxins.

In order to invoke a role for C5 derived complement fragments in the induction of neutrophil accumulation, the presence of the precursor, C5, in the lung must be ascertained. To date complement components have been infrequently sought in bronchoalveolar lavage fluid, and I am unaware of studies which have sought these components with idiopathic pulmonary fibrosis. Minimal levels of C3, C4 and C6 have been identified within the lower respiratory tract secretions of man (102,134). Robertson, et al. (135), have demonstrated the presence of factor B and an intact alternate complement pathway in the respiratory secretions of normal humans. Recent studies in rabbits have been directed at determinations of functional C5 activity in bronchoalveolar lavage fluid. Functional C5, but very little functional C3 was found in these studies (136). Similar studies in the baboon, in which hemolytic C5 activity was expressed as a ratio of albumin concentration and compared with baboon serum, found two-fold to five-fold greater C5 activity per mg of albumin in bronchoalveolar lavage fluid than in serum (136). These observations suggest that alveolar C5 may not be derived from serum but may be synthesized locally in the lung, possibly in alveolar macrophages.

FIGURE 14

MECHANISMS OF GRANULOCYTE RECUITMENT



Therefore, it seems likely that C5 is available in the lung for generation of C5a and C5a des-Arg. Figure 14 outlines the mechanisms potentially involved in neutrophil accumulation. C5 in airspaces or interstitium, derived from blood or alveolar macrophages, may be cleaved by macrophage- or neutrophil- derived proteases or by the activation of complement pathways. This cleavage would result in the formation of C5a. Removal of the C- terminal arginine from the C5a by blood or interstitial, or even perhaps alveolar carboxy-peptidase yields the potent stable phlogistic mediator C5a des-Arg. The C5a des-Arg may then attract neutrophils from the capillary directly or by inducing release of chemotactic factors from the resident alveolar macrophages. Additionally, immune complexes present in the alveolus may induce the secretion of alveolar macrophage chemotactic factors. Upon exposure to C5a des-Arg, alveolar macrophages are also stimulated to secrete proteases, which can cleave C5 and further enhance the reaction. The action of infiltrating inflammatory cells includes increased permeability and thus leakage of more precursors such as C5 from the blood. The neutrophils themselves are induced by a variety of circumstances and stimuli to secrete toxic oxygen radicals and then granule constituents, including C5-cleaving and tissue destructive proteases. Clearly this proposed mechanism is critically dependent on the presence and influx of controlling factors and inhibitors within the alveolar milieu.

