UNION CARBIDE CORPORATION OLD RIDGEBURY ROAD, DANBURY, CT 06817
Corporate Health, Safety and Environmental Affairs Department

February 20, 1985

Dr. R.B.K. Tucker
18, Rockridge Road,
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Re: Agenda Item 6.1 - 12th Meeting of AIA/MAP:
AIA/20/1/2/HAS Asbestos and Simulative Diseases

Dear Ron,

I have struggled with this item and have produced the attached draft for your consideration. I must confess that I have largely plaguerized the referenced articles (copies of references 1, 2 and 4 are attached hereto) and suppose that, if we decide to publish this, permission would have to be obtained to reproduce the tables and we should indicate our obligation to the referenced authors.

I have not sent copies of this draft to anyone else. When you have reviewed the draft, please make any additions, deletions, comments, etc. and forward to AIA for action if you think it would be appropriate. Please let me know what you decide to do.

I am not certain about my future as a member of the MAP at the present time and will not know until mid-March whether I will continue to represent the Asbestos Information Association of North America or not.

Kind regards to your wife,

Sincerely,

Hilton

Hilton C. Lewinsohn, MB.BCh., FCCP, MFOM, DIH.
Assistant Corporate Medical Director

HCL:jsh

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THE DIFFERENTIAL DIAGNOSIS OF ASBESTOSIS FROM OTHER FORMS OF INTERSTITIAL LUNG DISEASE

Introduction

The diagnosis of asbestosis can only be made with certainty in the presence of an exposure history. The symptoms of asbestosis are similar to those of other forms of interstitial lung disease and may not be helpful in distinguishing between them. The object of this paper is to focus on the importance of making a distinction between asbestosis in particular and pulmonary fibrosis (interstitial lung disease) in general, since this will affect therapy, medical management, workers compensation and other issues.

Definition

The term interstitial lung disease is applied to "a heterogeneous group of diseases grouped together because of common clinical, roentgenographic, physiologic and pathologic features."[1] According to Fulmer[1] the most prevalent interstitial diseases are those caused by occupational and environmental inhalants, predominantly due to inorganic dusts.

Clinical Features

Irrespective of the etiology of the interstitial lung disease, the clinical presentation is virtually the same in all cases. Breathlessness,

usually first noted on exertion, is the first recognizable symptom in the majority of cases and is invariably present once the disease process has become fairly extensive. The chest x-ray pattern at this stage will be that of a diffuse infiltrative lesion. The pulmonary fibrosis which develops affects the gas exchanging areas of the lung and in some cases a reduction in the carbon monoxide diffusing capacity may be the earliest indication of the disease process. The interstitial lung diseases are characterized by impairment of gas transfer and a restrictive ventilatory defect. The histological appearances in the final stages of the interstitial lung diseases are non-specific and are those of a progressive diffuse chronic pulmonary fibrosis with few, if any, distinguishing diagnostic features. The disease process involves the alveoli and associated connective tissues.

VanOrdstrand[2] points out "that there is no occupation in which the worker is immune to nonoccupational diseases". He believes that in some cases the usual routine diagnostic procedures such as work history, chest x-rays and other tests, are not adequate to differentiate occupational from nonoccupational diffuse lung disease. VanOrdstrand feels that there is a place for the use of lung biopsy in such cases.

Table I is based on information extracted from Fulmer's[1] classification of the Interstitial Lung Diseases combined with information extracted from a similar classification found in Chapter 18 (Interstitial lung disease) in "Color Atlas of Respiratory Diseases" (Edited by D. Geraint James and Peter R. Studdy).[3] The interstitial lung diseases are grouped

according to whether the etiology is known or unknown. According to Fulmer[1] one third have a known etiology. Tables 2-6 complement Table I as indicated and are reproduced from James and Studdy's "Color Atlas".

VanOrdstrand's approach[2] is to group the radiologic masqueraders of various pneumoconioses in tabular form and Table 7 is in fact his Table 3.

Differential Diagnosis

Murphy et al.[4] point out that minimal interstitial pulmonary fibrosis caused by the inhalation of asbestos can be difficult to detect. They state that symptomatology is subjective and pulmonary function studies are often nonspecific. X-rays are not able to indicate the etiological factors responsible in the production of diffuse pulmonary fibrotic lesions. Thus, symptoms and signs per se, do not enable asbestosis to be differentiated from other fibrotic lung diseases and it is necessary in each and every case to obtain a detailed medical history and occupational history.

There are some features of asbestosis and some details in the medical history which may assist in the differential diagnosis. Fulmer[1] discusses the diagnostic approach to patients with interstitial lung disease and emphasizes the need for a systematic approach stating that "A detailed occupational history is mandatory in diagnosing the inorganic dust diseases." Some of the issues which should be covered when taking the medical history include the following few examples:

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1. Detailed occupational history - the long latent interval between first exposure to asbestos and development of disease must be recognized and taken into account

- contact with household members exposed to asbestos may result in exposure not recognized by the patient

- casual workplace exposure may be responsible for the lesions and in some cases living in the neighborhood of a plant may raise suspicions of cause and effect.

