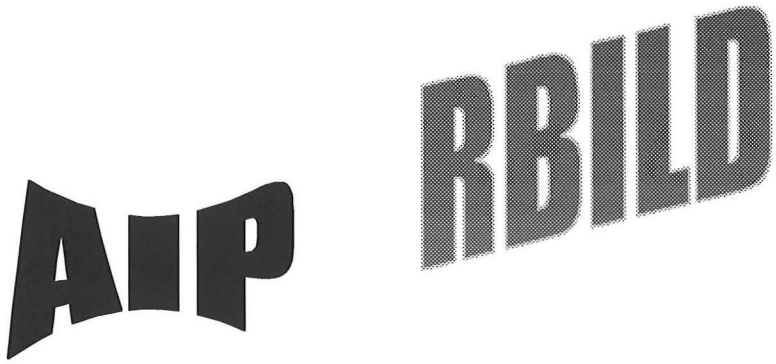
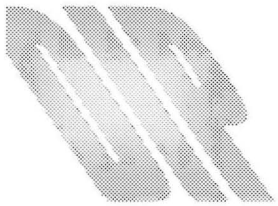
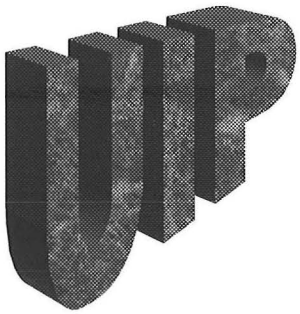




IDIOPATHIC INTERSITIAL PNEUMONIAS:

MAKING SENSE OF ALPHABET SOUP!



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Internal Medicine Grand Rounds
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This is to acknowledge that Dr. Mageto has disclosed no financial interests or other relationships with commercial concerns related directly to this program. Dr. Mageto will be discussing off label uses in her presentation

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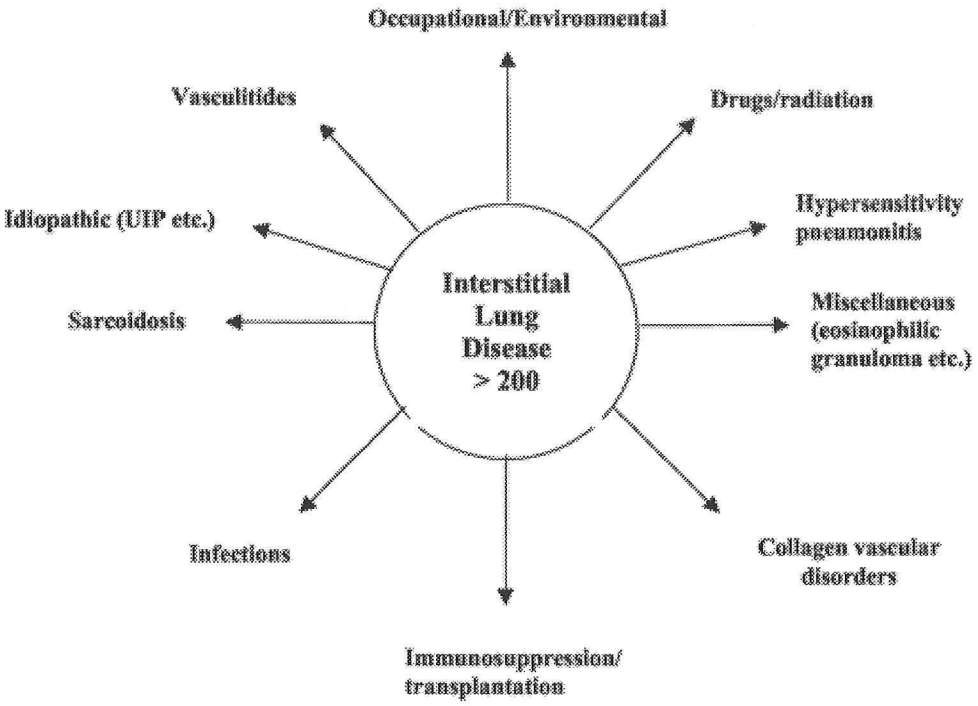
Academic Interests: Interstitial lung disease specifically, epidemiology, diagnosis and therapy.

Introduction

Idiopathic interstitial pneumonias are part of a much larger group of disorders classified as diffuse parenchymal lung disease collectively referred to as interstitial lung diseases encompassing approximately 200 entities in which the lung is altered by a combination of interstitial inflammation or granulomatous inflammation, or fibrosis.

Most of these disorders affect the interstitium, pleura, airways, blood vessels, and alveolar and bronchiole epithelial cells [1]. Many have similar clinical, radiologic and pathologic manifestations[2] and usually present in an acute, subacute or chronic manner. While the most commonly identifiable causes of diffuse parenchymal lung disorders are environmental/occupational exposures, drug reactions, collagen vascular disorders or granulomatous disorders (e.g. sarcoid) one of the common and important groups are the idiopathic interstitial pneumonias (IIP) [3] (fig. 1).

Fig. 1: Spectrum of Interstitial Lung Disease



In the last 5-6 years there has been tremendous growth in our understanding of these pneumonias. The difficulty and confusion surrounding these disorders (even among pulmonologists) has been related to our inability to correctly diagnose them and due to a lack of knowledge regarding the natural history and pathophysiology of these disorders. Until recent years everything that was not obviously sarcoid, hypersensitivity pneumonitis or COP (BOOP) was classified as IPF/UIP. It was noted that around 20% of these individuals would respond to steroids and the other 80 percent would progress to endstage fibrosis at varying rates[4].

The diagnosis and management of Idiopathic Interstitial Pneumonias (IIP's) has challenged physicians since their description more than a century ago by Sir William Osler [5]. In 1892 he described chronic intersitial pneumonia also called 'cirrhosis of the lung' as a "fibrinoid change, which may have its starting point in the tissue about the bronchi and blood-vessels, the interlobular septae, the alveolar walls or in the pleura. So diverse are the different forms and so varied the conditions under which this change occurs that a proper classification is extremely difficult". Those words ring true even today.

Hamman and Rich [6] in 1944 described 4 cases of acute diffuse interstitial fibrosis in which the lungs showed connective tissue hyperplasia. Even though all 4 cases were acute in their onset the Hamman –Rich syndrome was subsequently employed to describe any diffuse idiopathic fibrotic process primarily Idiopathic Pulmonary Fibrosis (IPF). We now know this to be Acute Interstitial Pneumonia (AIP).

This nomenclature remained until the 1960's when significant progress in understanding intersitial lung disease was made with the recognition of collagen vascular disorders, drugs and occupational exposures as potential causes of interstitial lung disease.

In 1969 Liebow and Carrington[7] were the first to propose a pathologic classification of interstitial pneumonia. They proposed five histopathologic subgroups (Table 1). In the original description of these disorders Liebow emphasized that they represented pathologic patterns and did not focus on the idiopathic aspects [8, 9]. The concept of idiopathic interstitial pneumonias appears to have developed in the late 70's and 80's. During the 80's both LIP (lymphocytic interstitial pneumonia) and GIP (Giant Cell Interstitial Pneumonia) were dropped. LIP was determined to be a lymphoproliferative disorder and GIP was found to be associated with hard metal (Cobalt) pneumonoconiosis.

Following this classification several new classifications of IIP's were described including Cryptogenic-organizing pneumonia (BOOP), and AIP by Katzenstein and Myers [10] (Table 1). There have been several revisions of this classification over the past decade.

Table 1: Classification of IIP's

PREVIOUS CLASSIFICATIONS OF THE IDIOPATHIC INTERSTITIAL PNEUMONIAS

Liebow 1969	Katzenstein 1997	Muller & Colby 1997
Usual interstitial pneumonia	Usual interstitial pneumonia	Usual interstitial pneumonia
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia/respiratory bronchiolitis interstitial lung disease	Desquamative interstitial pneumonia
Bronchiolitis obliterans interstitial pneumonia and diffuse alveolar damage		Bronchiolitis obliterans organizing pneumonia
	Acute interstitial pneumonia	Acute interstitial pneumonia
	Nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia
Lymphocytic interstitial pneumonia		
Giant cell interstitial pneumonia		

Table 1 from Travis WD, King TE, Bateman ED, et al. ATS/ERS International Multidisciplinary Consensus Classification of Idiopathic Interstitial Pneumonia. Am J Respir Crit Care Med 2002; 165:281.

The third classification of importance is that by the American Thoracic Society (ATS) and European Respiratory Society (ERS). In 2002 they revised the classification Schema of Katzenstein and Myers [10] to emphasize the importance of an integrated and clinical and pathological approach the diagnosis of IIP (Table 2). The classification combines the histopathological pattern seen on lung biopsy with clinical information to arrive at a final clinicopathological diagnosis.

Idiopathic interstitial pneumonias are often regarded as the black box of ILD – their etiology; epidemiology and therapy are ofttimes nebulous at best. This new classification helped to overcome the lack of an international standard in IIP's thus alleviating confusing diagnostic criteria and nomenclature.
Despite these guidelines IIP remains a diagnosis of exclusion requiring an extensive investigation, careful history taking, and review of any radiological findings (including old films).

Table 2: ATS/ERS Classification of IIP

THE ATS/ERS CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS[3]

Histologic Patterns	Clinical-Radiologic-Pathologic Diagnosis
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis
Nonspecific interstitial pneumonia Cellular pattern Fibrosing pattern	Nonspecific interstitial pneumonia
Organizing pneumonia	Cryptogenic organizing pneumonia
Diffuse alveolar damage	Acute interstitial pneumonia
Respiratory bronchiolitis	Respiratory bronchiolitis interstitial lung disease
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Lymphocytic interstitial pneumonia	Lymphocytic interstitial pneumonia
Unclassifiable Interstitial Pneumonia	

Epidemiology:

The epidemiology of these disorders is fraught with a paucity of information. There are essentially three types of studies performed in this patient group 1.) The quantification of disease broken down into incidence, prevalence and mortality data 2.) The identification of etiological factors and 3.) Clinical epidemiological studies. Due to earlier difficulties in the classification process the incidence and prevalence of ILD in the literature will vary depending on what study is reviewed and its time of publication. Most available data is derived from registries or hospital clinics and thus has a strong selection bias and are not likely representative of the general population [11]. Based on most of these studies sarcoid and IPF appear to be the most frequently occurring ILD's followed by hypersensitivity pneumonitis and ILD associated collagen vascular disease [12, 13].
A review of several case studies examining the relative distribution of 4 histopathological subgroups of IIP also finds that UIP is the most common subgroup (50-60%), followed by NSIP (14-36%), DIP, RBILD, (10-17%), and AIP being rare at (0-2%)[14-17].

The most representative epidemiological study of ILD to date was published in 1994 by Coultas et al [18] in Bernallio New Mexico where the authors used data from an IPF registry, examined death certificates and. estimated the incidence of IPF at 31.5 per 100,000 per year with approximately 1/3 in the ILD category, and an estimated incidence of 20.2 per 100,000 for men and 13.2 per 100,000 for women. (Table 3)
Earlier US estimates of ILD were 3-5 per 100,000 [19] thus the Coultas data implies a significant increase in the prevalence of IPF over the last decade. Just under half of all the ILD's in this study were IPF in both men and women, men having a slightly higher predilection for IPF than women. Whether or not this reflects a true increase in prevalence or is representative of increased awareness of the disorder remains unclear. It is likely that earlier studies underestimated the prevalence of IPF because they were based on selected populations in combination with a decreased awareness of the disease i.e. many people with the disease may be diagnosed with CHF or "double pneumonia".