FIGURE 15

SPECULATIVE PATHOGENESIS

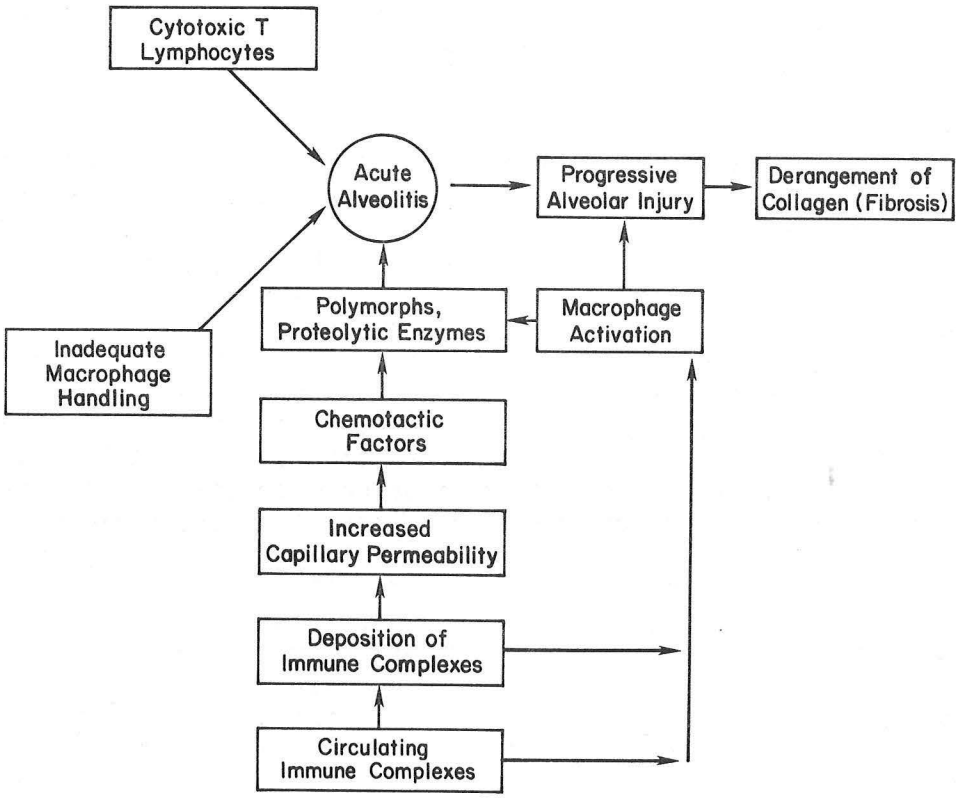


Figure 15 outlines in summary form a speculative pathogenesis of idiopathic pulmonary fibrosis. In response to one of many potential inciting agents, systemic immune complexes form and deposit within alveolar walls and capillaries. The antigen involved in these complexes may be either the inciting agent itself or an altered tissue component. In either case, the stimulus for antibody production must persist for a considerable time and, in some cases, elicit the non-specific production of rheumatoid and anti-nuclear factors. Complement containing complexes deposited within the pulmonary parenchyma would increase capillary permeability and allow an influx of chemotactic factors from the blood. Additionally, complement might be activated with generation of chemotactic factors within the alveolar space itself. Chemotactic factors would lead to the recruitment of polymorphonuclear leukocytes resulting in an acute alveolitis. Release of proteolytic enzymes from the recruited granulocytes would lead to destruction of surrounding pulmonary tissue and progressive alveolar injury and eventually to derangement of interstitial collagen or fibrosis. An alternate or additional sequence of events postulates that the immune complexes would lead to alveolar macrophage activation. The results of alveolar macrophage activation would be the secretion of an alveolar macrophage chemotactic factor for granulocytes which would recruit granulocytes to the alveolar spaces leading to an acute alveolitis. Additionally, the activated macrophages themselves could be involved through the secretion of proteases which would lead to progressive alveolar injury and eventual derangement of collagen. Additionally, patients with idiopathic pulmonary fibrosis have a substantial population of lymphocytes that recognize collagen as nonself, and produce migration inhibition factor, a lymphokine that induces macrophages to remain in the local area. The production of this lymphokine could serve to augment the acute alveolitis. Finally, it is possible that inadequate handling of the inciting agent by the resident alveolar macrophages is in some way related to the production of the acute alveolitis.

DIAGNOSIS

While classification of interstitial disorders based on histology alone can cause a great deal of confusion, these diseases cannot be properly categorized without the perspective of histological information to complement the clinical, roentgenographic and physiologic data. Thus, it is critical that the clinician have access to the morphology of the lower respiratory tract. The past few years have seen a proliferation of lung biopsy techniques, including a variety of needles and air driven drills. Surpassing all these methods has been the adaptation of the fiberoptic bronchoscope to sample the distal lung via the so called transbronchial biopsy (137). As attractive as this method is in terms of its relatively low morbidity compared with the open biopsy, the use of the transbronchial biopsy in patients with idiopathic pulmonary fibrosis still presents problems. First, there is a risk of pneumothorax with patients with compromised pulmonary function and non-compliant lungs (138); second, there is risk of hemorrhage in patients with disorders often associated with occult pulmonary arterial hypertension (139); and finally the size of the biopsy specimen is very small (140). The last is the major limitation to the usefulness of the transbronchial biopsy in evaluating patients with interstitial disease. When the biopsy reveals a localized histological entity (e.g., granulomata), it is very helpful. Unfortunately, the histologic presentation of idiopathic pulmonary fibrosis is not localized and requires a larger piece of parenchyma to

make a proper assessment of the type of alveolitis which is present (140). Thus, an overview of the literature suggests that transbronchial biopsy can be useful in the selected disorders mentioned earlier, but in the case of idiopathic pulmonary fibrosis, the biopsy is most often not definitive. For these reasons I believe that the correct recommendation, if an invasive procedure is to be performed, is that of an open lung biopsy.