- farmers' lung and psittacosis may be suggested by a history of exposure to moldy hay or bird droppings respectively

- other organic dust exposure possibilities such as use of home humidifiers, vaporizers, saunas

- exposure to organic chemicals

2. Detailed drug use history. - Three major groups of drugs are responsible for most drug-induced interstitial diseases. They are listed by Fulmer as the cytotoxic and immunosuppressive agents (bleomycin, nitrosoureas, methotrexate, etc.); the neuroactive and

vasoactive agents (methysergide, Phenytoxin, etc.) and antimicrobial agents (Nitrofurantoin, sulfonamides, etc.).

3. Family history - sarcoidosis
   - collagen vascular disorders
     - mixed connective tissue disease
     - rheumatoid lung

(Skin and eye manifestations of sarcoidosis, collagen-vascular disorders, neurofibromatosis and Wegener's granulomatosis may help in the differential diagnosis).

Investigating the patient with an interstitial lung disease may include, in addition to the medical history, interpretation of chest radiographs, and pulmonary function evaluation, special investigations such as serological studies, bronchoalveolar lavage, conjunctival, skin and lymph node biopsy, fiberoptic bronchoscopy and transbronchial biopsy and finally, open lung biopsy may be indicated. In the case of a suspected occupational lung disease, where the diagnosis will determine eligibility for compensation, and where death benefits may be payable to defendants, the opportunity to confirm the clinical diagnosis at autopsy should be vigorously pursued.

The chest x-ray is of diagnostic value in only a few types of diffuse interstitial pulmonary fibrosis. Radiographic appearances can be correlated with laboratory data in many instances to yield diagnostic information. According to Fulmer, diffuse interstitial infiltrates with sparing of the

costophrenic angles in a young male is suggestive of histiocytosis-X. In a young black patient in the USA hilar adenopathy with uveitis and skin lesions is thought to be diagnostic of sarcoidosis.

Pulmonary function studies are generally not helpful in the differential diagnosis of interstitial disease, including occupational lung diseases.

Serological studies are of value in the diagnosis of collagen-vascular disorder and sarcoidosis. Circulating immune complexes or antibasement membrane antibody can also be of use if studied in conjunction with lung tissue or lavage cellular analysis. Interest in the latter procedure has grown recently with regard to the diagnosis of intestitial diseases. Thus far it has proved to be of value only in alveolar proteinosis and the pulmonary hemorrhage syndromes. Hemosiderin-laden macrophages (indicative of pulmonary hemorrhage) and the presence of circulating antibasement membrane antibodies are necessary to diagnose Goodpasture's syndrome.

Brocho-alveolar lavage promises to develop into a useful diagnostic procedure. Two distinct cellular patterns have been described. Predominant lymphocytosis is suggestive of sarcoidosis, organic dust disease, acute idiopathic pulmonary fibrosis, certain collagen-vascular disorders, and acute histiocytosis-X. A predominant finding of polymorphonuclear leukocytosis may be seen in inorganic dust diseases, idiopathic pulmonary fibrosis, collagen-vascular disorders and advanced sarcoidosis. Further studies are

required before this procedure becomes useful in the differential diagnosis of interstitial lung diseases.

Transbronchial biopsy may be useful in the diagnosis of interstitial lung disease. Some conditions which may be diagnosed by this procedure are listed in Table 8 (Fulmer's Table 4[1]). Open lung biopsy is hardly ever justified unless the possibility exists that the outcome will affect treatment of a potentially curable condition.

The diagnosis of asbestosis is based upon a history of adequate exposure, radiographic evidence consistent with diffuse interstitial pulmonary fibrosis, a restrictive pulmonary function defect and the presence of bilateral basilar crackles in the lungs. Dyspnoea, cough, sputum production and clubbing of the fingers are usually late, non-specific manifestations. The chest radiograph may provide important clues to the asbestos-related etiology of a case of interstitial lung disease. Pleural plaques are fibrotic areas mainly affecting the parietal pleura. They are usually bilateral, smooth or nodular, and discrete. They are most frequently seen on the posterolateral or anterolateral chest walls, run along the rib margins (most commonly the sixth-tenth ribs) and are also found on the domes of the diaphragm. The apices and costo-phrenic angles are usually clear. Calcification may occur as the years go by. They are considered to be a unique radiographic sign presumptive of asbestos etiology.[5]

The small irregular opacities seen on a chest x-ray do not have characteristics which differentiate those seen in cases of asbestosis from those seen in a number of other conditions. Some normal adults will exhibit these radiographic patterns as a part of aging, especially in persons who had repeated pulmonary infections (e.g. bronchitis, pneumonitis). There will be an overlap in the frequency distribution of small opacity profusion in normal and pneumoconiotic individuals at the low levels of profusion.(6) Caution must be exercised by the interpreter of radiographs showing such low levels of profusion and unless the exposure history is clear-cut, a positive diagnosis may not be possible without further observation and investigation. Higher levels of profusion of small irregular opacities may also pose problems of interpretation in the absence of an adequate occupational exposure history. Scleroderma, lipoid pneumonia, desquamative interstitial pneumonitis and sarcodosis may produce basal irregular patterns similar to those seen in asbestosis.(6) The American College of Radiology's Asbestos Working Group's monograph describes many other diagnosis features of value in making a diagnosis of asbestosis and they point out the differences between early and late findings.(5)

Recommendations

1. Obtain a detailed medical history, including a meticulous exposure history.

2. In the absence of exposure, a diagnosis of asbestosis can only be made when other etiological agents or conditions have been eliminated to a reasonable degree of certainty.