Very little data from population-based registries is available from other countries. Published data suggests that the prevalence of IPF varies between countries. In Japan it is estimated to be 4.1 per 100,000 [20, 21], 7-12/100,000 in the Czech republic [22], and 16-18/100,000 in the Finnish registry[23]. We do not know if these variations are reflection of true disease prevalence or differences in registry methodology and lack of completeness of case ascertainment.

Table 3: Prevalence in1988-1990 of ILD in New Mexico[18]

	Prevalence per 100 000 (*n*)		Incidence per 100 000 per year (*n*)	
ILD category	Men	Women	Men	Women
Occupational/environmental	20.8 (35)	0.6 (1)	6.2 (21)	0.8 (3)
Drug/radiation	1.2 (2)	2.2 (4)	1.8 (6)	1.1 (4)
Pulmonary haemorrhage syndromes	0.6 (1)	2.2 (4)	1.5 (5)	0.8 (3)
Connective tissue disease	7.1 (12)	11.6 (21)	2.1 (7)	3.0 (11)
Pulmonary fibrosis				
Fibrosis (post-inflammatory)	10.1 (17)	14.3 (26)	3.9 (13)	4.1 (15)
IPF	20.2 (34)	13.2 (24)	10.7 (36)	7.4 (27)
Interstitial pneumonitis	1.8 (3)	2.8 (5)	1.8 (6)	1.4 (6)
Sarcoidosis	8.3 (14)	8.8 (16)	0.9 (3)	3.6 (13)
Other	10.7 (18)	11.6 (21)	2.7 (9)	3.9 (14)
Total	80.9 (136)	67.2 (122)	31.5 (106)	26.1 (96)

Mortality data in England, Wales, Scotland, Australia and Canada have shown increasing mortality rates while rates in New Zealand and Germany have remained stable and decreased in the US [24]. The decline in the us data may be explained by changes in ICD-9 coding practices as other studies show a rise in the mortality in the same period [25]. Although these changes do not appear to be related to changes in diagnostic criteria, mortality data is often based on death certificates that consistently have been noted to under-report the incidence and prevalence of ILD [26].

A study by Weycker et al, [27] examined the healthcare costs in pulmonary fibrosis specifically IPF. This was a retrospective cohort study of IPF conducted using an integrated database of medical and pharmacy claims from private health plans in the US from January 1996 to December 2000. The data was analyzed using a broad case definition (medical claim with diagnosis of IPF and no subsequent claims with a diagnosis of ILD or IPF) and a narrow case definition (same a broad case definition but with a medical claim for lung biopsy or CT of the thorax). Health care use and charges were estimated using all paid medical fees and pharmacy claims for 2000 for these IPF cases.
The prevalence of IPF was estimated at 54/100,000, adults using the broad case definition and 17/100,000 using the narrow case definition. IPF prevalence increased with age, most patients were over 65 years of age. The incidence of IPF was estimated to be 25/100,000 per year using the broad case definition and 10/100,000/year using the narrow case definition. It is thought based on clinical practice the narrow definition is likely to be a lower limit estimate of the true occurrence of disease and the broad definition will likely include some false positives but will also have less than 100 % specificity; the truth likely lies somewhere in between. The data are consistent with the Coultas data from New Mexico [18].

The average patient healthcare costs related to IPF in 2000 were approximately $33,000 – $40,000 per patient based on the broad and narrow definitions respectively. Hospital admissions accounted for the majority of the costs (75%) and the rest accounting for outpatient costs. Thus despite the lack of quality data available there is enough evidence to suggest that IPF is increasing in many Western nations.
The epidemiology of the other IIP's is largely unknown.

Clinical Presentation and Diagnostic evaluation:

The Clinical presentation and diagnosis of IIP's is indeed a challenge. Although the clinical and radiographic evaluation can make the diagnosis in some cases, many patients will require an open lung biopsy or Video

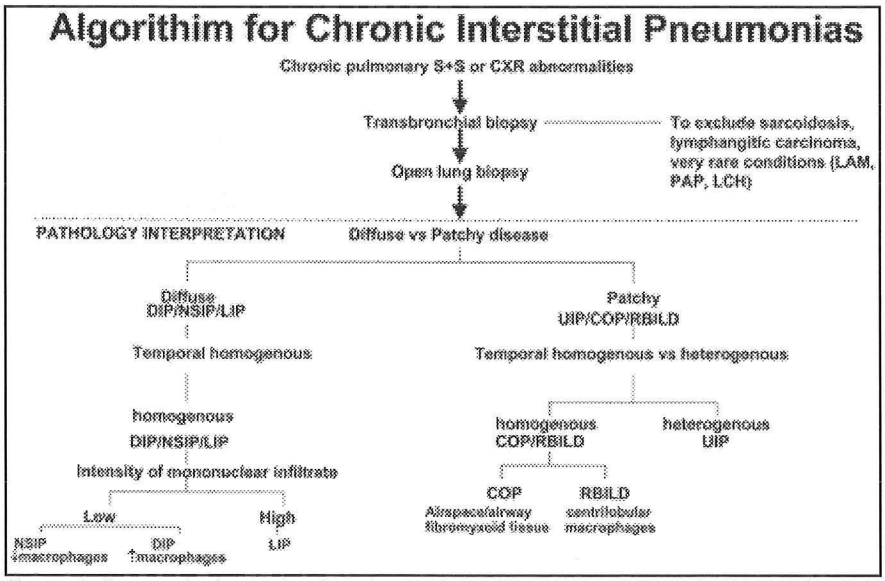
assisted thorascopy (VATS) to make the diagnosis. This is because many of these subgroups are clinically indistinguishable. As seen by the reclassification system proposed by the American Thoracic Society and the European Respiratory Society pathologic classification is a dynamic process requiring close clinical –radiographic correlation.

When considering the biopsies one needs to ask three important questions to make a correct diagnosis [28]. This is vital when one considers there are significant prognostic implications of the specific IIP's [28].

1. First: Is the disease process diffuse or patchy (i.e. are there areas of alternating normal lung with inflammation and fibrosis)
2. Secondly: What are the primary anatomic sites involved. For example, subpleural or paraseptal involvement as seen in IPF, alveolar septal involvement as seen in NSIP and DIP, Bronchiolocentric involvement suggests Respiratory bronchiolitis interstitial lung disease.
3. Third: Is there temporal Homogeneity or temporal Heterogeneity. Temporal Homogeneity indicates the age of the lung injury is the same, that is, all acute, chronic or Subacute in nature. With Temporal Heterogeneity on the other hand one can identify areas of chronic (honeycombing), subacute (interstitial or airspace fibromyxoid connective tissue) and acute (alveolar epithelial cell necrosis and hyaline membranes)

Finally the overall phase of injury should be identified which may predict response to therapy i.e. acute changes will likely be more responsive than chronic (honeycombing) change. Once these features have been identified **and** correlated with the clinical and radiologic finding a diagnosis should be possible (fig. 2).

Fig. 2: Diagnostic Approach and Pathological interpretation in IIP [28]



One should note however that this requires open lines of communication between the radiologist, pathologist, and Clinician; as the diagnosis of IIP occurs on several levels and is multidisciplinary; involving the primary care physician, pulmonologist, radiologist and pathologist. Each individual contributes to the overall picture.

Diagnosis should be ascertained in a methodical stepwise fashion

1. Clinical presentation, history and physical examination. The first line of diagnosis is at the level of the primary care physician. These patients often present with symptoms of dyspnea, +/- a dry hacking cough, perhaps general fatigue and are often diagnosed with 'double pneumonia' or congestive heart failure and are given antibiotics or shipped off to a cardiologist. Indeed these diagnoses are in the differential for these clinical symptoms but a thorough medical history in the context of a few tests will usually point one in the right direction. The differences between them are subtle but significant and should not be ignored as there are significant prognostic implications.

2. Radiologic chest radiograph or CT scan findings. Rarely will any of these patients have normal radiographs or HRCT. Abnormalities often overlap and can range form ground glass, and alveolar filling defects to diffuse honeycombing.

3. Pathologic findings or histology. The pathological findings are generally distinct but not necessarily pathognomonic for a particular IIP as each histopathological diagnosis has a myriad of clinical associations.

An easy way to remember the different IIP's is to consider them in term of the acuity of their presentation; acute, subacute or chronic (Table 4).

Table 4: IIP's Clinical Time Course on presentation

Acute Onset (Hours – Days_	
Acute Interstitial Pneumonitis	AIP
Subacute (Weeks-months)	
Nonspecific intersitial pneumonitis	NSIP
Diffuse interstitial pneumonitis	DIP
Respiratory bronchiolitis intersitial pneumonia	RBILD
Cryptogenic Organizing Pneumonia	COP
Lymphocytic interstitial Pneumonia	LIP
Chronic (months to years)	
Idiopathic Pulmonary Fibrosis	IPF

Idiopathic Interstitial Pneumonias by subset:

1. Acute Interstitial Pneumonitis (AIP):

Definition: AIP otherwise known and Hamman Rich syndrome, is a rare, rapidly progressive fulminant form of lung injury. The term is synonymous with diffuse alveolar damage (DAD) seen in ARDS. In fact it only differs from ARDS in by the absence of a known precipitating cause or preexisting disease and lack of a systemic disorder that predisposes to DAD [29, 30]. It is in fact a diagnosis of exclusion.

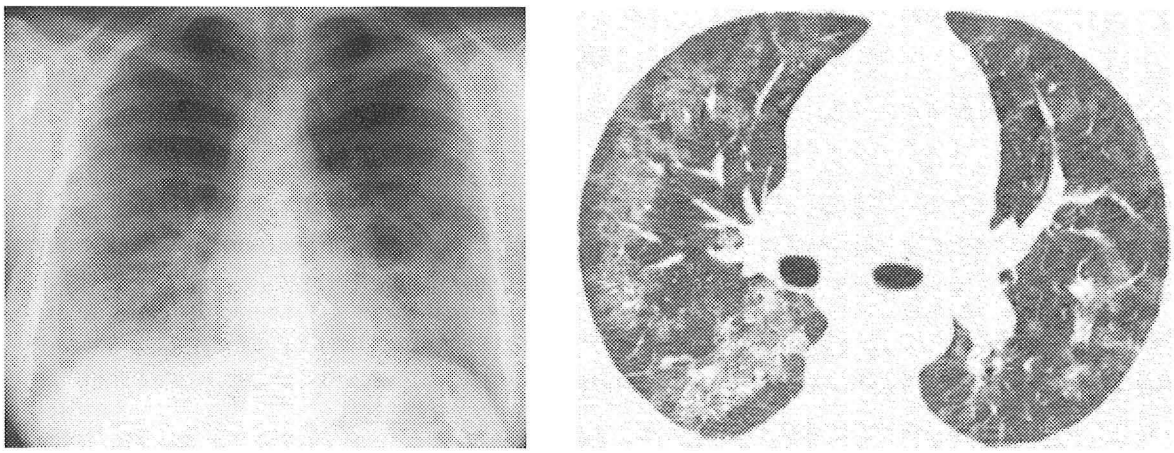
Diagnosis: To make this diagnosis one must have a high index of suspicion and the diagnosis should be considered in a patient presenting with severe community acquired pneumonia/ARDS who fails to respond to broad spectrum antibiotic therapy and in whom no causative agent is identified. The disease occurs equally in men and women of middle age (mean age 34)[31-35].