Another diagnostic tool being used to evaluate the interstitial disorders is the adaptation of the fiberoptic bronchoscope to collect the inflammatory and immune effector cells present in the lower respiratory tract of these patients (102-104). Since the cells comprising the alveolitis are the critical distinguishing feature of many of these disorders, there is good reason to think that categories of interstitial diseases will give characteristic patterns of cells recovered by lavage. Of the nearly 150 interstitial lung disorders known, only a few have been studied by bronchoalveolar lavage. Although almost all patients investigated have had increased numbers of monocytes and macrophages as part of their alveolitis, the classification of the alveolitis rests upon a quantitation of the relative numbers of neutrophils and lymphocytes recovered from the alveolar structures.

TABLE 19

CLASSIFICATION OF THE INTERSTITIAL LUNG DISORDERS

Cell Differential		
Neutrophils	Lymphocytes	Disorder
None	Increased	Hypersensitivity pneumonitis Sarcoidosis
High	Normal	Idiopathic pulmonary fibrosis Familial pulmonary fibrosis Asbestosis
Variable	Normal	ILD associated with rheumatoid arthritis
Low	Normal	ILD associated with PSS, SLE, and overlap syndrome Histiocytosis-X

The disorders with high proportions of lymphocytes include hypersensitivity pneumonitis (103) and sarcoidosis (104,141,142). Those disorders associated with normal numbers and ratios of lymphocytes are often characterized by the presence of the neutrophil, a cell rarely found within the alveolar structures of normal, non-smoking individuals. In this regard, idiopathic pulmonary fibrosis is by far the most impressive, with an average lavage neutrophil count of 20 percent of the cells recovered (103-104). Other forms of interstitial disease characterized by the persistent accumulation of high proportions of neutrophils within lavage fluids include familial pulmonary fibrosis [an interstitial disease with a familial clustering that is indistinguishable from idiopathic pulmonary fibrosis (99)], and asbestosis (142). The other interstitial disorders with an alveolitis characterized by normal proportions of lymphocytes such as the collagen vascular diseases (103,104) also have neutro-

phils in lavage fluids, but the proportion of these cells has been very low, and the percentages highly variable due to the small number of patients thus far studied.

This method holds great promise as a non-invasive means of categorizing interstitial disorders, but before this method can be recommended clinically, larger groups of patients will need to be evaluated in this fashion.

NOMENCLATURE

It is the hope of all clinicians, that a procedure which allows the acquisition of an adequate sample of tissue from the involved organ will allow classification of the disease which affects his patient. If the etiology of the group of disorders are known, the classification is simplified by grouping the diseases according to the causative agents. Unfortunately, the etiologies of many interstitial disorders are unknown; these diseases must, therefore, be categorized by the use of clinical, roentgenographic, physiologic and therapeutic criteria to complement the morphology present on the biopsy. A heavy reliance on morphology has, in my opinion, caused some considerable confusion in the area of idiopathic pulmonary fibrosis.

When Averill Leibow marched us from unlettered barbarism to horizons of pulmonary vision, the truth seemed imminent, even immanent. He assured us that digestion of the diagnostic alphabet soup of BIP, DIP, GIP, LIP and UIP, would provide histopathologic truth and enlighten us about prognosis and therapy. As is often the case, the British remained aloof. While physicians in the United States worried about how one decided if a disease was "desquamative" or not, the British played their own game. Their sport was called "alveolitis" and was played by Pepys (144), and Scadding (21) and their colleagues. In simple terms, Leibow considered desquamation as a *type*, while the British considered this finding as a *phase* of the process. While my view of the controversy is clear, I would like to briefly present both sides of this argument.