3. Radiographs must be of good quality, serial films should be available and interpretation should be by a radiologist expert in the diagnosis of pneumoconiosis in particular and chest disorders in general.

4. Pulmonary function tests should only be used to confirm the presence of a restrictive syndrome once there are no specific physiological differences between the many varieties of interstitial lung disorders.

5. Other diagnostic tests should be considered and used in all doubtful cases to rule out conditions which can masquerade as asbestosis.

References:

1. Fulmer, Jack D., The Interstitial Lung Diseases. Chest 1982; 82:172-178.

2. VanOrdstrand, H.S., Pneumoconioses and Their Masqueraders. J. Occup. Med 1977; 19:747-753.

3. Color Atlas of Respiratory Diseases, Chapter 18, pages 161-182 Edited by D. Geraint James and Peter R. Studdy. Published by Year Book Medical Publishers Inc., Chicago. 1982.

4. Murphy, Raymond L.H. et al., Crackles in the Early Detection of Asbestosis. Am. Rev. Respir Dis. 1984; 129:375-379

5. Asbestos Related Diseases: Clinical, Epidemiologic, Pathologic, and Radiologic Characteristics and Manifestations. Prepared by the Asbestos Working Group (Chairman: Russel H. Morgan). Published by American College of Radiology, 20 North Wacker Drive, Chicago, Illinois 60606 (1982).

6. Morgan, R.H., Donner, M.W., Gayler, B.W., et al.: Decision processes and observer error in the diagnosis of pneumoconiosis by chest roentgenography. Am. J. Roentgenol. 1973; 117:757-764.

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Table 1: Classification of Interstitial Lung Disease*

Known Etiology	Unknown Etiology
Occupational and Environmental	Idiopathic pulmonary fibrosis
Inhalants:	
Inorganic (see Table 2)	Necrotising angiitis (see Table 6)
Organic (see Table 3)	Collagen disorders
Fumes, gases, vapors, aerosols (see Table 4)	- rheumatoid arthritis
	- progressive systemic sclerosis
Drugs (see Table 5)	- Sjogren's syndrome
Poisons	- ankylosing spondylitis
Radiation	Inherited disorders
Infectious agents - schistosoma mansoni	- tuberous sclerosis
	- neurofibromatosis
Pulmonary oedema (cardiac disease)	Miscellaneous
Uremia (metabolic diseases)	- sarcoidosis
	- pulmonary hemorrhagic syndromes
	- eosiophilic granuloma
	- idiopathic hemiosiderosis
	- amylodosis
	- veno-occlusive disease
	- Lymphangioleiomyomatosis

*Data compiled from combination of Fulmer's[1] Table 1 and James and Studdy's Table on page 161 of "Color Atlas of Respiratory Diseases."[3]

TABLE 2.

Causes of occupational interstitial lung disease.

Inorganic dust	Industrial hazard
Aluminium	Grinding
Asbestos	Mining Fireproofing Lagging Dock workers
Beryllium, Cadmium	Alloys Electronics Nuclear workers
Coal, Diatomaceous earth, Graphite, Kaolin, Mica	Mining Processing Polishing
Iron oxide (Siderosis)	Welding
Silica	Mining and manufacturing Drilling, blasting Foundry and glass workers
Talc	Ceramics and cosmetics
Titanium	Paint

TABLE 3

Nature and sources of organic dust antigens in extrinsic allergic alveolitis.
(Probably IgE mediated obstructive airways disease)

Disease	Dust exposure	Nature of antigen to which precipitin shown
Farmers' lung	Mouldy overheated hay	Thermophilic actinomycetes Micropolyspora faeni Thermoactinomyces vulgaris
Fog-fever in cattle	Mouldy hay	Micropolyspora faeni
Bagassosis	Mouldy overheated sugar-cane bagasse	Mouldy bagasse Thermoactinomyces sacharii
Mushroom workers' lung	Mushroom compost dust	Thermophilic actinomycetes (*see* farmers' lung)
Maltworkers' lung	Mouldy barley or malt	Aspergillus fumigatus Aspergillus clavatus
Bird fanciers' lung	Pigeon and budgerigar droppings Wax coating feathers – 'pigeon bloom'	Avian serum protein antigens
Pituitary snufftakers' lung	Powder of porcine and bovine posterior-pituitary extract	Serum protein and pituitary antigens
Wheat weevil disease (Millers' lung)	Infested wheat flour	Sitophilus granarius
Maple strippers' lung	Maple bark	Cryptostroma (Coniosporium) corticale
Sequoiosis	Mouldy redwood sawdust	Aureobasidium (Pullularia) – pullulans – graphium
Suberosis	Oak bark, cork dust	Mouldy oak bark P. frequentans
Woodworkers' lung	Sawdusts of oak, cedar, etc.	Sawdust extracts
Cheese-washers' lung	Moulds on cheese	Penicillium casei
'New Guinea' lung	Mouldy thatch dust	Extracts of thatch
Smallpox-handlers' lung	Smallpox scabs	
Paprika splitters' lung	Mouldy paprika pods	Mucor stolonifer
Humidifier or forced-air-system lung	Fungal spores in air-conditioning ducts and in home humidifiers	T. candidus T. vulgaris Naegleria gruberi
Coptic lung	Cloth wrappings of mummies	
Poultry handlers' lung	Poultry feathers and products	Turkey and chicken proteins
Coffee and tea growers' disease	Green coffee bean Tea fluff	

TABLE 4

Fumes causing interstitial lung disease.