Differential diagnosis of acute interstitial pneumonia[36]

Acute eosinophilic pneumonia
Connective tissue disease
Cryptogenic organizing pneumonia (acute variant)
Diffuse alveolar hemorrhage
Drug-induced lung disease
Acute hypersensitivity pneumonitis
Idiopathic pulmonary fibrosis (accelerated and acute exacerbation)
Infection
Inhalation/toxic exposures

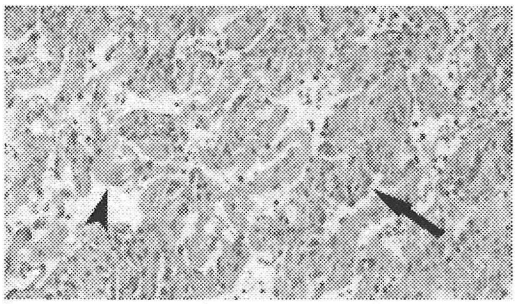
Clinical presentation: These patients present with a flu like prodrome that consists of headache, myalgias, sore throat, malaise, and cough [35, 37]. Typically the cough is non-productive. The development of dyspnea often follows within several days. Occasionally, it can develop late in the course and these patients appear acutely ill. On examination most are tachypneic, tachycardic and hypoxemic. Lung examination typically reveals crackles and wheezes. Evidence of pleural disease or other extrapulmonary manifestations should raise the possibility of an alternative diagnosis. Most patients will develop hypoxemic progressive respiratory failure, requiring mechanical ventilation. They will typically require several weeks on mechanical ventilation. In one series the median duration of mechanical ventilation was 19 days [35].

Fig. 3: AIP radiographic findings



Radiographic Findings: On chest films they start out as mild interstitial changes rapidly progressing to bilateral diffuse infiltrates resembling ARDS. On HRCT one may see evidence of mild intersitial markings suggestive of infectious atypical pneumonia, which will progress to bilateral areas of ground-glass attenuation areas of consolidation with air bronchograms (fig. 3).

Fig. 4: AIP Histopathology



Pathology: The characteristic lesion of AIP is organizing DAD as shown in fig4. There is wide spread injury to most lung fields. The lesions are temporally homogenous suggesting they derive from a single common insult[29] .

Therapy: There are no established therapies for AIP. Parenteral corticosteroids, often at high doses are frequently used but their efficacy is unproven. Alternative therapies include other immunosuppressive agents such as Cytoxan, Cyclosporine Mycophenolate, and Azathioprine. None of these therapies have been studied in a rigorous fashion.

Survival: The acute case fatality ratio for AIP is approximately 70%. In North American studies the fatality ratio is 12.5% to 62 % and is even higher in international studies[29, 30, 36]. The mortality from AIP is higher than that of ARDS[38, 39]. Although there is little longitudinal data on AIP the available information suggests that survivors seem to follow one of four patterns 1.) Complete recovery of lung function, 2.) Stable but persistent abnormalities in lung function 3). Progressive pulmonary fibrosis and 4.) Recurrent AIP[30, 35].

2. Respiratory Bronchiolitis Interstitial Lung Disease: RBILD:

Definition: RBILD is a mild form of interstitial lung disease characterized histologically by chronic bronchiolitis in which pigmented macrophages accumulate within respiratory bronchioles and adjacent alveolar spaces[2]. This histologic lesion is commonly encountered as an incidental finding in lung specimens in smokers. It may the only abnormality in patients with interstitial lung disease. In this setting the appropriate term is RBILD [3]. A large number of authors have described the histologic changes in the bronchioles of cigarette smokers. Many of these authors use the term small airways disease or respiratory bronchiolitis[40-43]. Myers et al., [44] described six cigarette smoking patients with Respiratory Bronchiolitis who presented with ILD. One cannot discuss RBILD without mentioning DIP as there is a strong relationship between smoking and both RB-ILD and DIP. This has led to the hypothesis that these disorders are a spectrum of smoking induced ILD

(association causation not proven). DIP is considered to be a more extensive form of pigmented alveolar macrophage accumulation while in RB-ILD the macrophages are peribronchiolar[3, 10, 44, 45]. However because there are differences in the clinical presentation, radiographic findings, the ATS/ERS panel has addressed them separately.

Differential diagnosis:

DIP, Asbestosis and Langerhans' cell histiocytosis.

Clinical presentation: The incidence and prevalence cause and pathogenesis of RB-ILD is unknown. However, all patients with RB-ILD are either current or past heavy cigarette smokers[46]. The mean age of onset is 36 years with no sex predilection. Presenting symptoms are cough and the insidious onset of exertional dyspnea. The cough is not always productive [46-49]. On examination bibasilar end-inspiratory rales are present but clubbing is rare. Routine laboratory studies are nonspecific and generally not very helpful. Pulmonary function tests may be normal or show only an increase in residual volume. When abnormal a mixed obstructive/restrictive pattern with a slightly reduced diffusing capacity is common. Mild hypoxemia may be present at rest or with exercise.

Diagnosis: The diagnosis of RB-ILD requires a patient with a smoking history within the last 6 months, appropriate clinical and radiologic manifestations and a biopsy that identifies RB-ILD and rules out more serious causes of diffuse parenchymal lung disease especially IPF[45, 46].

Fig. 5: RBILD Poorly defined centrilobular nodules

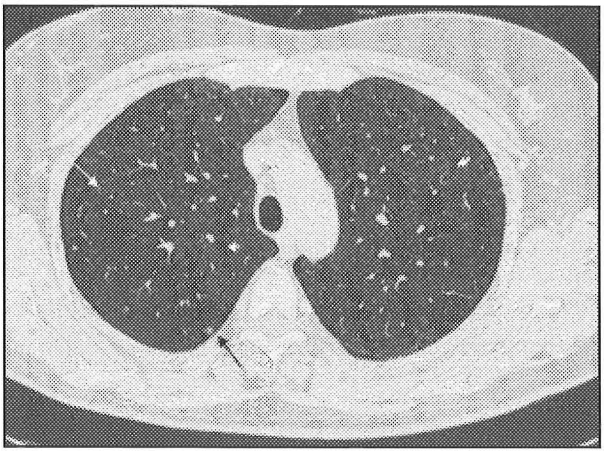
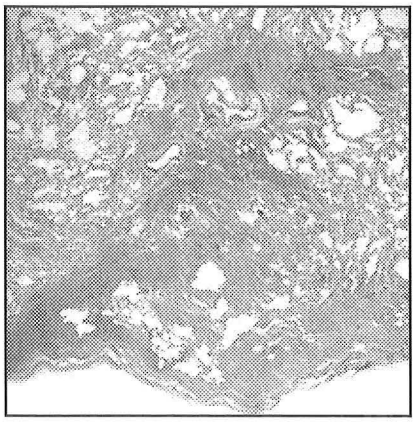


Fig. 6: RBILD



Radiographic findings:

Radiographic abnormalities usually consist of ground glass opacities and bronchial wall thickening. Less common findings include a fine reticular or reticulonodular pattern. The chest radiograph is normal in 20-30 % of patients [49, 50]. The main findings on HRCT are bilateral areas of ground –glass attenuation and centrilobular and nodular opacities. They may be diffuse or have either upper or lower lung zone predominance. The findings can often be mistaken for DIP or hypersensitivity pneumonitis. Reticular opacities may be present and occasionally predominate[49, 50] (fig. 5).

Pathology: The histologic lesion is the accumulation of alveolar macrophages within respiratory bronchiole with the infiltrate extending into neighboring alveoli. Macrophages are characterized by glassy eosinophilic cytoplasm with light brown and finely granular pigmentation that often is superimposed and is believed to represent constituents of cigarette smoke. Fibroblasts are <u>not</u> a feature. The wall of the bronchioles may show chronic inflammation and fibrosis. The patchy nature of the disease is important in differentiating RBILD from DIP (fig. 6).

Treatment and Prognosis: The clinical course and prognosis for this IIP is good. Since smoking appears to play a role in the pathogenesis smoking cessation is important in the resolution of these lesions [51]. These patients generally have a favorable response to a course of corticosteroids. However there are a small subset of individuals that deteriorate despite therapy[46].

3. Diffuse Interstitial Pneumonia: DIP

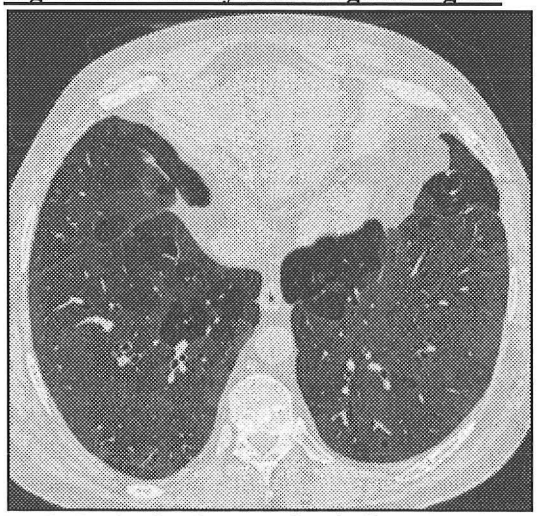
Definition: DIP and RBILD are very similar by definition; both are smoking related and both are characterized by mononuclear cell infiltration of the airspaces without prominent fibrosis or honeycombing. It used to be thought the DIP was the early phase of UIP and patients that were treated in the early phase had a survival advantage over those treated in the UIP phase [19].

Differential diagnosis:

UIP
RB-ILD,
Eosinophilic pneumonia,
Chronic hemorrhage,
Histiocyte rich infections – MAC or cryptococcus and Rhodococcus equi,
Giant cell interstitial pneumonia
Veno-occlusive disease
NSIP cellular and fibrosing patterns

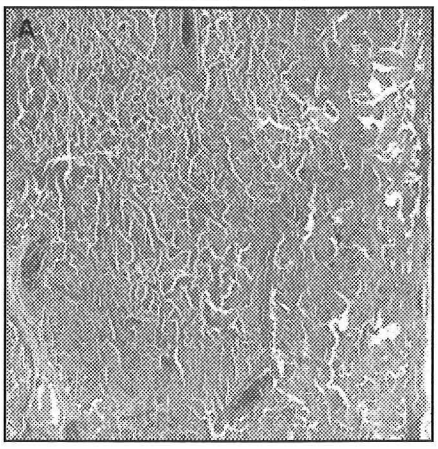
Clinical Findings: The epidemiology and etiology of DIP are not known. It is rare, seen in less than 10% of patients with IIP. Most patients will present in the 4th decade of life with a subacute illness characterized by cough and dyspnea. Physical examination reveals dry inspiratory rales and patients may have clubbing. Unlike RB-ILD pulmonary function studies show a restrictive pattern with a reduced DLCO and hypoxemia.