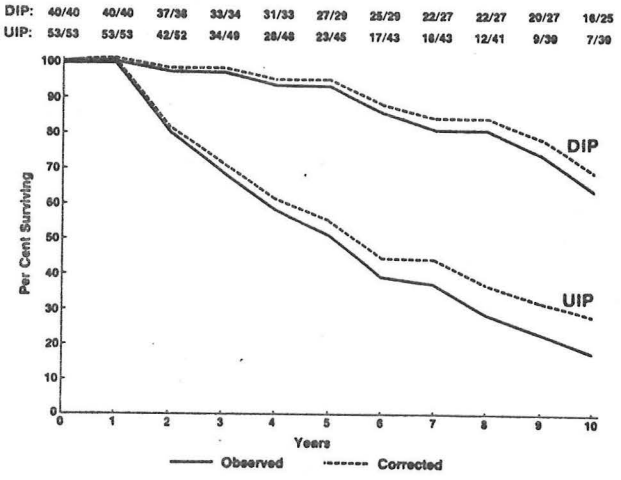
The proponents of "alveolitis" argued that it is the only term that described the characteristic histology of the disease and many would add the word "fibrosing" to this description (33). Critics of this viewpoint maintain that fibrosing suggests active scarring rather than collagen derangement and that alveolitis suggests that the disease is confined to the alveoli, whereas, it clearly involves the small airways as well (48). Those favoring the UIP-DIP terminology prefer to split the idiopathic pulmonary fibrosis patient population into two groups; those with a great deal of intra-alveolar cellularity and little interstitial disease are labeled as DIP, and those with less cellularity and more interstitial disease, as UIP (25,145). Proponents of this scheme argue that since patients with DIP generally have a more favorable clinical course, splitting these patients into two categories is useful clinically (146). In contrast, the non-splitters argued that the separation of DIP and UIP is artificial since almost all patients with idiopathic pulmonary fibrosis have characteristics of both (41,147); that DIP is a misnomer since the intra-alveolar cells are predominently macrophages rather than desquamated alveolar epithelial cells (148,149); and that DIP is early idiopathic pulmonary fibrosis while UIP is late idiopathic pulmonary fibrosis (41,33). Additionally, the detractors would

argue that in many instances, pathologists and clinicians utilize the terms DIP and UIP on purely morphological grounds, thus, confusing the literature by labeling the interstitial disease caused by radiation as UIP or the alveolitis of drug induced interstitial disease as DIP (150,151). It would seem that in contrast to "fibrosing alveolitis" or "UIP-DIP", the term idiopathic pulmonary fibrosis suggests no hypothesized pathogenesis or etiological specificity (41). For these reasons, I would agree (with what I believe are the majority of pulmonary physicians,) that until the etiology of this disorder is clear, idiopathic pulmonary fibrosis is the most useful term available. However, regardless of the term used, it must be remembered that idiopathic pulmonary fibrosis, fibrosing alveolitis or DIP-UIP describe a clinical syndrome, and are not just histological descriptions of a lung biopsy.

PROGNOSIS AND TREATMENT

Regardless of this argument, it would seem apparent that as Scadding and Henson stated (21), "Classification on histologic grounds would be useful ..... if it could be correlated with prognosis or response to treatment in such a way that it permitted forecasts that could not be deduced from other data". Such would seem to be the case.

FIGURE 16



Two lines of investigation have proven fruitful in the classification of idiopathic pulmonary fibrosis. First, histologic examination of biopsy material has shown wide differences in cellular content of lung tissue from patients with otherwise apparently similar clinical disease. Carrington, et al. (152), have reported on 93 patients with confirmed interstitial pneumonitis who were initially classified histologically into "desquamative" (n=40) and "usual" (n=53) types, and followed for 1-22 years. Figure 16 plots the ten year survival curves of patients with DIP and UIP. To separate the effect of the younger age of patients with DIP, the data were corrected for normal life expectency, which are the dotted lines. At the end of five years, the corrected mortality was 44 percent for UIP and only 5 percent for DIP. At the end of 10 years, the corrected mortality was 71 percent for UIP and 30 percent for DIP. Mean survival for DIP was 12.2 years as compared to 5.6 years in UIP.

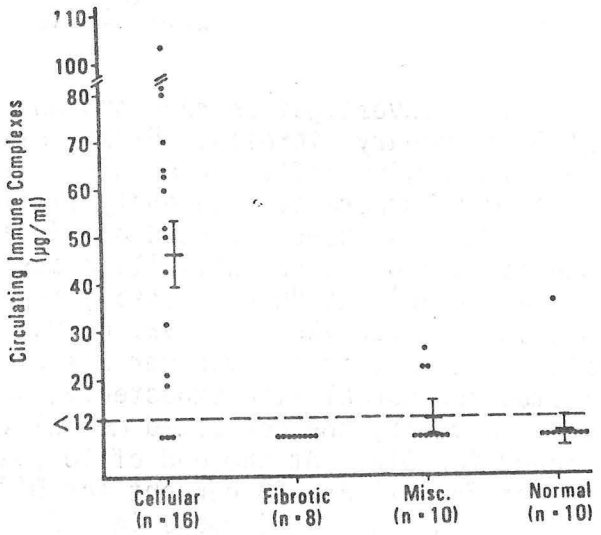
TABLE 20

TREATMENT OF IPF

Untreated	DIP	UIP
No. of patients	32	48
Observation period (yrs)	6.8 ± 6.8	4.5 ± 4.0
Improved	21.9%	0%
Unchanged	15.6%	14.6%
Worse	62.5%	85.4%
Steroid Treated		
No. of patients	26	26
Mean yrs of treatment	3.1 ± 2.8	2.1 ± 2.3
Mean yrs since start of treatment	5.9 ± 4.1	2.6 ± 2.4
Improved	61.5%	11.5%
Unchanged	11.5%	19.3%
Worse	27.0%	69.2%