Exposure	Vapour inhaled
Swimming pools	Chlorine gas
Ore-smelting	Sulphur dioxide
Nose drops	Oil
Vineyard spray	Bordeaux mixture of copper sulphate and lime
Insecticides	Pyrethrum

TABLE 5

Causes of drug-induced chronic interstitial lung disease.

Busulphan	Diphenylhydantoin
Bleomycin	Gold salts
Chlorambucil	Nitrofurantoin
Cyclophosphamide	Paraquat
Methotrexate	Penicillin
Nitrosoureas	Pentolinium
Procarbazine	Sulphonamides
Vincristine	

TABLE 6

Causes of necrotising angiitis.

Polyarteritis nodosa
- Classical
- HBsAg associated in 20 per cent

Churg–Strauss eosinophilic granulomatosis

Wegener's granulomatosis (*see* page 155)

Systemic lupus erythematosus (*see* page 145)

Behçet's syndrome (*see* page 146)

Henoch–Schonlein purpura

Arteritis
- Hypersensitivity angiitis
- Giant-cell temporal
- Takayasu's pulseless aortic
- Retinal vasculitis
- Rheumatoid arthritis (*see* page 143)
- Rheumatic fever

Table 7: Radiologic Masqueraders of Asbestosis*

Sarcoidosis

Scleroderma

Rheumatoid Lung

Adult Respiratory distress Syndrome

Pseudolymphoma

Idiopathic Pulmonary Hemosiderosis

Alveolar Proteinosis

Thesaurosis

Drug Infiltrates

Goodpasture's Syndrome

Bronchiectasis Universalis

Hamman-rich Syndrome

Pneumocystis Carinii

Chemical Pneumonias

Amyloidosis

Histiocytosis

Parenchymal Hodgkins Disease

Pulmonary Edema

Inclusion Body Pneumonia

Cholesterol Pneumonitis

*This is Table 3 in VanOrstrand's publication previously referred to in the text. (reference number 2).

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TABLE 8 - INTERSTITIAL LUNG DISEASES THAT CAN BE DIAGNOSED BY TRANSBRONCHIAL BIOPSY.*

Sarcoidosis

Organic dust diseases (hypersensitivity pneumonitides)

Histiocytosis-X

Pulmonary hemorrhage syndromes

Inorganic dust diseases

Eosinophilic pneumonias

Drug-induced interstitial diseases

Lymphangioleiomyomatosis

Infectious agents

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*This list includes diseases in which diagnostic tissue can be obtained, as well as those in which tissue is suggestive but the diagnosis must be made by clinical and laboratory correlation.

The Interstitial Lung Diseases*

Jack D. Fulmer, M.D., F.C.C.P.

The interstitial lung diseases are a heterogenous group of diseases grouped together because of common clinical, roentgenographic, physiologic, and pathologic features.[1-4] Most patients present with insidious breathlessness and have a diffuse infiltrative pattern on chest roentgenogram (Fig 1A). Not uncommonly, an isolated reduction in carbon monoxide diffusing capacity (Dco) on routine pulmonary function testing is the first indication of underlying interstitial disease. The pathology of these diseases is characterized by an inflammatory cellular infiltration and an apparent increase in connective tissue of alveolar septae; in some, there are inflammatory cells within alveolar airspaces (Fig IB). Many of the interstitial diseases also have disease of airways, pulmonary vasculature, and sometimes pleural disease.[1,3,4]

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This review will deal mainly with chronic, progressive, interstitial diseases. A classification and recent advances in the pathogenesis and pathophysiology of the diseases will be discussed. Finally, an approach to the diagnosis and management of these diseases will be presented.

Classification

One approach to the classification of these diseases is to group them according to whether the etiology is known or unknown (Table 1).[1,3] Approximately one third of these diseases have known etiology; the remaining must be classified by clinical-pathologic features.

The most prevalent interstitial diseases are those caused by occupational and environmental inhalants. Of these, the inorganic dust diseases predominate. The organic dust diseases (hypersensitivity pneumonitides) are caused by inhalation of foreign proteins or complex polysaccharides to which the person has been previously sensitized.

