Fibrosing alveolitis

PETER THOMAS,* MB, MRCP(UK), FRCP[C]

Fibrosing alveolitis is a disease of unknown cause mainly involving the gas-exchanging portions of the lungs. It may occur in isolation and be called cryptogenic or idiopathic, in which case the clinical manifestations are mainly respiratory, or it may be associated with other disorders, such as rheumatoid arthritis. The histopathologic abnormalities of the pulmonary tissue are identical in either instance. Other names used for the disease have included usual interstitial pneumonia, desquamative interstitial pneumonia and the Hamman-Rich syndrome; these terms may describe different stages of the same pathologic process. Many authors in North America and those in the United Kingdom favour the term fibrosing alveolitis when describing chronic interstitial pneumonias. There may be accompanying nonspecific immunologic abnormalities, which may denote that fibrosing alveolitis is part of the wide spectrum of diseases known as connective tissue disorders. Recently immune complexes have been found in the lung parenchyma; they probably result in the granulocyte destruction and reticuloendothelial proliferation seen in the acute phase of the disease.

There are no specific diagnostic tests for the disease apart from lung biopsy, which can be performed at the time of thoracotomy or transbronchially, with the use of a flexible fibreoptic bronchoscope. Lavaged cells from the alveoli have also been obtained via the bronchoscope; in persons with fibrosing alveolitis a high proportion of these cells are neutrophils, and after corticosteroid treatment the proportion decreases. The progress of the disease can be followed by examination of these washings as well as by lung scanning with gallium-67 citrate. Newer methods of treatment using combinations of corticosteroids and immunosuppressant drugs are being evaluated and are initially proving to be successful.

L'alvéole fibreuse est une maladie d'histoire inconnue intéressant les parties du poumon où se font les échanges gazeux. Elle peut être isolée et considérée comme idiopathique lorsque les manifestations cliniques sont surtout respiratoires, ou associée à d'autres troubles, comme l'arthrite rhumatoïde. Les anomalies histopathologiques du tissu pulmonaire sont les mêmes pour les deux variétés. On a aussi désigné cette maladie sous le nom de pneumonie interstitielle, pneumonie interstitielle exfoliative et syndrome d'Hamman-Rich; il se peut que ces noms désignent les stades différents d'un même processus. Plusieurs auteurs nord-américains, de même que du Royaume-Uni, préfèrent "alvéole fibreuse" pour représenter les pneumonies interstitielles chroniques. Des anomalies immunologiques non spécifiques peuvent s'ajouter, ce qui peut démontrer l'appartenance de l'alvéole fibreuse à la grande famille des maladies du collagène. Tout dernièrement on a découvert des immunocomplexes dans le parenchyme pulmonaire; il est probable qu'on leur doive la destruction des granulocytes et la prolifération reticuloendothéliale qu'on observe au cours de la phase aiguë de la maladie. La biopsie pulmonaire mise à part, il n'existe pas d'épreuve diagnostic. On peut procéder à la biopsie au cours d'une thoracotomie ou par voie transbronchique à l'aide d'un bronchoscope flexible à fibres optiques. Au moyen de ce dernier on a aussi récolté, provenant des alvéoles, des cellules de lavage. Une forte proportion de ces cellules sont des neutrophiles, et cette proportion baisse à la suite d'un traitement aux corticostéroïdes. On peut donc se rendre compte de l'évolution de la maladie en examinant ces cellules de lavage, et également par la scintigraphie pulmonaire avec l'aide du citrate de gallium-67. Des traitements encore plus récents, où immunosuppresseurs et corticostéroïdes sont employés de pair, sont actuellement évalués; les premiers résultats sont prometteurs.