Fig. 7: DIP Patchy areas of ground glass



Radiographic findings: The predominant finding on chest CT and Chest radiograph is the presence of bilateral symmetric areas of ground-glass opacification involving mainly the lower lung zones. Mild localized areas of fibrosis cause a reticular patten that can be seen on the radiograph and HRCT in approximately 50% of patients[52, 53]. Any fibrosis is usually limited to the subpleural lung regions of the lower lung zones. The areas of ground glass attenuation seen on HRCT have a predominantly peripheral distribution in 60% of patients, a patchy distribution in 25% and diffuse in 15%[52]. With therapy these abnormalities generally improve [52, 53].

Fig. 8: DIP alveolar spaces filled with macrophages



Pathologic findings: The hallmark of the DIP patten is a diffuse, marked intra-alveolar macrophage accumulation. A more technically correct term for it would be alveolar macrophage pneumonia [3]. The macrophage accumulation may be accentuated around the respiratory bronchioles, but it extends diffusely throughout the lung parenchyma. There is little fibrosis with only mild or moderate thickening of the alveolar walls. There is no remodeling of the lung architecture. Interstitial inflammation is mild and consists primarily of lymphocytes and a few plasma cells. In some cases Blue bodies may be present [54]. These are nonspecific inclusions consisting mostly of calcium carbonate with lesser amounts of mucopolysaccharide matrix and iron, and may be seen in any disorder associated with alveolar macrophage accumulation[54].

Treatment and Prognosis: Smoking cessation is the primary treatment, often leading to spontaneous regression of disease[55]. Patients with severe symptoms and moderate to severe gas exchange abnormalities often respond to corticosteroids. The disease can recur particularly if the patient starts smoking again or is exposed to passive smoke. The 5-year survival is 100% and the majority of patients do well. However, DIP is known to progress in a small group of patients [52] and these patients do poorly. Fulminant DIP leading to death is rare and lung transplantation has been performed in patients with endstage disease for DIP however disease recurrence in the transplanted lung has been reported[56, 57].

4. Cryptogenic Organizing Pneumonia:

Definition: Organizing pneumonia is defined by a distinct histologic pattern. When certain corresponding clinical-radiological findings are present in combination with this histologic pattern, the diagnosis is cryptogenic organizing pneumonia (COP). This occurs when no definite cause (i.e. infection) or characteristic clinical context (collagen vascular disease) is found. It is a diagnosis of exclusion as the histologic pattern is a common nonspecific reaction to a variety of different types of lung injury (Table 5). The hallmark lesions are excessive proliferations of granulation tissue (consisting of fibroblasts and myofibroblasts embedded in a loose connective matrix), within small airways and alveolar ducts, associated with chronic inflammation in the surrounding alveoli. COP is also known as Bronchiolitis Obliterans organizing pneumonia aka BOOP[2, 58].

Table 5: Causes of Organizing Pneumonia

COP (idiopathic BOOP)
Collagen Vascular diseases
Drug reaction
HIV infection
Viral Infection (HSV, CMV, influenza)
Hypersensitivity Pneumonitis
Localized organizing pneumonia
Cocaine abuse
Myelodysplastic syndrome
Radiation
Vasculitic syndromes (Wegener's)
Hemorrhage
Abscess, infarct or neoplasm
Infection PCP, Crypto, Plasmodium Vivax, certain bacterial pneumonias

Clinical Features: The incidence and prevalence are unknown and disease onset is usually in the fifth or sixth decade of life. It has no predilection for either sex and is not associated with smoking. It has occasionally been reported in childhood[58-61].
Symptoms generally develop subacutely with a flu-like syndrome that lasts for a few weeks and is accompanied by mild fever, anorexia; weight loss, sweats, nonproductive cough and mild dyspnea. Chest pain, hemoptysis, and bronchorrhea are uncommon. Most patients are diagnosed with atypical pneumonia. However antibiotics are not effective even when drugs from different classes are used successively. The diagnosis is often not made for 6-12 weeks on average and rarely will a patient present with a fulminant process like ARDS.
Physical examination is relatively non-specific. Fine crackles are heard over affected areas of lung , but there are no wheezes. In contrast to the other IIP's the crackles are usually focal and clubbing does not occur. 25% of patients will have a normal lung exam[62].
Laboratory testing is nonspecific with findings of leukocytosis in up to 50% of patients and elevated ESR as high as > 100mm/hr. The CRP is positive in 70-80% of patients [58, 63].
Pulmonary function tests usually show a restrictive defect however, lung function will occasionally be normal. Gas exchange abnormalities are common and the DLCO is reduced in most patients. Hypoxemia at rest and with exercise is almost always present.

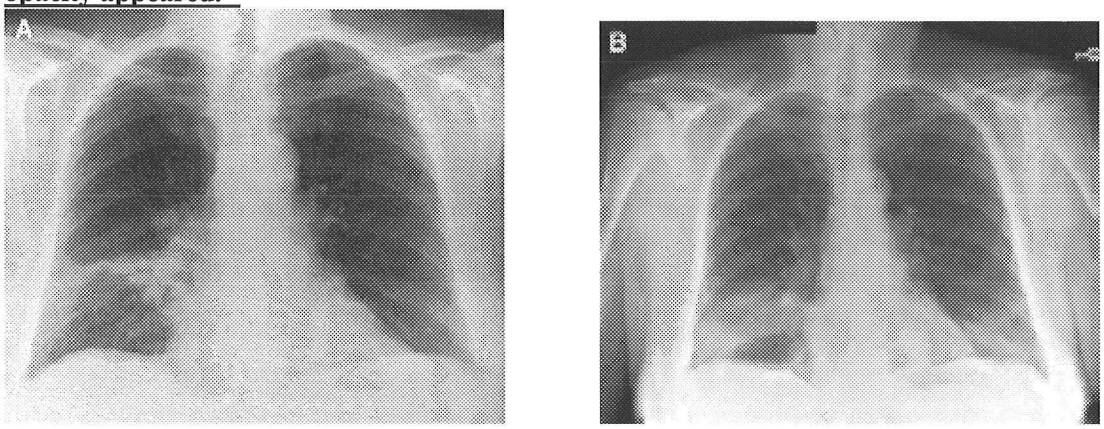
Radiographic Findings: There are <u>three</u> distinct radiographic manifestations of COP. The first is what is known as classic COP. Here the chest radiograph has patchy alveolar opacities usually bilateral and may be migratory. They usually predominate in the lower lung zones (fig.9). On HRCT the alveolar opacities vary in density from ground glass to consolidation. Their size ranges from a few centimeters to an entire lobe. The

infiltrates are generally peripheral but can occur in a peribronchovascular location (fig. 10.1). This patten is easily recognized by experienced radiologists[64-66].

The second distinct clinical imaging presentation of COP is that of a solitary focal nodule or mass (fig. 10.2) and is often seen in the upper lobes. Patients may be asymptomatic or have a clinical syndrome of chronic non-resolving pneumonia with persistent fever and other signs suggestive of pneumonia that remain persistent despite antibiotics, these patients may have hemoptysis and the mass can be cavitary. Often the diagnosis and cure are obtained by surgical excision, usually performed for a suspected carcinoma [58].

The third distinct clinical imaging presentation of COP is that of infiltrative lung disease. On HRCT intersitial opacities are often associated with superimposed small alveolar opacities early in the disease process however some reticular subpleural opacities and eventually honeycombing may develop over the long term. This type of COP requires further analysis because it is associates more with interstitial mononuclear inflammation and likely overlaps with other intersitial lung disease particularly NSIP[58].

Fig. 9: (*A*) Patchy alveolar opacity of right lower lobe. (*B*) Six days later, a new contralateral basal opacity appeared.[58]



Pathology: The major histologic feature is organizing pneumonia: as evidenced by intraluminal-organizing fibrosis in distal airspaces (bronchioles, alveolar ducts, and alveoli). There is a patchy distribution, preservation of lung architecture, uniform temporal appearance and mild interstitial chronic inflammation. There should be an *absence* of granulomas, neutrophils, necrosis, hyaline membranes or prominent airspace fibrin. There should also be no prominent infiltration of eosinophils, and no evidence of vasculitis[2, 3].

Fig. 10.1: Bilateral Extensive consolidation with air bronchograms[58]

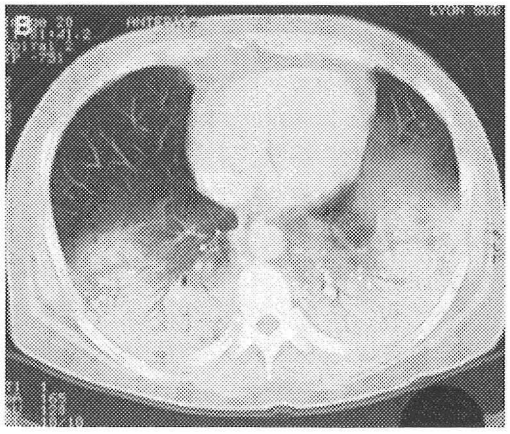


Fig. 10.2: Pseudoneoplastic process [58]

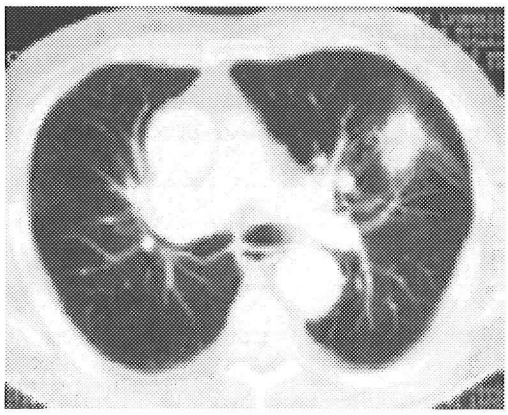
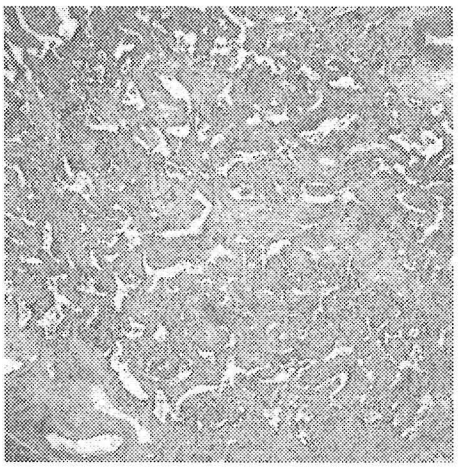


Fig. 11: Alveolar Space Organization in COP[67]



Treatment and Prognosis: The mainstay of treatment in this patient group is corticosteroids. There have been reports of spontaneous remission or a response to erythromycin however corticosteroids are still the mainstay of therapy. Patients should be treated for a minimum of 3-6 months, any less than this and patients will frequently relapse. However they usually respond to reinitiating corticosteroid treatment if this occurs [62] . Patients with predominantly interstitial opacities on the chest radiograph have a poorer prognosis than those with airspace opacities. The overall prognosis however is much better than those with other IIP's. Rapidly fatal COP can occur but is rare and may actually represent AIP or organizing DAD.