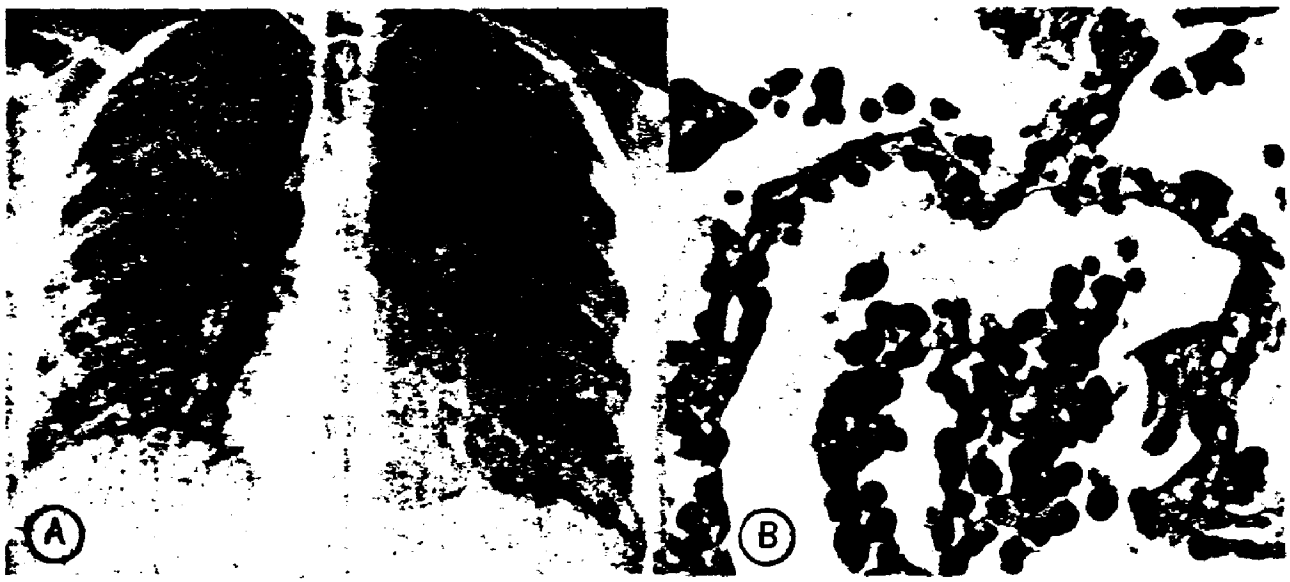

Figure 1. 30-year-old woman with idiopathic pulmonary fibrosis. *(A)*, Chest roentgenogram. Diffuse reticular pattern. *(B)*, Open lung biopsy specimen showing interstitial and intra-alveolar inflammatory process (alveolitis) and connective tissue derangement. Cuboidal cells replace normal alveolar epithelium. (H&E, original magnification × 600).

Table 1—*Classification of the Interstitial Lung Diseases*

Known Etiology	Unknown Etiology
Occupational and environmental inhalants	Idiopathic pulmonary fibrosis
Inorganic dusts	Interstitial diseases associated with collagen-vascular disorders
Organic dusts	Sarcoidosis
Gases, fumes, vapors, aerosols	Histiocytosis-X
	Vasculitides
Drugs	Pulmonary hemorrhage syndromes
Poisons	Lymphocytic infiltrative disorders
Radiation	Inherited disorders
Infectious agents	Ankylosing spondylitis
Cardiac disease	Eosinophilic pneumonias
Metabolic diseases	Lymphangioleiomyomatosis

Nearly 30 clinical organic dust diseases have been defined by either antigen (*eg*, aspergillosis) or specific environmental exposure (*eg*, farmer's lung).[1,3] Most antigens are fungal spores, although bacterial and animal proteins have been described; recently synthetic organic compounds have been implicated.[3] The remaining interstitial diseases of known etiology are caused by drugs, poisons, radiation, infectious agents, and cardiac or metabolic diseases.

Sarcoidosis is the most prevalent interstitial lung disease of unknown etiology and is estimated to be 20/100,000 persons worldwide.[4] Idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis) is also common, but no data are available on the prevalence of this disease. The interstitial diseases associated with the collagen-vascular disorders are a wide spectrum. Clinically significant chronic interstitial disease is most common in mixed-connective tissue disease, rheumatoid arthritis, and progressive systemic sclerosis. In contrast, interstitial disease is rare in polymyositis, systemic lupus erythematous, and Sjögren's syndrome.

The pulmonary vasculitides are an important group of interstitial diseases;[5] there is, however, no acceptable classification. One approach, is to group those vasculitides in which lung is always involved (Table 2). Of those, Wegener's granulomatosis, the Churg-Strauss syndrome, overlap vasculitis, and lymphomatoid granulomatosis are the major diseases. Lymphocytic angiitis and granulomatosis is often grouped with lymphomatoid granulomatosis; some believe, however, that it is a separate disease. An additional group of pulmonary vasculitides are those in which the primary pathology is a vasculitis, and lung may be involved (Table 2). In many of these, pathologic documentation of a pulmonary vasculitis may not exist and is only inferred by the association with the cutaneous vasculitis. Included in this group are the Henoch-Schönlein syndrome and disseminated leukocytolastic vasculitis. Classic polyarteritis nodosa rarely involves lung. Often classified with the vasculitides, Goodpasture's syndrome, and idiopathic pulmonary hemosiderosis are the major hemorrhage syndromes.

One of the most difficult groups of interstitial diseases are the lymphocytic infiltrative lung disorders. Some of these disorders are associated with defined clinical syndromes, such as Sjögren's syndrome and Waldenström's macroglobulinemia; others cannot be classified, and many (10 to 15 percent) may progress to a lymphoid malignancy.

The remaining interstitial diseases of unknown etiology are uncommon; some, such as lymphangioleiomyomatosis, are quite rare.

Pathogenesis

Regardless of etiology, current data suggest that the majority of the interstitial diseases have a common pathogenesis.[1,3] Initially, there is some type of injury to lung cells. Many of the known agents (poisons) are directly toxic to alveolar or capillary endothelial cells. Other agents (inorganic dust) injure lung through the generation of toxic radicals by inflammatory cells. The organic dusts and some drugs injure lung through immune mechanisms. Similarly, many of the interstitial diseases of unknown etiology are associated with alterations in the immune system. For example, immune complexes have been described in idiopathic pulmonary fibrosis, the collagen-vascular disorders, histiocytosis-X, and some of the pulmonary vasculitides.[3,5] Whether they are pathogenic or an epiphenomenon is not known.