Results also differed in response to therapy. Without treatment, 21.9 percent with the desquamative but none with the usual type improved. Sixty two and a half percent of the DIP had worsened at the end of the observation period as compared to 85.4 percent of the UIP at the end of the observation period. With corticosteroid therapy, 61.5 percent with desquamative and only 11.5 percent with usual interstitial pneumonia improved, whereas, 27 percent and 69.2 percent respectively had worsened. It would appear from this study that the histologic classification of idiopathic pulmonary fibrosis does permit forecasts of prognosis and response to treatment that connot be deduced from other data.

FIGURE 17

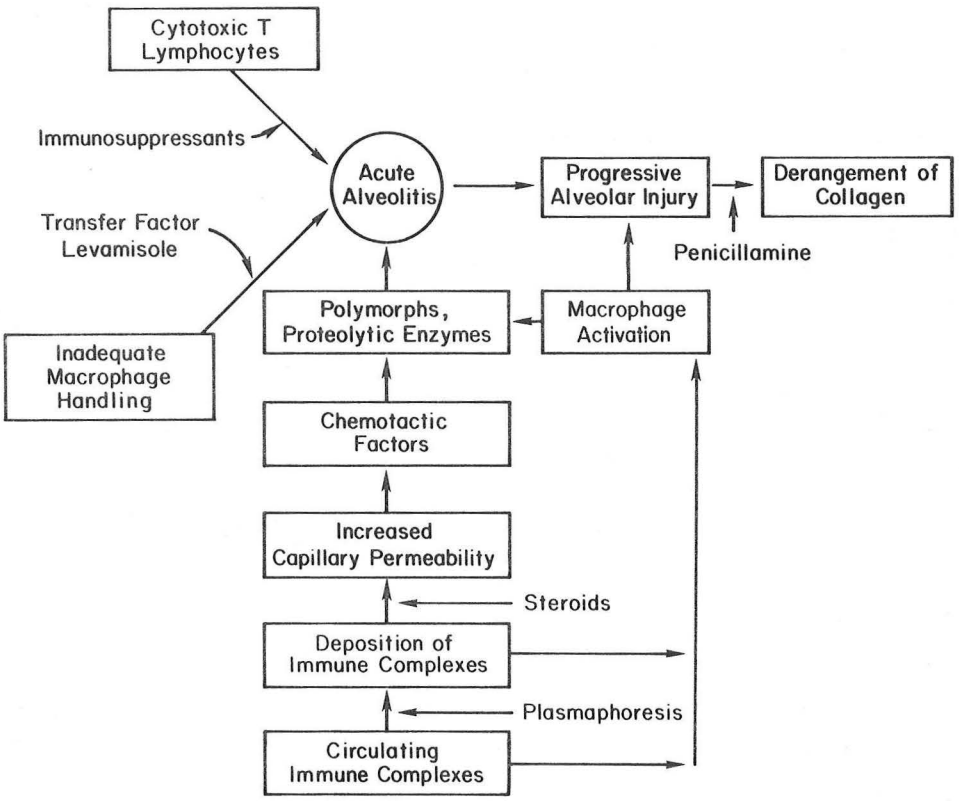


Second, the detection of circulating the fixed immune complexes has been found to correlate remarkably well with lung cellularity, suggesting that fibrosing alveolitis may occur in two stages, as an early inflammatory, cellular, immune complex mediated disease and as a later predominant fibrotic disease without evidence of inflammatory cells or immune complexes, Figure 17. Patients were divided into cellular (n=16) and fibrotic (n=8) types. Thirteen of sixteen patients with cellular disease had circulating immune complexes, whereas, none were found in eight patients with diffuse fibrosis. Granular deposits of IgG, usually with C3, was present in 94 percent of the patients with elevated levels of immune complexes, but in only 11 percent of those with normal levels (128).