The term diffuse fibrosing alveolitis was suggested by Scadding1 in 1964 for a disease characterized by an inflammatory process in the lung beyond the terminal bronchiole, having as its essential features cellular thickening of the alveolar walls with a tendency to fibrosis, and the presence of alveolar mononuclear cells within alveolar spaces. In 1965 Liebow, Steer and Billingsley4 described 18 patients with a more benign diffuse pulmonary disease, and the term desquamative interstitial pneumonia was born. Scadding and Hinson5 considered this condition to be one end of the spectrum of fibrosing alveolitis. Since that time Liebow and colleagues have coined the terms usual interstitial pneumonia, lymphoid interstitial pneumonia, giant cell interstitial pneumonia and a variant of usual interstitial pneumonia with bronchiolitis obliterans. These conditions have been reviewed by Liebow and Carrington.6

Adding to the confusion of nomenclature is the Hamman-Rich syndrome, which, according to its first description, in 1935,6 has the characteristic features of thickened alveolar walls, little or no alveolar cellular infiltrate and an acute fulminating course. As described, this condition

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CMA JOURNAL/NOVEMBER 18, 1978/VOL. 119 1211

REVIEWS

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Adding to the confusion of nomenclature is the Hamman-Rich syndrome, which, according to its first description, in 1935,6 has the characteristic features of thickened alveolar walls, little or no alveolar cellular infiltrate and an acute fulminating course. As described, this condition
was almost certainly acute fibrosing alveolitis or acute usual interstitial pneumonia.

Do all these terms describe the same pathologic process, or do they represent totally different diseases? A collaborative British and American study is under way to try to resolve this question.4

In this review I have used the terms suggested by Scadding and Hinson5 — namely mural diffuse fibrosing alveolitis when mainly the walls of the alveoli are affected, and desquamative diffuse fibrosing alveolitis when mainly the alveolar spaces are affected. The word interstitial may be incorrect because, as Heard6 pointed out, usually both interstitial and intra-alveolar sites are involved in conditions labelled as only interstitial. The term desquamative may also be incorrect to describe the conditions with mainly intra-alveolar involvement, since the cells in the intra-alveolar spaces are mainly macrophages and not desquamated type II pneumocytes, as was originally thought.5,6 The terms fibrosing alveolitis mainly in the cellular phase and fibrosing alveolitis mainly in the fibrotic phase may be more relevant and correct. However, there is some benefit in dividing fibrosing alveolitis into mural and desquamative types when the clinical response to corticosteroid therapy is noted.5,9

Turner-Warwick8 has subdivided widespread pulmonary fibrosis into four broad groups according to pathogenesis: (a) granulomas; (b) conditions with alveolar exudates; (c) lesions caused by inorganic dusts; and (d) conditions of unknown cause such as fibrosing alveolitis. It may not be possible, however, to determine what caused the disease if the pulmonary process has progressed to "end-stage lung."11 — that is, if a biopsy specimen of the lung parenchyma reveals only nonspecific fibrosis.

Clinical features

The average age at the onset of symptoms of fibrosing alveolitis is 49 years,11 although the disease can present at any age. The interval from the onset of symptoms to the time of diagnosis averages 2.9 years.7 The disease is probably equally frequent in the two sexes, although some authors have indicated a preponderance in one sex or the other.11,12 If another connective tissue disease is present there is a female preponderance.7,13 Since most reports have come from Britain and North America most patients described have been white.13 Dyspnea with effort is almost always the presenting feature, and cough, which is characteristically nonproductive, is commonly associated.7,12 Vague constitutional findings including influenza-like symptoms, fatigue, weight loss and arthralgias may also be present. Fine end-inspiratory rales or, less often, coarse rales may be heard by auscultation of the chest.7,12 Finger clubbing occurs in 70% to 90% of patients.5,11-14 However, it is not usually associated with hypertrophic osteoarthropathy, in contrast to the clubbing found in persons with malignant disease.7 Right ventricular failure may be the terminal event, but 80% of patients die of respiratory failure, often following an infection.7,12-13 About a third of patients relate the beginning of their disease to a viral syndrome accompanied by chest symptoms.12

There are reported familial clusterings of the disease, which may indicate that some people have an inordinate predisposition to the disease.7,12

Roentgenographic appearance

Early in the course of fibrosing alveolitis the chest roentgenogram may be normal. Later, a diffuse micronodular or nodular pattern may be seen at both lung bases. streaky or reticular shadows can be associated. Still later, translucencies 2 to 5 mm in diameter may be seen; "honeycombing", as this finding has been called, is not specific for fibrosing alveolitis.12 As end-stage lung is approached there may be elevation of the hemidiaphragms, unfolding of the aorta, kinking of the trachea and signs of heart failure.11,12 Examples of typical roentgenograms are shown in Figs. 1 and 2.