As a result of injury to lung cells, there is an influx of inflammatory and immune-effector cells into alveolar septa resulting in an alveolitis (Fig 2). Unchecked, the alveolitis will become chronic and structural derangement will result.[1,3] The final common pathway for most interstitial diseases is the end-stage (honeycomb) lung. Importantly, injury, alveolitis, and repair coexist; fibrosis is a result of

Table 2—*Pulmonary Vasculitides*

Diseases in which lung is always involved
Churg-Strauss syndrome
Overlap vasculitis
Wegener's granulomatosis
Lymphomatoid granulomatosis
Lymphocytic angiitis and granulomatosis
Necrotizing sarcoid granulomatosis
Bronchocentric granulomatosis
Diseases in which lung may be involved
Henoch-Schonlein syndrome
Disseminated leukocytoclastic vasculitis
Disseminated giant cell arteritis
Behcet's syndrome
Classic polyarteritis nodosa
Takayasu's disease
Essential cryoglobulinemia

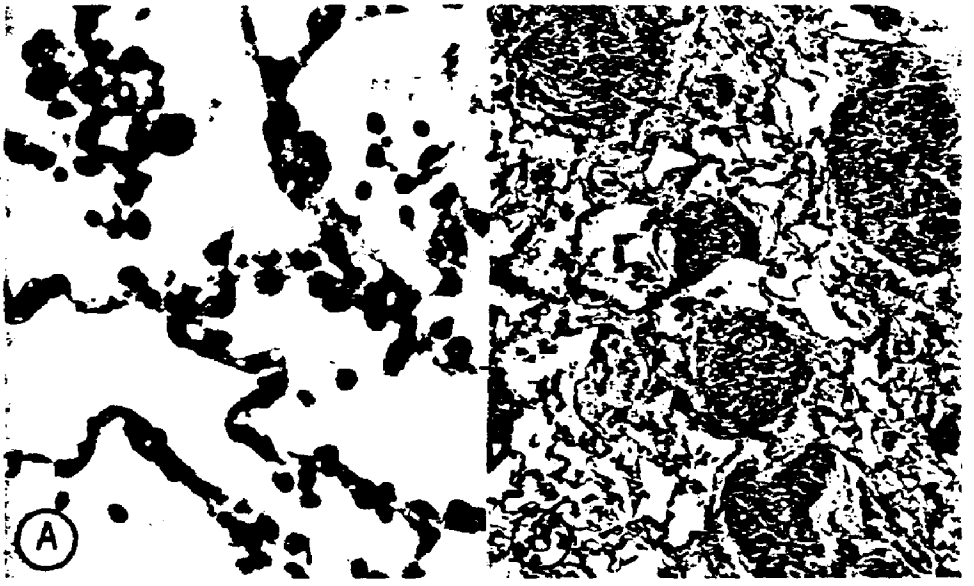

FIGURE 2. Pathogenesis of sarcoidosis. *(A)*, Early sarcoidosis showing interstitial and intra-alveolar lymphocytes; rare granulomas were present (H&E, original magnification × 500). Unchecked *(B)*, alveolitis becomes chronic, granulomas form, and connective tissue becomes deranged (H&E, original magnification × 130).

the inflammatory and reparative process.[1]

The alveolitis of these diseases is being intensively investigated. Many of the interstitial diseases (inorganic dust, idiopathic pulmonary fibrosis) have an alveolitis that consists mainly of alveolar macrophages and polymorphonuclear leukocytes. Other interstitial diseases mainly have a lymphocytic alveolitis (sarcoidosis, organic dust). In contrast, the eosinophil and the macrophage are the major immune-effector of immune cells in the eosinophilic pneumonias. Recent use of bronchoalveolar lavage has allowed characterization of inflammatory and immune-effector cells in the interstitial diseases (Fig 3).[1-4] Considerable data indicate that the major effector cells in both sarcoidosis and organic disease are T-lymphocytes.[3-4] Furthermore, T-lymphocyte subtyping has suggested that patients with active sarcoidosis have an increased number of lung helper T-lymphocytes that are likely important in granuloma formation.[6]

PATHOPHYSIOLOGY

The interstitial diseases are classically included in the restrictive lung disorders; vital capacity (VC)

FIGURE 3. Bronchoalveolar lavage cell preparation in sarcoidosis. *(A)*, Lymphocytic (T cell) alveolitis (Giemsa, original magnification × 500). *(B)*, Lymphocyte-macrophage rosetting typical of many granulomatous diseases (Giemsa, original magnification × 1,200).

is reduced, and respiratory flow rates are preserved.[1-3] Additional physiologic features of these diseases are a reduction in lung compliance, reduced Dco, and hypoxemia that worsens on exercise.

Lung volume alterations in the interstitial diseases vary; a moderate to severe reduction in VC is characteristic of acute idiopathic pulmonary fibrosis and acute organic dust disease. In contrast, the more common subacute or chronic forms of these diseases may not exhibit a reduction in VC until the disease is in mid-course. As the disease progresses, however, lung architecture becomes revised, fibrosis develops, and severe reductions in lung volumes result.

