Interstitial Lung Disease of Unknown Etiology*

Margaret Turner-Warwick, D.M., Ph.D.

There are a large number of interstitial diseases of unknown etiology, including common ones, such as sarcoidosis, and ones of great rarity, such as lymhangiolo-endotheliomatosis, idiopathic pulmonary hemosiderosis, and cryptogenic organizing pneumonia (ie, bronchiolitis obliterans and organizing pneumonia). This presentation will focus on cryptogenic fibrosing alveolitis (CFA).

The characteristic features of CFA are well known, and there is remarkable agreement throughout the world on these. The most common age at presentation is 50 to 60 years; occasionally, however, cases with identical clinical and histologic features occur in infants a few months old, and in other patients symptoms develop for the first time after the age of 80 years. Most large series indicate that the sexes are affected equally, with perhaps a slight male predominance. A most characteristic physical sign is the frequency of finger clubbing, present in about 60% of cases. This may sometimes precede the chest symptoms by several years. Now that we have the capability of early diagnosis with lung permeability measurements and computed tomographic (CT) scans, there is an interesting opportunity to reevaluate patients with unexplained finger clubbing.

Examination of the chest characteristically reveals fine "Velcro" crackles over the lower zones. The physiologic abnormality characteristically involves a restrictive defect unless there is associated airflow obstruction or destructive emphysema. When the latter occurs, the lung volumes are preserved, but the transfer factor is extremely low due to the compounding effect of destruction of the pulmonary capillaries, in part due to emphysema and in part due to the interstitial inflammatory disease. The severity of apparent fibrosis on the plain chest radiograph often seems to be trivial compared with the severity of breathlessness in these cases. The explanation for this is evident on fine-cut CT scans, which reveal the extent of emphysema, which may be much more profound than the posteroanterior chest radiograph.

The histology of CFA shows an inflammatory infiltrate of plasma cells and lymphocytes in the interstitium with a variable accumulation of macrophages in the air spaces. Neutrophils and eosinophils, although occasionally seen, are uncommon. Light microscopic appearances are in striking contrast to the percentage of inflammatory cells observed on bronchoalveolar lavage (BAL), where neutrophils and eosinophils predominate. The explanation for this discordance is not completely understood, but there is some evidence that the granulocyte population in a BAL specimen may be derived from the airways. Their importance in the pathogenesis of the interstitial inflammation therefore has to be reconsidered.

Response to treatment will be covered by others in this symposium, but, at best, some 20% of patients respond objectively to high-dose corticosteroids, and a further 20% respond to cyclophosphamide. Some patients will respond to cyclophosphamide, having failed to respond to corticosteroids. Both drugs are therefore worth trying. There is considerable evidence that delays in starting treatment are associated with a less favorable response. Therefore, treatment should be started as early as possible, even when the patient has few symptoms, and the lung function is little disturbed.

CFA WITH AND WITHOUT COLLAGEN VASCULAR DISEASE

There continues to be considerable controversy as to whether "lone" CFA and CFA associated with collagen vascular disease (especially rheumatoid arthritis, systemic sclerosis, and systemic lupus erythematosus) have a similar pathogenesis, natural history, and responsiveness to treatment. A recent detailed comparative histologic study of CFA comparing lone CFA with systemic sclerosis showed that the frequency of each inflammatory, vascular, and fibrotic component was identical. Using fine CT scans, it has been possible to study very early pulmonary systemic sclerosis by screening all patients with skin manifestations. Early cases can be identified before there are pulmonary symptoms, signs, or physiologic abnormalities. The history shows

*From the Cardiothoracic Institute, Brompton Hospital, London, England.
not only an inflammatory infiltrate but considerable interstitial fibrosis occurring pari passu. Thus, while the extent of disease is very slight, the fibrotic response is already well developed. However, in these biopsy specimens there was no evidence of a "growing edge" of inflammation separating areas of well-established inflammation and fibrosis from normal lung. A substantial inflammatory stage preceding the fibrosis is not always seen in a clinical context, which means that our theories on pathogenesis must be reconsidered. Further, the objective of treatment may need to be redefined. If disease of very slight extent can be identified and treated to prevent extension at an early stage, this may be more important than measuring actual improvement.