Results of laboratory investigations

Pulmonary function tests

The number of ventilated alveoli, as well as their distensibility, is reduced in fibrosing alveolitis; Gibson and Pride18 found the former to be more important. Lung volumes, including forced vital capacity and total lung capacity, are correspondingly diminished, particularly in mural fibrosing alveolitis because of the greater degree of pulmonary fibrosis.9 Since the forced vital capacity is reduced, the forced expiratory volume in 1 second is also reduced, but the ratio of the latter to the former is preserved, at more than 70%. Any obstruction to airflow that reduces the percentage to less than 70 is probably related to coexisting cigarette smoking in most patients.9 Hypoxemia is found in most patients; Wagner and coworkers15 have determined that this is mainly due to ventilation-perfusion mismatching and is not a simple diffusion abnormality. Hypoxemia is thought to occur in all patients after exercise, even if it is not present at rest.11,12 Carrington and associates8 found that after exercise there was a significant increase in the alveolar-arterial difference in oxygen pressure in some patients with usual interstitial pneumonia (which probably corresponded to mural fibrosing alveolitis) but not in those with desquamative interstitial pneumonia (which probably corresponded to desquamative fibrosing alveolitis).

Seroimmunologic studies

These investigations, although non-specific, are very helpful in differentiating fibrosing alveolitis from conditions with similar features. Antinuclear antibodies have been found in 7% of an American group of patients with fibrosing alveolitis,18 but in 31% of a British group.19 Rheumatoid factor was present in 14% of the former and 30% of the latter. In the British series rheumatoid arthritis, as defined by the American Rheumatism Association's criteria, developed in 14% of the patients with fibrosing alveolitis; a further 10% had transient polyarthralgia. Lupus erythematosus cells were found in 3% of the American patients with fibrosing alveolitis of unknown cause, and cryoglobulins were found in 41%, an elevated IgA, IgG or IgM concentration in 52% and decreased complement activity in 6%.

Turner-Warwick8 found non-organ-specific complement-fixing antibodies in 19% of patients with fibrosing alveolitis and 2% of matched
controls; in 9% the antibodies were antimitochondrial. Turner-Warwick and other workers have also demonstrated deposits of IgM and rheumatoid factor in the alveolar walls of patients with fibrosing alveolitis.

Circulating immune complexes have been found in a large proportion of patients with the cellular phase of the disease but not the fibrotic phase,15 and this strongly correlated with the intrapulmonary deposition of the complexes. When circulating immune complexes were detected the disease responded better to corticosteroid therapy than when they were not detected.

The HLA histocompatibility antigens A29 and B12 are more frequent in patients with this condition than in the general population.7

**Analysis of bronchoalveolar washings**

Fibreoptic bronchoscopy has recently been used to obtain washings of bronchoalveolar cells.7,9-13 The proportion of neutrophils in the washings averages 33% in patients with fibrosing alveolitis as compared with 3% in controls. Following corticosteroid therapy the proportion falls to 14%. Eosinophils are also invariably found in the washings from patients with fibrosing alveolitis, but their proportion does not decrease after corticosteroid therapy. In contrast to the finding in extrinsic allergic alveolitis, the proportion of lymphocytes in the washings of patients with fibrosing alveolitis is not greatly increased.

There is an increased concentration of IgG in the washings of patients with fibrosing alveolitis, but a decreased concentration of IgE. IgM is not found in the washings of these patients, whereas it is found in the washings of patients with extrinsic allergic alveolitis. Concentrations of the C4 and C6 components of complement are decreased in the washings of patients with fibrosing alveolitis.

**Histologic examination**

There is no histopathologic difference in the lung tissue between fibrosing alveolitis of unknown cause and that associated with other diseases such as rheumatoid arthritis.7

The disease is commonly widespread throughout the lungs, but may initially be basal and bilateral. Two general groups of histologic detail may be noted10 — a mural type and a so-called desquamative type. In the former there is interstitial infiltration of inflammatory cells, mainly lymphocytes, macrophages and plasma cells. A feature that is not so well recognized is the presence of eosinophils and neutrophils. There is always associated fibrosis of alveolar septa, which may be focal, generalized, multifocal or widespread, with associated loss of normal pulmonary architecture.