5. Lymphoid Interstitial Pneumonia:

Fig. 12: LIP sheets of lymphocytes fill alveoli

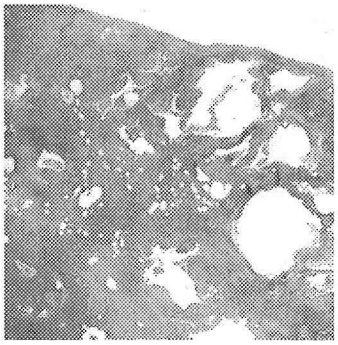
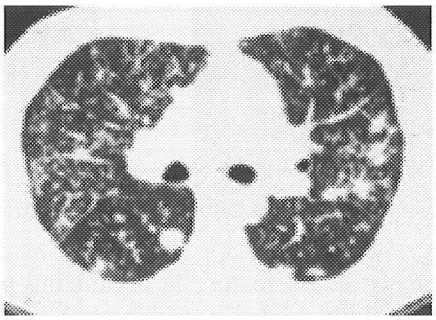


Fig. 13: HRCT small nodular densities



Most experts no longer consider LIP an IIP however it was included in the most recent classification by the ATS/ERS because idiopathic LIP has been described. Sheets of lymphoplasmacytic cells that expand the interstitium more commonly characterize it. The major differential diagnosis from a clinical standpoint is the separation of LIP form low-grade lymphoma, particularly the extranodal marginal Zone B-cell lymphoma of MALT[2, 68] characterize the pathology and adenopathy and small nodules are seen on CT (figs. 12-13).

6. Nonspecific Interstitial Pneumonia Cellular and Fibrotic type:

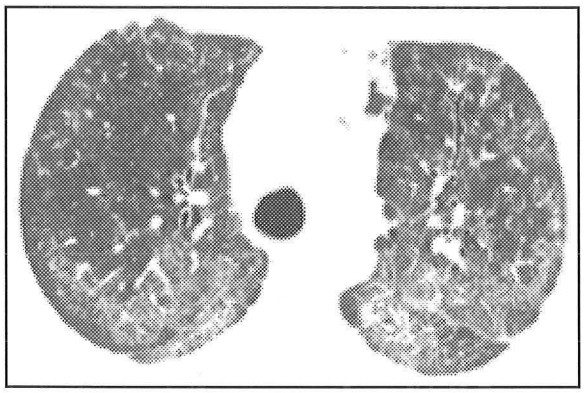
Definition: The main histologic feature of NSIP is the temporally uniform, homogenous appearance of *either* inflammation or fibrosis. Most cases of NSIP are of unknown etiology, however this histologic pattern can be found in association with a number of disorders especially connective tissue diseases, drug induced ILD, and chronic hypersensitivity pneumonitis.

Differential Diagnosis:

Collagen Vascular disease
Hypersensitivity pneumonitis
Drug-induced pneumonitis
Infection
Immunodeficiency including HIV infection
No detectable cause (Idiopathic NSIP)

Clinical Features: The incidence and prevalence are yet to be determined. However while less common than IPF it appears to the second most common IIP's [14-17]. The cause of idiopathic NSIP is unknown and it has been well described in patients with a variety of systemic disorders particularly the collagen vascular diseases [69, 70]. The average duration of illness to diagnosis is 8-18 months [69, 71], and the average age ranges from 47-57 years [14, 69, 72]. It has also been described in children [72], and has a slight predilection for women. Patients with idiopathic NSIP cellular type are more likely to be younger than those with idiopathic UIP or with Idiopathic NSIP fibrosing pattern (30yr vs. 50yr) [14, 17]. Up to 2/3 patients are either current or previous smokers. Patients with NSIP present with exertional dyspnea, cough, and fever. Crackles are commonly found on chest examination and clubbing has been reported in 21-40% of patients [14, 71]. Pulmonary function testing usually shows a restrictive pattern and gas exchange abnormalities are frequently noted on presentation [14].

Fig. 14: NSIP (note the reticular infiltrates and lack of honeycombing)



Radiologic findings: The chest radiograph and HRCT findings are variable and nonspecific. The most common findings are areas of consolidation or ground glass opacities, which may be diffuse but tend to predominantly involve the lower lung zones. Other findings include a reticular patten or a combination of interstitial and airspace patterns [73]. On HRCT areas of ground glass are seen in virtually all cases [52, 73] (Fig. 14). Radiographic and HRCT findings commonly mimic those of DIP and hypersensitivity pneumonitis. Occasionally they may resemble those of COP or IPF.

Pathologic findings: Like all IIP's NSIP is a diagnosis of exclusion in that the histologic pattern lacks features of UIP DIP, idiopathic COP, and DAD/AIP, and there is no evidence suggestive of a specific diagnosis. It encompasses a broad spectrum of different histologic lesions. The separation of cellular from fibrosing patterns of NSIP is an important concept as each carries a different prognosis. Those patients with cellular type NSIP have a better prognosis than those with fibrotic type NSIP [15, 16] (fig. 18).
NSIP Cellular Pattern: Major features include; mild to moderate chronic interstitial inflammation, Type 2 pneumocyte hyperplasia, areas of inflammation, and preserved areas of architecture. Its minor features include organizing pneumonia, lymphoid aggregates, focal alveolar macrophages, bronchiolar inflammation, bronchiolar fibrosis, chronic pleuritis, squamous metaplasia cholesterol clefts and thickened arteries. Pertinent *negative* findings include an absence of honeycombing, granulomas, eosinophils, and lack of viral inclusions or organisms on special stains [2].

NSIP Fibrotic Pattern: The major features include dense or loose interstitial fibrosis lacking the temporal heterogeneity and/or patchy features of UIP. Lung architecture is preserved and interstitial chronic inflammation is mild or moderate. The minor features are the same as those for NSIP cellular type with the addition of Type 2 pneumonocyte hyperplasia, rare eosinophils, atypical pneumonocyte hyperplasia, Blue bodies, and metaplastic calcification. Negative findings include an absence of fibroblastic foci, airway centricity. Other pertinent negative findings are the same as those for NSIP cellular type [2].

Treatment and Prognosis: NSIP is generally responsive to steroids particularly if started early on in the course of the illness. No spontaneous remissions have been reported thus untreated patients are expected to experience disease progression and decreased survival [17]. Treatment with steroids with or without concomitant immunosuppressive agents, results in improvement or recovery in up to 75% of patients with NSIP [15]. Travis et al. [17], Nagai et al [15] and Nicholson et al. [16] found that[15] patients with cellular NSIP have a 100% 5-year survival, significantly better than for those with NSIP fibrotic type. At the same time these studies showed that fibrotic NSIP has a better survival than IPF.

7. Idiopathic Pulmonary Fibrosis:

Definition: Usual interstitial pneumonia is a histologic patten seen in the clinical setting of diffuse bilateral intersitial lung infiltrates. The histologic changes are often distributed along the subpleural and paraseptal regions, and are characterized by patchy, temporally heterogenous fibrosis with scattered fibroblastic foci at the edges of dense fibrotic scars. This is the most severe of all the IIP's, unfortunately the most common but also the most investigated. It is known as a distinct type of chronic fibrosing interstitial pneumonia of unknown cause, limited to the lungs, and associated with a surgical lung biopsy showing UIP.

The term UIP is used in two ways; as a pathologic pattern and as a clinical pathologic syndrome [3, 17]. As an idiopathic clinicopathologic syndrome UIP is synonymous with IPF. However, one must remember that the UIP pattern occurs in a variety of clinical settings. If other known causes of this pattern such as drug toxicity, environmental exposures and collagen vascular disease have been ruled out then IPF is the appropriate terminology.

Differential Diagnosis: All other IIP's, Connective tissue disease, Asbestosis, Hypersensitivity pneumonitis, sarcoidosis, CHF, COPD.

Clinical features:_The epidemiology has been discussed in a previous section. While the cause of IPF is unknown, several risk factors have been identified that appear to be associated with an increased risk of disease; Genes, Tobacco, Environmental factors, e.g. occupational exposure to wood or metal dust, chronic aspiration associated with GERD and infectious agents including EBV, CMV, hepatitis C virus to name a few. There has also been a suggestion that exposure to antidepressant medication is also a risk factor in IPF.

The majority patients present in the 6th decade of life complaining of an insidious onset of dyspnea on exertion and/or cough (however the disease has been reported in all age groups). They rarely will have any systemic symptoms. Frequently patients will underestimate the length of their dyspnea and it is imperative that a thorough history is taken. Most patients will initially assume they are getting old and so do not necessarily seek medical attention until the disease has progressed or they have sought medical attention but were initially misdiagnosed and treated for an alternative disorder such as CHF or 'double pneumonia'.

On exam patients have dry harsh end-inspiratory crackles. 20-25 % will present with clubbing [3]. Cardiac findings are generally normal until the late stages of the disease, when findings of pulmonary hypertension, (i.e. augmented P2, right sides lift and S3 gallop) occur. Similarly cyanosis is also a sign of late disease.

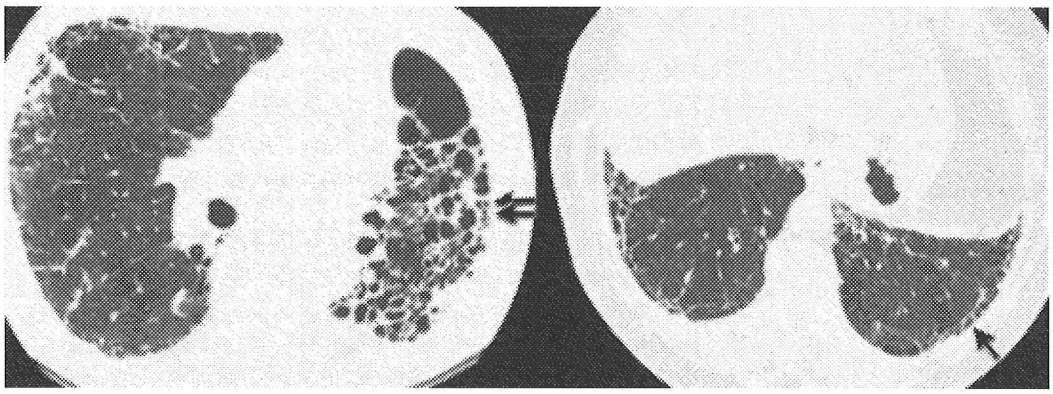
Laboratory testing is generally not helpful except to rule out other possible causes of IPF. Therefore lab testing should be performed for collagen vascular disease (ANA, RF, SCl-70, CPK and aldolase, Jo –1 antibody, ANCA and hypersensitivity panel)[3]. Pulmonary function tests can be relatively normal early on in the disease process and thus do not exclude the diagnosis of IPF. However, they are more typically restrictive with reduced FVC and TLC. There is evidence of impaired gas exchange with decreased DLCO and increased A-a gradient[74]. Lung volumes can be normal in patients with superimposed COPD[75] and significant air trapping.

Recent data suggests that exercise testing via the 6 minute walk test is a more sensitive measure of changes in gas exchange and in progression of disease than are PFT's[76]. Essentially, after baseline vitals are measured, patients are instructed to walk as far as they can in a 6-minute time period. They can stop as often as necessary and use supplemental oxygen if needed to maintain oxygen saturation. The primary endpoint is walking distance, but other endpoints, such as oxygen saturation and level of dyspnea are also very useful. It has been suggested that repeat measures using 6-MWT can provide information regarding response to therapeutic interventions and change in functional capacity. In patients where a primary pulmonary process is suspected, exercise desaturation can indicate the presence of different disorders such as ILD, pulmonary hypertension and obstructive lung disease. The specificity of the test is low but when taken in conjunction with other clinical data ILD may be suspected and further testing such as HRCT may be indicated[3, 76].