Gas exchange abnormalities are one of the earliest physiologic alterations in the interstitial diseases, particularly Dco.[1] Whereas early interstitial lung disease is characterized by normal resting arterial blood gases, ventilation-perfusion defects are amplified by exercise so that the alveolar-arterial oxygen tension difference ($P[A\text{-}a]O_2$) widens and arterial oxygen tension (PaO_2) falls. Advanced interstitial disease is characterized by severe resting hypoxemia. Ventilatory capacity, however, is maintained until the disease becomes end-stage when resting or exercise hypercapnia may be present.

Whereas standard measures of airway function (timed spirometry and airways resistance) are typically normal, many of the interstitial diseases (*eg*, idiopathic pulmonary fibrosis) exhibit physiologic and morphologic changes consistent with small airways disease.[1,3] Patients with both inorganic and organic dust disease, however, may have major obstructive defects. Reversible airflow obstruction is characteristic of only a few of the interstitial diseases—the eosinophilic pneumonias, the Churg-Strauss syndrome, and overlap vasculitis.[1,5]

Diagnosis

A systematic approach to patients with interstitial disease forms the basis for diagnosis. A detailed occupational history is mandatory in diagnosing the inorganic dust diseases. Whereas silicosis results from prolonged exposure, asbestosis can result from only a brief exposure. Asbestosis can also result from exposure to contaminated clothing by household members or from living in proximity to a processing plant.[1] The diagnosis of organic dust disease can be suggested from an exposure history (*eg*, farming or breeding pigeons); however, the exposure may not be obvious. A detailed history of the use of home humidifiers, vaporizers, saunas, or exposure to organic chemicals is important. Another important clinical feature of organic dust disease is a history of recurrent pneumonias, particularly if correlated with an environmental exposure.[1,3]

A detailed drug use history is also important in evaluation. Virtually any drug should be suspect; however, most drug-induced interstitial diseases result from three major groups (Table 3). The cytotoxic and immunosuppressive agents constitute the major offenders. Whereas bleomycin and the nitrosourea agents are dose-related, methotrexate is not. There may, however, be synergism between some cytotoxic agents (*eg*, cyclophosphamide and bleomycin).

A family history can be useful in the diagnosis in some of the interstitial diseases; sarcoidosis and many of the collagen-vascular disorders can be familial. Family history is particularly important in mixed-connective tissue disease and rheumatoid lung disease, since lung involvement can antedate other systemic manifestations of the disease. Dermatologic or ocular manifestations of sarcoidosis, the collagen-vascular disorders, neurofibromatosis, and Wegener's granulomatosis can be useful, and at times diagnostic.[1,3,5]

Table 3—*Drug-induced Interstitial Lung Disease**

Cytotoxic and immunosuppressive agents
Busulfan
Bleomycin
Cyclophosphamide
Chlorambucil
Nitrosourea
Carmustine
Semustine
Methotrexate
Metomycin
Melphalan
Procarbazine
Mercaptopurine
Neuroactive and vasoactive agents
Methysergide
Phenytoin (diphenylhydantoin)
Ganglionic blocking agents (hexamethanoium)
β-Blocking agents (practolol)
Carbamazepine
Antimicrobial agents
Nitrofurantoin
Sulfonamides
Aminosalicylic acid
Penicillin
Miscellaneous
Hydrochlorothiazide
Chlorpropamide
Sulfapyridine
Gold salts
Drug-induced SLE (hydralazine)

*Including only drugs that cause chronic, progressive interstitial disease.

Only a few of the interstitial diseases have a chest roentgenogram that is considered diagnostic. The roentgenogram of chronic eosinophilic pneumonia showing rapidly progressive, nonsegmental, peripheral dense pneumonic infiltrates is considered to be diagnostic.[1] Many roentgenographic patterns are suggestive of certain interstitial diseases when correlated with laboratory data, however. Diffuse interstitial infiltrates with sparing of the costophrenic angles in a young male is suggestive of histiocytosis-X. Similarly, hilar adenopathy with uveitis and skin lesions in a young black person is considered to be diagnostic of sarcoidosis.

As with the chest roentgenogram, pulmonary function is generally of little value in the diagnosis of most interstitial diseases. An exception to this generalization is physiologic data consistent with emphysema in a young, nulliparous female with interstitial disease; these data are strongly suggestive of the diagnosis of lymphangioleiomyomatosis.

Other laboratory studies may be useful in establishing a specific diagnosis. Serologic studies can be specific for the collagen-vascular disorders. Precipitins to specific organic antigens can be useful in diagnosing the organic dust diseases. However, precipitins alone are not diagnostic; the antigens are ubiquitous, and many normal persons have them. Additionally, patients with organic dust disease can have false negative tests.[1] Once viewed as useful in diagnosing sarcoidosis, serum lysozyme is now known to be nonspecific. In contrast, serum angiotensin converting enzyme can be a valuable aid. Rarely falsely positive (<2 percent) and present in only Gaucher's disease and leprosy, false negative values approach 30 percent and are most common in stage 1 and stage 4 sarcoidosis.[1,4,7] Circulating immune complexes or antibasement membrane antibody can also be useful studies if correlated with lung tissue or lavage cellular analysis.

There has been recent interest in bronchoalveolar lavage cellular analysis in the diagnosis of interstitial diseases.[1-6] However, only two diseases can be diagnosed if correlated with clinical or other laboratory data: alveolar proteinosis and the pulmonary hemorrhage syndromes. In the case of the latter, the finding of hemosiderin-ladened macrophages indicates pulmonary hemorrhage, and circulating antibasement membrane antibodies are necessary to diagnose Goodpasture's syndrome. Idiopathic pulmonary hemosiderosis cannot be diagnosed by lavage, however. It has been suggested that electron microscopy of the lavage cells can be diagnostic of histiocytosis-X. However, these cells have also been described in malignant diseases and in idiopathic pulmonary fibrosis.