With the light microscope one sees an apparent increase in the content of collagen (fibrosis). However, studies of specimens from open lung biopsies show that the amount of collagen per unit of dry weight is normal. There are several postulated reasons for this apparent discrepancy. First, the light microscope detects only fibrillar (type I) collagen; if there is a decrease in the amount of reticulin (type III collagen) the amount of fibrillar collagen will be

*FIG. 1—Fibrosing alveolitis: diffuse reticulonodular infiltrate throughout both lungs, more marked in the left lower lobes.*

*FIG. 2—Enlargement of portion of Fig. 1: diffuse pulmonary infiltrate in left lung and honeycombing in left lower lobe.*
relatively increased although the lung weight will be the same. Second, the amount of collagen may be increased together with the amount of other lung components; therefore the amount of collagen per unit weight will be constant. Third, there may be a rearrangement of collagen rather than an overall increase in amount. One or other of these interpretations may be important in fibrosing alveolitis.7,8

In fibrosing alveolitis there is a nonspecific increase in the number of type II pneumonocytes (surfactant-producing cells). Only occasionally are monocytes found in the alveolar spaces. Proteinaceous alveolar exudates are sometimes seen in early lesions.

In the desquamative type of fibrosing alveolitis there is a predominance of mononuclear cells in the intra-alveolar spaces.5 These cells were thought to be type II pneumonocytes, but they are probably mainly macrophages.5 There is minimal interstitial cellular infiltrate and no proteinaceous exudate in the alveoli.5 Type II pneumonocytes are also increased in number, as in the mural variety of the disease. Since similar cells are found in the interstitium and alveolar spaces of both the mural and desquamative varieties, it is possible that these types represent different stages of the same disease. In both types there is peribronchial thickening and narrowing of the airways. Cholesterol ester clefts in air spaces are common and may indicate pulmonary hypertension since medial hypertrophy and fibrous intimal proliferation of pulmonary arteries are usually associated.8 Vascular studies have shown a marked increase in the number of bronchial arteries and many bronchopulmonary anastomoses.8 Patients with fibrosing alveolitis do not have arteritis or granuloma formation in their lungs.7

With histologic examination it can be difficult to differentiate the early lesions of fibrosing alveolitis from those of such diseases as viral pneumonia or allergic hypersensitivity, and it can be difficult to differentiate the older lesions of fibrosing alveolitis from those of other conditions producing widespread fibrosis.8,9

Typical examples of the histologic detail of the two main varieties of fibrosing alveolitis are shown in Figs. 3 and 4.

**Nuclear scanning**

The most useful of the scanning methods employs gallium-67 citrate.6,7 This procedure is being used to monitor the disease's progress by indicating lung inflammation — the alveolitis of the disease. Perfusion lung scans, in which macroaggregated albumin labelled with technetium-99m is used, show that there are underperfused areas, especially at the bases. This is probably due to localized loss of the capillary bed.7 Inhaled xenon-133 or xenon-127 is used to assess ventilation abnormalities.7,28 There may be a patchy decrease in ventilation corresponding to areas of fibrosis and the abnormal areas of the 99mTc-microaggregated albumin scan.

**Diagnosis**

The history of dry cough and dyspnea, and the findings of fine end-inspiratory rales at the lung bases and finger clubbing should lead one to suspect fibrosing alveolitis. There may be associated diseases such as rheumatoid arthritis,29-30 systemic lupus erythematosus,31-33 systemic sclerosis,34-37 myositis,37,38 celiac disease,39 renal tubular acidosis,40 chronic active hepatitis,41 thyroiditis,41 Sjögren's disease,41-42 myelosclerosis,43 purpura,44 Raynaud's phenomenon,45 pernicious anemia46 or ulcerative colitis.47 The numbers of cases described for many of these combinations are small, and therefore no definite association can be formulated. Of interest is the association of salicylazosulfapyridine (used to treat ulcerative colitis) with pulmonary disease presenting in a fashion similar to that of fibrosing alveolitis.48 Gold, used to treat rheumatoid arthritis, may also give rise to pulmonary fibrosis, but the histologic features differ from those of fibrosing alveolitis.49 It may be that other drugs are responsible for some of the pulmonary manifestations ascribed to fibrosing alveolitis, but not proven by biopsy.