Radiologic findings: Chest radiographs in patients with IPF are almost always abnormal at the time of diagnosis. Key findings include reduced lung volumes (except in those with both COPD and IPF), Reticular opacities, and honeycombing[77-79]. The findings are usually bilateral, symmetric and concentrated in the periphery and lower lung zones in 80% of cases[77, 80]. It is important to note that these reticular opacities can also be seen in asbestosis and certain connective tissue diseases, such as scleroderma and rheumatid arthritis. While features consistent with IPF can be identified on chest radiograph a diagnosis cannot be made on the basis of a chest radiograph alone. All patients with suspected IPF should get a HRCT [3]. HRCT manifestations of IPF are characteristic consisting of reticular opacities, and honeycombing in the subpleural lung regions[81-83]. Honeycombing will be evident on HRCT at presentation in 80-90 % of patients with IPF while only seen in 30% of cases on chest radiograph[81]. Early on there is irregular thickening of the interlobular septa and irregular pleural vascular and bronchial interfaces with the lung parenchyma. With progression the irregular line become coarser and there is progressive distortion of the lung architecture, with the development of traction bronchiectasis with extensive honeycombing[84, 85] (fig. 15). While ground glass attenuation has been described in these patients it is rare and should lead one to consider the possibility of an alternative diagnosis. A normal HRCT does not rule out the diagnosis if IPF as up to 5% of patients with IPF can have a normal HRCT[86].

Pathology: Major features of UIP are patchy lung involvement, frequent subpleural, paraseptal and/or peribronchiolar distribution, and dense fibrosis causing remodeling of lung architecture with frequent honeycombing, fibroblastic foci poised between the edges of the dense scars and mild to moderate intersitial inflammation as they migrate forward into normal lung. In essence, temporal heterogeneity should be present. No active lesions of other intestinal disease i.e. sarcoid, no marked interstitial chronic inflammation and no substantial inorganic dust deposits such as asbestos should be present[17] (fig. 16).

Fig. 15: IPF in its early (right) and late stages (left)



Diagnosis of IPF: This is clearly a challenge given the similarities between IPF and the other IIP's. Based on these similarities it would appear that all patients with any IIP would need some type of biopsy. History in combination with the physical examination, pulmonary function testing and radiologic evaluation should aid in making the diagnosis once any possible causes such as, exposure, or connective tissue disease or drug toxicities. However the evaluation is not complete without an open lung biopsy. This leaves us in something of a quandary, as there are times when these patients are too ill to undergo open lung biopsy or the risk of surgery outweighs any benefits obtained. In view of this and that a number of studies have revealed that the clinical diagnosis can by both sensitive and specific under the right conditions[87], the ATS/ERS developed Major and Minor criteria that must be met in order to make a clinical diagnosis of IPF in the absence of an open lung biopsy[3] (Table 6).

Table 6: Diagnosis of IPF in the absence of a surgical lung biopsy

ATS CRITERIA FOR DIAGNOSIS OF IDIOPATHIC PULMONARY FIBROSIS IN THE ABSENCE OF A SURGICAL LUNG BIOPSY[a3]

Major Criteria

Exclusion of other known causes of ILD such as certain drug toxicities, environmental exposures, and connective tissue diseases

Abnormal pulmonary function studies that include evidence of restriction (reduced VC often with an increased FEV1/FVC ratio) and impaired gas exchange (increased $AaPO_2$ with rest or exercise or decreased DLCO)

Bibasilar reticular abnormalities with minimal ground-glass opacities on HRCT scans

Tran bronchial lung biopsy or BAL showing no features to support an alternate diagnosis

Minor Criteria

Age > 50 years

Insidious onset of otherwise unexplained dyspnea on exertion

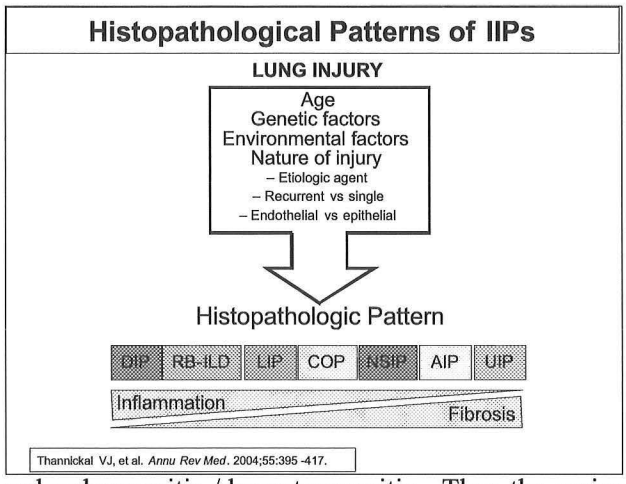
Duration of illness = 3 months

Bibasilar, inspiratory crackles (dry or "Velcro" type in quality)

Pathophysiology of IPF: Current knowledge and Future Directions

A review of the histopathological patterns of IIP's suggests some type of injury to the lung. The degree and etiology of that injury remains unknown. This 'injury' needs to be realized and evaluated in the context of age, genetic factors, environmental factors and the nature of the injury (i.e. localized or diffuse). This can correlate with an etiological agent, recurrent versus single 'hits' to the lung or predominantly endothelial vs. epithelial damage to the lung or a combination of both.[88].

Fig. 15:



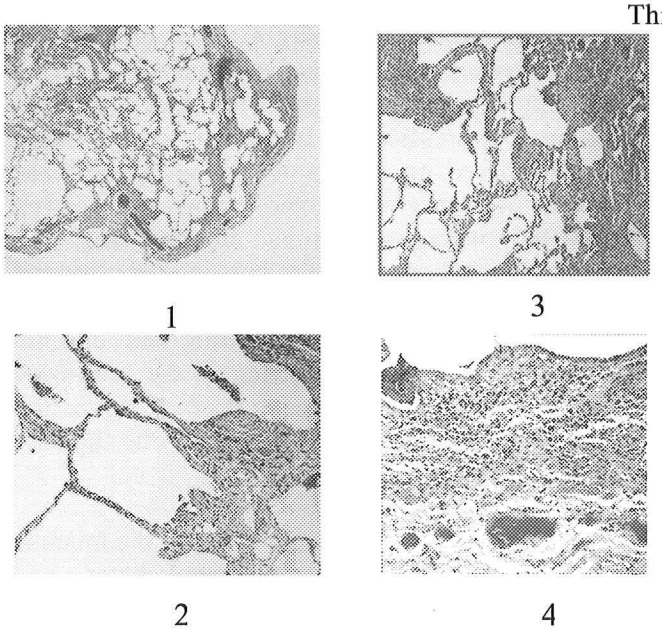
Ultimately this leads to a response in the lung that can be quite varied with overlapping patterns of inflammation and fibrosis, from DIP associated with areas of predominant inflammation to the end of the spectrum being IPF/UIP (fig. 16), which has areas of normal lung interspersed with scant inflammation, honeycomb lung and fibroblastic foci (fig. 17).

The majority of research in this area has been performed looking at animal models of pulmonary fibrosis. Over the last 30 years, with the refinement of the pathologic description of idiopathic interstitial pneumonias [3, 33, 89] it is important to understand that the UIP pattern described on a biopsy specimen can be observed in connective tissue diseases such as scleroderma, rheumatoid arthritis, and polymyositis /dermatomyositis. Thus the major refinement is **the presence of fibrosis in a lung biopsy does not equal a diagnosis of IPF**.

This is an important fact to recognize as it carries prognostic and treatment implications. IPF is the most common IIP and carries the worse prognosis. The mean survival is 2-5 years[90-92] from diagnosis. It has been the primary focus of most pathological studies into the underlying causes of pulmonary fibrosis. It is important to recognize that UIP is now a distinct pathologic entity characterized by the presence of [3, 93](fig. 16):

1. Patchy chronic interstitial inflammation
2. Fibrosis (oldest disease) being peripheral in the lung acinus or lobule
3. Transitions to uninvolved lung in the biopsy (i.e. temporal heterogeneity) and,
4. Leading edge of fibroblastic foci and microscopic honeycombing.

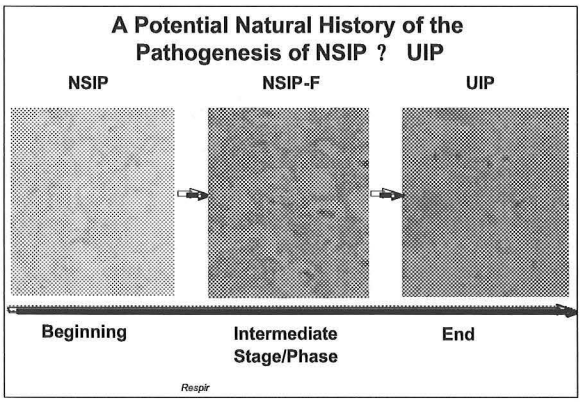
Fig. 17: Major histological findings on biopsy for the diagnosis of UIP



This lies in direct contrast to patients with the other IIP's, (NSIP, DIP, RBILD, COP). With the exception of AIP the other idiopathic interstitial pneumonias carry a better prognosis and are more responsive to treatment with corticosteroids or immunosuppressive agents. One possible exception to this may be Nonspecific Interstitial Pneumonia (NSIP) Fibrotic type.

NSIP has been subdivided into two forms; a cellular form more responsive to therapy and a fibrotic form that is clinically similar to IPF but carries a better prognosis and is often associated with collagen vascular disease. There are those that argue that NSIP is a precursor to IPF and the coexistence of IPF and NSIP has been documented by several investigators [94] thus raising the question about a possible relationship between IPF and NSIP

Fig. 18: Natural history of NSIP to IPF



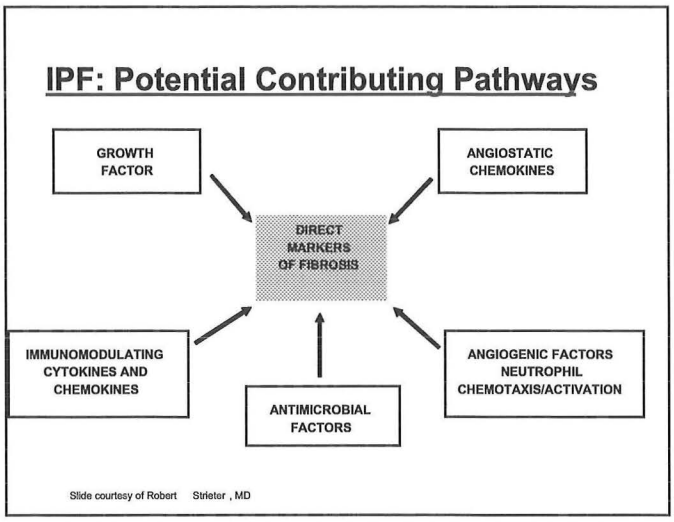
An Evolving Paradigm

Pulmonary fibrosis is the most extreme and most common of the Idiopathic Interstitial Pneumonias. Its pathophysiology has been the most difficult to elucidate and remains poorly understood. It is only in the last 5-10 years have we begun to develop some understanding of this process. In the 70's and 80's pulmonary fibrosis was believed to be the end result of an uncontrolled inflammatory process. This was based largely on the observation that bronchoalveolar lavage fluid from patients with IPF had increased numbers of inflammatory cells relative to normal individuals [95]. By targeting the inflammatory response, the belief was that the fibrosis could be limited or prevented. It appears that the more likely scenario is that a structural abnormality in lung architecture alters inflammatory cell trafficking[93].