These workers also noted that patients with immune complexes and cellular biopsies were more likely to respond to high doses of corticosteroids. After a trial of 3-6 months of corticosteroid therapy, seven of eight treated patients with detectable circulating complexes objectively improved, whereas, one of four treated patients with no detectable complexes fulfilled the criteria outlined. If supported, this study would suggest that it is possible to divide idiopathic pulmonary fibrosis into therapeutically relevant groups with the use of immunopathological testing.

FIGURE 18

POINTS OF THERAPEUTIC INTERVENTION



Because there is increasing evidence that idiopathic pulmonary fibrosis is influenced by immunologic processes against which corticosteroids have only a limited effectiveness, there has been a growing interest in the use of immunosuppressive agents (e.g. azathioprine, chlorambucil, cyclophosphamide, vincristine, vinblastine, methotrexate) to treat these disorders (153,154). Although there are scattered anecdotal reports of their use, there has been only one control trial to determine the efficacy of these agents (155). In that study, patients with idiopathic pulmonary fibrosis in mid-course were treated with prednisone alone or with prednisone plus azathioprine; analysis of the data after one year showed azathioprine did not have an additive effect. Thus, although there is a tempation to use these types of agents in patients whose disease is progressive, it must be remembered that all of these agents carry a certain risk that must be weighed against the theoretical, but unproven, efficacy. Although the chronic alveolitis might cause progressive injury to parenchymal structures, it is the derangement of interstitial collagen that is the major irreversible feature of the interstitial disorders. While stopping the chronic alveolitis will probably halt the progressive fibrosis, there are theoretical therapeutic approaches to slowing down the fibrotic process by interfering with mechanisms of collagen maturation. Although some of these agents (e.g., colchicine, which inhibits collagen secretion and penicillamine or β-aminopropionitrile, which prevents collagen crosslinking) have some effect on preventing pulmonary fibrosis in animal models (156-158), there has been no study demonstrating their effectiveness in human interstitial disease. Unfortunately, the major danger precluding their use is that collagen synthesis in some organs such as bone occurs at a rate much higher than that in the lung, including the fibrotic lung. Thus, if anti-collagen-maturation agents will prove useful in the interstitial disorders, methods will have to be developed to apply these agents locally to the lung to avoid systemic toxicity.

Patients with interstitial disease are relatively easy to oxygenate with supplemental oxygen (41), however, aside from the acute effect of aiding oxygen delivery to tissue, no studies have demonstrated that chronic supplemental oxygen provides any other benefit such as chronic reduction in pulmonary artery pressure or increased survival.

Many patients have problems terminally with airway clearance mechanisms. This, together with the fact that they are often being treated with corticosteroids, makes patients with chronic interstitial diseases susceptible to a variety of infections, the most common being the development of acute bacterial bronchitis. This disorder is treated in a conventional manner together with vigorous preventive measures between acute episodes. Parenchymal bacterial and fungal infections, which are often late sequelae in these patients (41,29), must be treated early and aggressively.

SUMMARY

Idiopathic pulmonary fibrosis is a specific, independent disease entity, with clearly defined clinical, roentgenographic, physiologic, morphologic, and bronchoalveolar lavage features including:

1) Clinical. A history of breathlessness, particularly with exercise; no history suggesting a known etiology; no history

or clinical evidence suggesting left ventricular failure or a defined collagen-vascular disease; no evidence of bronchitis; no history suggestive of hypersensitivity pneumonitis; and no exposure to inhalants or drugs known to cause interstitial disease;

2) Roentgenographic. A diffuse interstitial pattern on chest film; and no adenopathy;
3) Physiologic. Reduced total lung capacity or diffusing capacity; normal forced expiratory volume in one second/forced vital capacity; mild resting hypoxemia which worsens with exercise; and a deflation volume-pressure curve shifted downward and to the right;
4) Morphologic. Varying degrees of interstitial fibrosis; interstitial and intra-alveolar alveolitis consisting predominantly of macrophages and lymphocytes but also including neutrophils and eosinophils; parabronchial inflammation and fibrosis; and no vasculitis, granulomata or significant refractile bodies by polarized light microscopy;
5) Bronchoalveolar lavage. Fluid recovered reveals an increased proportion of polymorphonuclear leukocytes, normal lymphocyte subpopulations and elevated levels of IgG.