**NEW CHALLENGES**

A characteristic crescent of abnormality affecting the periphery of the lung over the lower zones posteriorly has been demonstrated with CT scanning. Serial studies show that as disease progresses, the crescent extends anteriorly and centripetally toward the hilum. Honeycombing develops within the affected areas and in later cases much larger air spaces are seen within the abnormal lung—an appearance not seen at all on conventional chest radiographs and one that is quite distinct from associated emphysema in the upper lobe. These observations must be accounted for in new explanations of pathogenesis.

Technetium-99m diethylene triamine pentaacetic acid studies to measure lung permeability have shown that lung leakiness is increased in CFA. This is found even in early cases and often improves in line with physiologic improvement. The vascular component of CFA is a neglected area of study. It may be very important in the development of CFA. The well-known special association with finger clubbing and the gross proliferation of fine systemic vessels in the diseased parts of the lung endorse the importance of a fundamental restudy of angiogenesis and endothelial abnormalities in CFA. With the new techniques now available, this should be an exciting area to study and could give a fundamentally new insight into pathogenesis, as well as raising the possibility of new modalities of treatment.

---

**The Treatment of Idiopathic Pulmonary Fibrosis**

*Richard H. Winterbauer, M.D., F.C.C.P.*

Prior to initiating treatment, the clinician must have reasonable assurance of the diagnosis of idiopathic pulmonary fibrosis (IPF). Hidden in this aphorism are the seeds of controversy, for it allows room for a clinical diagnosis of IPF.

Open lung biopsy has been correctly touted as the only diagnostic procedure capable of absolute certification of IPF. Yet absolute diagnostic accuracy established by thoracotomy in all patients, many of whom are elderly or severely incapacitated by their respiratory disease, represents too great a risk for the benefit obtained.

Although age at onset, duration of disease prior to diagnosis, and rate of progression after diagnosis are variable among patients with IPF, a subset of IPF patients is easily recognized clinically. Patients over 65 years of age, with a disease duration of more than 2 years, a pattern of slow progression without fever, diffuse reticulonodular infiltrates, and no extrathoracic symptoms typically have IPF. The age criterion eliminates most persons with sarcoidosis, and the duration of disease, slow progression, and absence of fever usually serve to eliminate bronchiolitis obliterans organizing pneumonia, neoplasm, and infection.

All patients should be evaluated for collagen vascular disease, pneumoconiosis, and drug-induced disease through history, physical examination, and serologic tests. Also, all patients should undergo fiberoptic bronchoscopy, which will with reasonable certainty allow recognition or exclusion of granulomatous disease, neoplasm, infection, and the specific entities histiocytosis X and pulmonary alveolar proteinosis.

The presence of fibrosis in a transbronchial biopsy specimen has no diagnostic positive predictive value. Patchy fibrosis can be demonstrated in a transbronchial biopsy specimen in numerous interstitial lung syndromes. The biopsy is helpful in establishing the diagnosis only through exclusion of the entities mentioned. The patient meeting these criteria may safely receive a clinical diagnosis of IPF.

The next important clinical parameter to establish is disease progression. A fibrotic reaction related to some past injury but without evidence of progression will be present in 15% to 20% of patients with IPF. It is quite important to recognize this group because treatment for them is ineffective and unnecessary. Progressive disease can be demonstrated by worsening dyspnea, advancing roentgenographic changes, or deterioration in pulmonary function test results. Insidiously progressive disease is sometimes difficult to recognize. Chest x-ray films obtained at 1-year intervals can be a deceptive basis of comparison. Films obtained 1 year apart may show little or no change, but comparison of films obtained 2 or more years apart will depict progressive disease. Also, older patients may deny progressive dyspnea but instead reduce their exercise pattern and attribute this to a normal aging process. The criteria for a significant change in pulmonary function are a 10% reduction in vital capacity, an increase in the P(A-a)O₂ at rest of 5 mm Hg while breathing room air, and a 20% reduction in the single-breath carbon monoxide diffusing capacity (Dco).

The response to treatment of IPF is inconsistent. Many patients do not have a beneficial response to the therapies listed below, and their disease relentlessly progresses. However, some patients have symptomatic, roentgenographic, and physiologic improvement, which translates to a substantial improvement in survival. There are few clues to recognize the subset of patients who will respond well to therapy for IPF. Generally, patients with disease of less than 1 year's duration; bronchoalveolar lavage fluid showing greater than 5% lymphocytes, less than 10% neutrophils, and less than 5% eosinophils; and an open biopsy specimen demonstrating more inflammation with less fibrosis have the greatest potential for improvement with therapy. However, none of these criteria so accurately predicts outcome that it allows exclusion of a patient population from treatment.