In the last decade a number of observations have lead to a revised hypothesis of the key players in the pathogenesis of pulmonary fibrosis. The role of inflammation in IPF remains controversial and it appears there may be some degree of chronic low grade inflammation contributing to disease progression. However, with improved technology and ability to study the various cytokines myofibroblast and fibroblastic foci newer concepts have emerged and it is generally agreed like everything in the human body the process is not quite so simple as previously believed.

Zuo et al., [96] were the first group to use gene markers to study the biological markers in pulmonary fibrosis. They used gene chip analysis of specimens of 8 patients with pulmonary fibrosis. Six had IPF two had collagen vascular disease associated pulmonary fibrosis

Fig. 19:

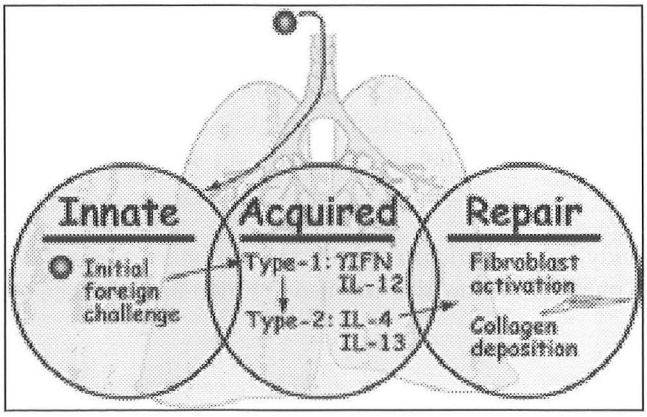


Six had IPF two had collagen vascular disease associated pulmonary fibrosis. They found the over expression of genes encoding 4 major groups; one group clustered to muscle markers, another group to extracellular matrix growth factors and proteases. The over expression in these two groups were expected based on our knowledge of the disease however two other unexpected groups of clustering identified were, cytokines, chemokines and antioxidants and complement, immunoglobulins and amyloid. The significance of this finding suggests that indeed chronic inflammation and chronic immune responses are occurring in the lung over time. This is particularly true in the over expression of immunoglobulin suggesting that the host is responding to some form of antigen.

One of the rationales for corticosteroids and immunosuppressive therapy for IPF has been to target the immune system. While this process has been effective in autoimmune disorders such as Wegener's granulomatosis and systemic vasculitides, it has not been effective in IPF. It is thought in some circles that contributing to pulmonary fibrosis are certain cytokine phenotypes that appear to be important in dictating the progression of inflammation and fibrosis in the lung. Reverse transcriptase PCR studies have suggested that increased production of TH2 cytokines, (IL-4, IL-5, and IL-13) occurs in lung tissue of patients with IPF [97]. It has been suggested that IL-13 and TGF –beta are key mediators in the fibrotic process. It has been shown that an over expression of IL-13 in these models resulted in an eosinophilic inflammation, mucus hypersecretion, goblet cell hyperplasia and subepithelial airway fibrosis [98-100]. The cytokine appears to be able to increase the fibrotic process directly by stimulating fibroblasts to increase collagen expression and via a cytokine network that involves the expression of TGF – beta-1 [98, 101].

The chemokine MCP-1/CCL2 was originally described as a specific chemotactic agent for the elicitation of mononuclear cells but has now found an additional role as a mediator involved in the maintenance of fibroblast activation and collagen deposition associated with pulmonary fibrosis[102]. While a number of cells have the ability to produce this chemokine it appears that patients with IPF produce it in abundance[103]. In addition a number of interventional therapies have begun to identify a role for this CC chemokine in chronic interstitial lung disease[104, 105].

Fig. 20: A possible pathway by which Fibrosis occurs due to an imbalance in the TH1/TH2 cytokines



Thus one possible pathway in the pathogenesis of pulmonary fibrosis involves an imbalance of the TH-1/TH2 cytokines (fig. 20). The evolution of chronic immune mediated lung disease in a naïve host depends on the persistence of an antigen or pathogen not cleared by the innate or Type 1 acquired response. The shift in the acquired response to a cytokine phenotype or Type 2 response is then characterized by high levels of IL-4 and IL-13 resulting in a greater reaction with the contribution of additional antibodies (IGE) and leukocytes. This continued persistent response could ultimately activate fibroblasts resulting in matrix deposition to 'wall off' the agent form the host[101].

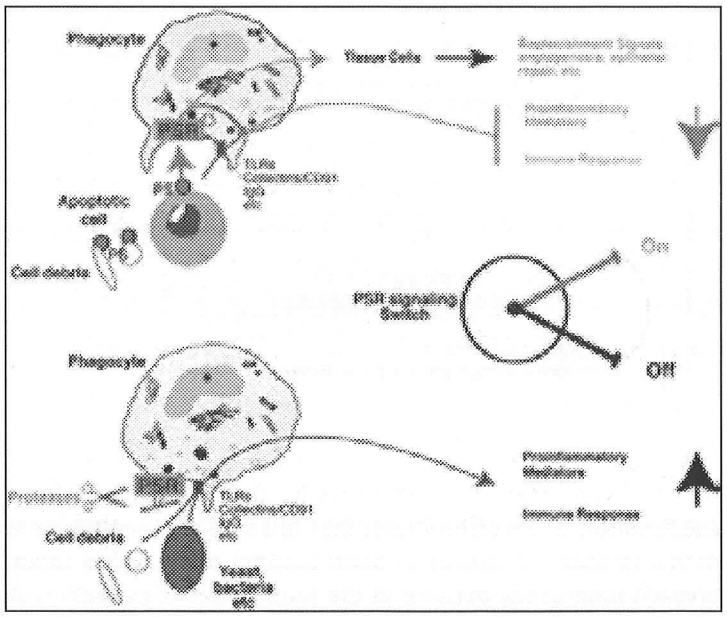
Epithelial Cell Apoptosis and Proliferation:

In recent years a number of studies have been published suggesting type II alveolar cell injury and apoptosis may be an important early feature in the pathogenesis of pulmonary fibrosis. A number of mechanisms have been proposed to explain epithelial cell apoptosis in pulmonary fibrosis.

In the normal host there is a balance between anti and proinflammatory consequences of apoptotic cells or cell debris recognition depending on the availability and or function of the phosphatidylserine (PS) receptor. Fig. 21 shows a proposed switching mechanism where by recognition of phosphatidylserine by a PS receptor leads to both suppression of inflammation and immunity with generation of possible replenishment signals for restoration of normal tissue structure and function. Foreign organisms and cell debris often do not express PS on the membrane and can lead via a variety of innate or adaptive immune receptors to the generation of proinflammatory mediators. However if the PS receptor is engaged the effects of many of these receptors are overcome and productions of proinflammatory mediators are suppressed. The susceptibility of the PS receptor to serine protease cleavage suggests that in the presence of a protease -antiprotease imbalance, the PS receptor switch is inactive and the inflammation may not be turned off [28, 106] (fig. 21).

Type II Alveolar injury and apoptosis have been demonstrated on EM studies performed on lung biopsies from patients with pulmonary fibrosis [107]. Bronchoalveolar lavage fluid from patients with IPF have demonstrated an increased expression of pro-apoptotic proteins in alveolar epithelial cells [108-110].

Fig. 21: Proposed Switching Mechanism



More recent data suggests there is an increased oxidative stress in the alveolar epithelium in patients with pulmonary fibrosis [93, 108, 110]. A number of investigators have demonstrated that there is an overproduction of oxidants in IPF and deficiencies in glutathione production [111]. This has resulted in ongoing studies examining the use of N-acetylcysteine in the treatment of IPF.

Experiments using the bleomycin model of lung injury and fibrosis in mice have shown that by inhibiting epithelial cell apoptosis using various approaches including, inhibiting the production of angiotensin, inhibiting the Fas-Fas ligand pathway and blocking caspase activation, block the development of fibrosis in these models[112].

Wang et al. suggested that IPF fibroblasts produce angiotensin peptides that promote epithelial cell apoptosis. Angiotensin II induces the proliferation of mesenchymal cells, including human lung fibroblasts and increases the expression of ECM proteins. Angiotensin peptides are involved in alveolar epithelial cell apoptosis induced by fibroblasts. Blockade of angiotensin II appears to be effective in a variety of experimental models of fibrosis and significantly decreases plasma levels of TGF-_ and endothelin in transplant patients with chronic allograft nephropathy [113, 114]. This has led to some considering ACE inhibitors as part of the treatment course for patients with IPF although there are no studies currently using this therapy.

An additional player in this process involves TNF - α, which has been shown to promote apoptosis in alveolar cells[115]. TNF-α receptor knock out mice do not develop bleomycin induced lung fibrosis, and over expression of TNF-α in animal models has been associated with increased lung fibrosis [116]. This has not only been shown in the animal model but in patients with IPF as well. TNF -α over expression has been demonstrated in type II

alveolar cells in patients with IPF[117]. This has led to current trials investigating the possible use of TNF-α inhibitors as a possible therapy for IPF.

One of the essential and unique elements of pulmonary fibrosis in IPF is the loss of integrity of the subepithelial basement membrane[107], a unique feature to IPF/UIP. A possible hypothesis for the loss is thought to be due to the loss of the alveolar epithelial cell from cell death leading to an absence of the protective barrier and exposure of the underlying basement membrane to oxidative injury; something the lung is particularly prone to given its constant contact with the external environment and high oxygen tension. Re-epithelialization is considered to be a vital and necessary step in the regulatory process. However in this instance of unregulated fibrosis it is likely that epithelial cell generation occurs as result of a *failure* of epithelial cells to attach to the underlying basement membrane and provide signals to terminate epithelial cell proliferation. This is supported by the presence of hyperplastic type II alveolar cell as a common feature of IPF [93, 107]. This may occur as a result of the accumulation of various growth factors that accumulate after epithelial cell injury to promote epithelial cell proliferation and healing in a normal host. These growth factors include TGF -β, TNF-α, insulin-like growth factor-1, platelet-derived growth factors, fibroblast growth factor –2, and hepatocyte growth factor. Many of these growth factors activate tryosine kinase signaling pathways promoting fibroblast proliferation and matrix production. An additional consequence of this excessive epithelial cell generation would be the recruitment of fibroblasts and myofibroblasts[93, 107] (figs. 22-23).