Thus, rather than being a disease of exclusion, idiopathic pulmonary fibrosis has a set of definable criteria that distinguishes it from other disorders. It is a disease that has protein manifestations to those affected, and all indications are that if therapy is to be successful early diagnosis and treatment are essential.

APPENDIX

DIFFERENTIAL DIAGNOSIS OF INTERSTITIAL PULMONARY DISEASES

I. Infectious

A. Bacterial
1. Miliary tuberculosis
2. *Staphylococcus aureus*
3. Salmonella species
4. Streptococci
5. *Klebsiella pneumoniae*
6. Brucellosis
7. Tularemia
8. Shigella
9. Pertussis
10. Actinomycosis
11. Nocardiosis

B. Fungal

1. Histoplasmosis
2. Coccidioidomycosis
3. Blastomycosis
4. Crytpococcosis
5. Aspergillosis
6. Candidiasis
7. Geotrichosis
8. Sporotrichosis
9. Mucor

C. Viral

1. Chickenpox
2. Influenza
3. Measles
4. Psittacosis
5. Cytomegalovirus
6. Adenovirus
7. Parainfluenza
8. Coxackie virus
9. ECHO virus

D. *Mycoplasma pneumoniae*

E. Rickettsial

1. Q fever
2. Rocky Mountain spotted fever

F. Spirochetal

1. Syphilus

G. Parasitic

1. Pneumocystis carinii
2. Schistosomiasis
3. Filariasis
4. Toxoplasmosis

II. Inhalational Diseases

A. Diseases of alveolar hypersensitivity

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

B. Inorganic dust pneumoconiosis

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

C. Inorganic chemicals

1. Nitrogen dioxide (Silo-filler's disease)
2. Nitrogen oxide (electric welding)
3. Chlorine
4. Smoke inhalation
5. Phosgene
6. Mustard gas
7. Lewisite
8. Carbon tetrachloride
9. Acetylene
10. Picric acid
11. Ammonia
12. Sulfur dioxide

13. Bromine
14. Hydrogen flouride
15. Nitric acid
16. Hydrochloric acid

III. Neoplastic

A. Bronchioloalveolar carcinoma

B. Lymphangitic carcinomatosis

1. Bronchogenic
2. Breast
3. Stomach
4. Thyroid
5. Pancreas
6. Larynx

C. Micronodular hematogenous

1. Renal cell
2. Thyroid
3. Sarcoma of bone
4. Choriocarcinoma

D. Hodgkins' disease

E. Lymphosarcoma

F. Leukemia

IV. Therapeutic Agents

A. Oxygen toxicity

B. Radiation therapy

C. Drugs

1. Nitrofurantoin (Furadantin)
2. Hexamethonium
3. Mecamylamine (Inversine)
4. Hydrochlorothiazide (Diuril)
5. Pteroylglutamic acid (Methotrexate)
6. Busulfan (Myleran)
7. Methysergide (Sansert)
8. Bleomycin

V. Connective Tissue Diseases

A. Scleroderma

B. Rheumatoid arthritis

C. Lupus erythematosis

D. Periarteritis nodosa

E. Dermatomyositis

F. Sjögren's syndrome

G. Wegener's granulomatosis

VI. Cardiovascular

A. Pulmonary edema

B. Hemosiderosis

C. Rheumatic pneumonia

D. Embolism from oily contrast media

VII. Aspirational

A. Gastric juice

B. Lipoid pneumonia

C. Hemoptysis

D. Post drowning

VIII. Airways Disease

A. Cystic fibrosis

B. Bronchiectasis

C. "Small airways" disease

D. Acute bronchiolitis

E. Riley-Day syndrome

IX. Trauma

A. Blast injury

B. Lightning stroke pulmonary edema

X. Miscellaneous or Idiopathic

A. Sarcoidosis

B. Goodpasture's syndrome

C. Pulmonary alveolar proteinosis

D. Eosinophilic granuloma

E. Sickle cell anemia

F. Letterer Seive

G. Neimann Pick

H. Hand-Schuller-Christian

I. Pulmonary alveolar microlithiasis

J. Amyloidosis

K. Waldenstrom's macroglobulinemia

L. Tuberous sclerosis

M. Pulmonary myomatosis

N. Wilson-Mikity syndrome

O. Infectious mononucleosis

P. Mycosis fungoides

Q. Spider angiomas in cirrhosis

R. Idiopathic interstitial pulmonary fibrosis

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