If none of the associated diseases are present and the diagnosis is still in doubt, fibrosing alveolitis of un-

![FIG. 3—Desquamative fibrosing alveolitis or desquamative interstitial pneumonia: moderate increase in amount of interstitial fibrous tissue, collections of macrophages in several air spaces, and scattered monocytes in interstitial fibrous tissue (hematoxylin–phloxine–saffron [HPS]; X 40).](image)
known cause can be diagnosed by obtaining a specimen of pulmonary parenchyma. It is especially important to rule out other diseases if treatment with corticosteroids is to be instituted. Many conditions can give rise to dyspnea with bilateral diffuse infiltrates seen on the chest roentgenogram. The most common of these are extrinsic allergic alveolitis such as farmer's lung, sarcoidosis, pneumoconiosis due to inorganic dusts, drug-induced lung disease, lymphatic carcinomatosis, eosinophilic pneumonia, tuberculosis and postirradiation fibrosis.

Lung tissue may be obtained by open lung biopsy through a thoracotomy, by needle aspiration biopsy, by trephine lung biopsy or by transbronchial biopsy through a flexible fibreoptic bronchoscope. Each method has its advocates. Needle biopsy yields a limited number of cells for diagnosis and a thoracotomy carries all the risks of a formal operation, whereas the bronchoscopic method yields a number of specimens from different sites and has proven effective and safe. The bronchoscope can also be used to retrieve lavaged bronchoalveolar cells for analysis.

**Treatment and prognosis**

To be effective, treatment must be started before pulmonary fibrosis has developed. This leads to the problem of treatment of relatively asymptomatic patients with potentially dangerous drugs. However, early response to treatment indicates a better prognosis, and it may thus be advisable to assess the stage of the disease by biopsy as early as possible and then start giving the patient medication. Corticosteroids have been the mainstay of treatment, other immunosuppressive agents being used in the patients whose disease does not respond to corticosteroids or who cannot tolerate these drugs. Clinical trials are progressing to evaluate the usefulness of prednisone and azathioprine in combination, compared with prednisone alone. Azathioprine or cyclophosphamide has been found useful in some cases in which fibrosing alveolitis does not respond to corticosteroid therapy.

Scadding and Hinson treated their patients with 20 mg of prednisone daily, increasing the dose if there was no response. They found, however, that if a response was going to occur, it would do so with 30 mg daily. Crystal and colleagues treated their patients with larger doses, 1 mg/kg, for the first 6 weeks, then decreased the dose by 0.05 mg/kg per week to 0.25 mg/kg. At 3-month intervals the patients underwent routine studies as well as Ga scanning and bronchoalveolar lavage.

In Scadding and Hinson's series the mural variety of fibrosing alveolitis showed little response to corticosteroid therapy, whereas the desquamative type fared better. This is not surprising since the mural type probably represents a later stage of the disease, with more fibrosis and thickening of alveolar walls.

Carrington and colleagues studied 40 patients with desquamative interstitial pneumonia and 53 with usual interstitial pneumonia for 1 to 22 years. The mortality in the two groups was 27.5% and 66.0% respectively, and the mean survival was 12.2 and 5.6 years respectively. With corticosteroid therapy 61.5% and 11.5% respectively improved. Scadding and Hinson's results comparing mural and desquamative fibrosing alveolitis were similar, which may indicate that desquamative and usual interstitial pneumonia and fibrosing alveolitis are the same disease at different stages of evolution.

In the most extensive prognostic study done, Stack, Choo-Kang and Heard found the mean survival to be 4 years and the range to be 0.4 to 20 years. Superadded pulmonary infection is common and may lead to respiratory failure and death. The degree of hypoxia rather than its duration seems to be the important preterminal event.

There have been several reports of bronchogenic carcinoma in patients with fibrosing alveolitis, but it is not clear whether the frequency is increased over that found in the general population.

I thank Dr. R.C. Ross for his expert advice on the histologic sections, Drs. A. Leznoff and I. Broder for their constructive criticism, and Mrs. L.A. Signorello for typing the manuscript.

**References**


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**FIG. 4**—Late stage of fibrosing alveolitis: dense fibrous tissue in interstitial spaces and few mononuclear cells (HPS; X40).


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