Fig. 22: Alveolar epithelial injury

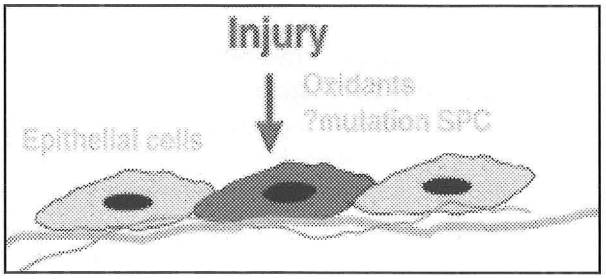
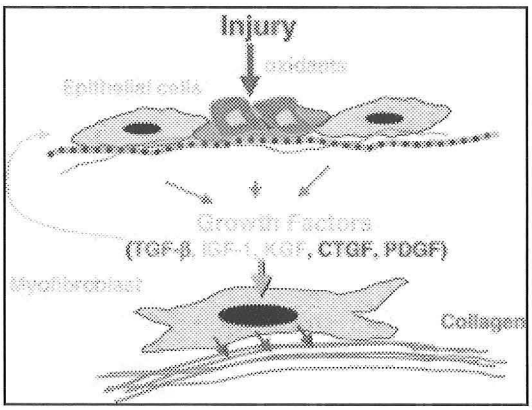


Fig. 23: Epithelial cell apoptosis Injury



Angiogenesis and Angiostasis:

The biology of IPF and cancer are considered to move in a parallel universe to each other. The unremitting recruitment and maintenance of fibroblasts with the generation of myofibroblasts that fail to die is analogous to the transformation of cancer cells. A hallmark of this process in cancer is angiogenesis to facilitate tumor growth. Keane and colleagues, [118] demonstrated increased angiogenic activity in the lung tissue of patients with IPF and in experimental models. This increased activity has been attributed to an imbalance of pro-angiogenic chemokines (IL-8, ENA-78) and anti-angiogenic CXC chemokines. Conversely recent reports indicate a decreased expression of vascular endothelial cell growth factors and endothelial cell pro-angiogenic proteins in the fibroblastic foci in UIP compared to the granulation tissue in organizing pneumonia [119]. One possible explanation for this discrepancy may be that enhanced angiogenesis occurs early in the disease where as a loss of blood vessels occurs in the more advanced stages.

Fibroblasts in pulmonary fibrosis

Matrix production and Degradation:

One of the hallmarks of IPF is an excessive production of extracellular matrix molecules. Fibroblastic foci are a cardinal feature of UIP. They contain fibroblasts with an altered activated phenotype [121, 122] developing at sites

of prior lung injury and are necessary for the diagnosis of UIP/IPF. There is ample evidence to suggest that cells in these areas of active fibrosis are the main cellular source for extracellular matrix expression that typifies fibrosis including collagen, tenascin, and proteoglycans. Fibroblasts participate in the repair and regenerative processes in almost every human tissue and organ, their primary function being to secrete extracellular matrix (ECM) proteins. UIP/IPF fibroblasts are highly synthetic and produce a number of ECM proteins and integrin molecules [120, 121, 123, 124]. This is accompanied by a decreased capacity for ECM degradation from imbalances in the production of Matrix metalloproteinases (MMP's) and tissue inhibitors of metalloproteinase (TIMP's)[120, 125, 126]. TIMP-2 expression appears to contribute to the irreversible structural remodeling of IPF [126, 127]. What is not known is if this increase in TIMP's is due to excessive production of TGF -β or is inherent to the disease process itself. This is an area that deserve further scrutiny

The presumed persistence of these cells may be the basis for disease progression, associated with progressive disease and poor clinical outcomes. [129].
The reference phenotype the myofibroblast is believed to be the primary source of type I procollagen gene expression in fibrotic lesions [130]. They have contractile properties and stain positive for αsmooth muscle actin. Because smooth muscle cells in fibrotic lung and other non-fibroblastic cell types do not appear to express this type of collagen it is likely that this α -smooth muscle cell expression plays a major role in the deposition of matrix [130]. In addition to this Myofibroblasts in UIP/IPF have been shown to secrete angiotensin peptides that may induce apoptosis of adjacent alveolar epithelial cells, and have an enhanced migratory capacity, diminished cyclo-oxygenase (COX-2) expression/prostaglandin (PG) E2 synthesis [128] again suggesting perhaps another possible treatment.

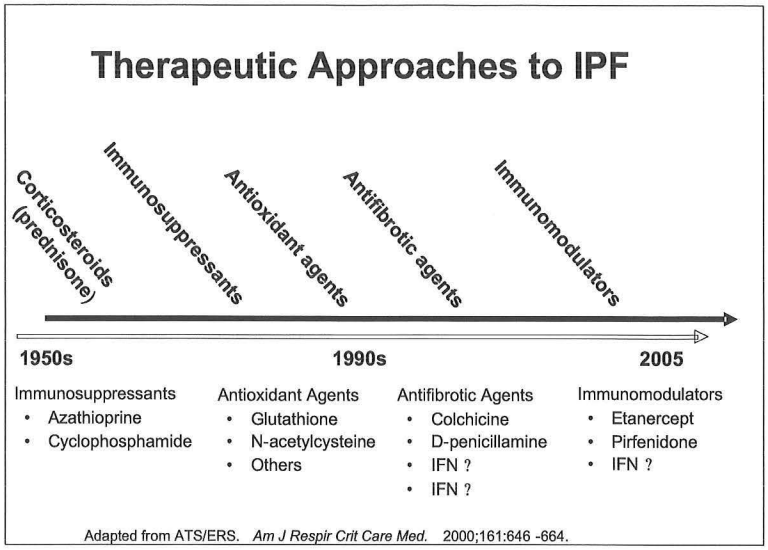
Inflammation in Pulmonary Fibrosis:
A related and controversial characteristic of pulmonary fibrosis is inflammation, which can be present as stated earlier in varying degrees depending in part on the etiology and in part on the stage of disease or disease activity. While minimal in IPF it is more intense in other IIP's [131]. Is inflammation critical for the pathogenesis of fibrosis? No one knows but the presence of inflammatory cells in fibrotic lesions has the potential of providing a source of pro-fibrogenic cytokines/mediators that may promote fibrosis. In fact the ability of the myofibroblast to elaborate the profibrotic cytokines such as TGF-β, MCP-1 indicates a potential role for inflammation given the inflammatory activity of these cytokines. In fact myofibroblasts have been shown to be the key source of such cytokines during later stages of fibrosis[28]. Yet another remarkable property of fibrotic tissue involves altered mechanical properties, namely decreased compliance or increased contractility. The myofibroblast exhibits an enhanced ability to contact collagen gels that is dependent on increased endogenous TGF β expression [28]. This mechanical property is also demonstrated in would healing [132] and likely plays a major role in the remodeling or the lung architecture. Thus the myofibroblast can participate directly in the pathogenesis of fibrosis, and be responsible for all three characteristics – matrix deposition, inflammation, and altered mechanical properties of the fibrotic lesion. [28]

One of the great challenges in elucidating the key mechanisms in pulmonary fibrosis is the very heterogeneity of the process. In fact there are now more questions than answers but it appears that most likely that there is most likely sequential lung injury as a key event in the pathogenesis of UIP but dysregulation of the host response to injury resulting in a profibrotic environment that propagates fibroblast proliferation, and exaggerated deposition of collagen and extracellular Matrix (ECM) [133, 13.4].
Alterations in the alveolar microenvironment of the lung likely account for the dysregulated repair and aberrant tissue remodeling characterizing the progressive fibrosis seen in UIP (fig. 19).

Treatment of IPF

There is no known cure for this disease other than a lung transplant and even then it is essentially trading one disease for another. Corticosteroids have not been shown to be beneficial. Over the years the approach to treatment has taken a number of directions as seen in fig. 24. Many physicians fall into one of two camps regarding therapy- the nihilists and the cautiously optimistic. The nihilists usually tell a patient to make out their will and will give no medications.

Fig. 24: Therapeutic Approaches to IPF



Alternatively they may elect not to tell the patient anything since there is nothing that can be done. The cautiously optimistic individuals will usually refer the patient for transplant if they are under age 65, start some cocktail of therapy in hope of retarding the rate of fibrosis or refer the patient to a center conducting clinical trials.

Two recent reviews of treatment for IPF were published by the Cochrane Central Register of Controlled Trials. The first review examined randomized controlled trials (RCT's) and controlled clinical trials (CCT's) between January 1966 and December 2002 that used corticosteroids alone for the treatment of adults with IPF. Fifteen studies were initially reviewed for inclusion in meta-analysis but none were suitable and all were excluded due to inadequate methodologies. The conclusion was that there is no evidence for the efficacy of corticosteroids alone in patients with IPF.

A similar review of RCT's and CCT's from January 1966 to April 2003 was conducted to determine the efficacy of non-corticosteroid immunosuppressive, antifibrotic and immunomodulatory agents in the treatment of IFP. Out of 59 studies identified, 3 were considered suitable for meta-analysis. Since each of these used a different agent (azathioprine, colchicine, and gamma IFN) direct comparisons could not be made. Their conclusion was that treatment with gamma-IFN showed benefit as measured by pulmonary functions and arterial oxygenation. Azathioprine was associated with a small long-term survival advantage. Despite this the authors concluded that there is currently little evidence to justify the use of theses agents in IPF but perhaps further investigation with larger groups of patients and better study design would yield more information.

The ineffectiveness of traditional therapies has prompted an aggressive search for newer agents. An improved understanding of the natural history and pathogenies of this disease have aided this process. A number of clinical trials are underway most using agents targeting a specific section of the pathway. Due to the natural history and pathophysiology of the disease it is likely that treatment will require some combination of therapies.

Conclusion:

In summary the IIP's are a challenging group of disorders presenting with similar clinical features, some overlap in radiological features and are primarily distinguished by pathology in conjunction with the clinical and radiographic presentation. All are a diagnosis of exclusion; and all require a relatively high index of suspicion. These are disorders that really do require a multidisciplinary approach and require due diligence of all involved.

What does a primary care physician need to know about these disorders?
One should know the clinical presentation i.e. cough and dyspnea with abnormal chest radiograph and a patient who is not responsive to antibiotics.
When should you refer your patient to a pulmonologist?
A patient who has progressive dyspnea greater than three months, unexplained dry cough for > 3 months, desaturation occurs on oximetry testing, chest radiograph is abnormal showing inflammation, fibrosis or lower lobe predominance. This is unlikely to be double pneumonia!
What tests should you do at baseline? Patients should have a chest radiograph and if indicated an HRCT of the chest. Pulmonary function studies in an accredited laboratory.

Table 7: Summary of theClinical Radiologic and Treatment Outcome of the IIP'S

Feature	IPF/UIP	NSIP	DIP/RBILD	COP/BOOP	AIP
Clinical Presentation					
Age (mean)	64	37-49	42	56	50
Duration of symptoms	1-3 years	8 months	2 wk-6 months	1-6 months	1-4 weeks
Mechanical Ventilation	Rare	Rare	Rare	Rare	Yes
HRCT					
Main findings	Irregular lines honeycomb lung	Ground glass attenuation	Ground glass attenuation, irregular lines	Consolidation	Consolidation
Distribution	Middle and lower lung zones	Diffuse or patchy	Middle and lower lung zones. Subpleural in 60%	Peribronchial or subpleural on 60%	Middle and lower lung zones; dependent lung regions
Clinical out come	20-50% 5 yr survival	90% 5 yr survival	90-100% 5 yr survival	90% 5 yr survival	10-50% recovery
Response to steroids	Poor	Good	Good (need to stop smoking)	Excellent	Poor

There are several caveats that I would like to leave with you:

1. These pneumonia are constantly evolving; keep an open mind.
2. To borrow the words of a famous LA attorney at a trial most of us would rather forget, "If the glove does not fit you must acquit" If a patient does not have a typical response to standard therapy go back to the drawing board and reexamine your initial diagnosis
3. All that crackles is not CHF! This is probably the most common misdiagnosis for these patients in the face of progressive dyspnea. Patients will be treated for CHF even in the face of a normal echo and normal BNP when they should probably be referred to a pulmonologist.
4. All lower lobe infiltrates are NOT double pneumonia. I am not sure what that is, but again if the clinical picture does not fit you must acquit.

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