Two major cellular patterns in bronchoalveolar lavage have emerged, a predominant lymphocytosis and a predominant polymorphonuclear leukocytosis. While the presence of lavage lymphocytosis is suggestive of either sarcoidosis or organic dust disease,[2-4] recent data indicate that acute idiopathic pulmonary fibrosis, some of the collagen-vascular disorders, and acute histiocytosis-X can also exhibit a lymphocytosis (Law DE, Fulmer JD, unpublished observations). Similarly, the inorganic dust diseases, idiopathic pulmonary fibrosis, collagen-vascular disorders, and advanced sarcoidosis may exhibit a polymorphonuclear leukocytosis.[2,6] Clearly, additional studies are needed before lavage cell analysis can be considered routine in the diagnosis of interstitial diseases.[9]

Additional relatively noninvasive procedures may be useful in diagnosing some of the interstitial diseases. Conjunctival or skin biopsy in a clinical setting can confirm the diagnosis of sarcoidosis.[1] Whereas lymph node biopsy is not recommended to diagnose sarcoidosis, it may be useful in diagnosing some of the lymphocytic infiltrative diseases.[1] Skin biopsy may also be useful in diagnosing some vasculitides, the Churg-Strauss syndrome, and disseminated leukocytoclastic vasculitis. However, care must be exercised, since a cutaneous leukocytoclastic vasculitis may be a feature of Wegener's granulomatosis, some of the diffuse infiltrating malignant diseases, and some drug-induced interstitial diseases.

Although some of the interstitial diseases of both known and unknown etiology can be diagnosed with reasonable accuracy without lung biopsies, most experts agree that lung biopsy is needed.[1] The major reasons are to exclude a more treatable type of interstitial disease (*eg*, organic dust disease) and to assess the activity of disease. The initial procedure of choice is fiberoptic bronchoscopy with transbronchial lung biopsy. Bronchopulmonary lavage performed at the time of bronchoscopy may be useful in diagnosing some infectious or neoplastic infiltrative diseases. Transbronchial biopsy can establish the diagnosis of many interstitial diseases (Table 4). As with any laboratory tool, clinical correlation is necessary. Drug-induced disease may pose a problem, but can be diagnosed if there is a search for typical bizarre granular pneumocytes. An adequate number of biopsies must be performed to exclude malignant disease or infection, however, and at least four biopsies are recommended. Transbronchial biopsy showing nonspecific pneumonitis and fibrosis (usual interstitial pneumonitis) is not diagnostic.[10,11] Areas in proximity to granulomas, infectious processes, and malignant diseases may have these features.

Table 4—*Interstitial Lung Diseases that Can Be Diagnosed by Transbronchial Biopsy**

Sarcoidosis
Organic dust diseases (hypersensitivity pneumonitides)
Histiocytosis-X
Pulmonary hemorrhage syndromes
Inorganic dust diseases
Eosinophilic pneumonias
Drug-induced interstitial diseases
Lymphangioleiomyomatosis
Infectious agents

*This list includes diseases in which diagnostic tissue can be obtained, as well as those in which tissue is suggestive but the diagnosis must be made by clinical and laboratory correlation.

In the absence of a specific diagnosis by transbronchial biopsy, open lung biopsy is recommended. Open lung biopsy can be performed with minimum morbidity and mortality and a very high (>90 percent) diagnostic yield.[11] The latter is maximized when the pathologist is aware of the clinical data. An area of average involvement on chest roentgenogram and direct observation should be biopsied. Areas with dense fibrosis will show end-stage lung disease. Immediate fixation after hyperinflation will minimize artifacts. Whereas fresh tissue is necessary for immunofluorescent studies, formalin-fixed tissues generally suffice for the diagnosis of most interstitial diseases. Open lung biopsy will not only establish the diagnosis, but give the best assessment of the severity of the disease process and the likelihood of response to therapy.[1,3]

Treatment

The overall treatment goals for the interstitial diseases are to identify and remove the injurious agent, suppress the inflammatory response to prevent progression of the disease, and to palliate the complications of the disease.[1,3]

The mainstay of drug treatment of these diseases is corticosteroids.[1,4] Current data indicate that immunosuppressive or cytotoxic agents are useful in the treatment of some diseases (*eg*, the pulmonary vasculitides).[1,5] Although data in experimental models suggest that agents known to alter collagen metabolism (*eg*, L-proline) may prevent fibrosis, there are no data indicating that these agents are clinically useful.

Identifying and removing etiologic agents is important in the management of the interstitial disease of known etiology.[1] Corticosteroid therapy is generally recommended for the acute inorganic dust exposure disease and acute radiation- and drug-induced disease, particularly if there is hypoxemia.[1] However, treatment of the chronic varieties of these diseases remains symptomatic. In contrast, corticosteroids are usually recommended for both acute and chronic organic dust disease.

Considerable data support the use of corticosteroids in idiopathic pulmonary fibrosis.[1] Patients with early disease with an active alveolitis (*eg*, increased cellularity) and minimal fibrosis respond best. Clinical and chest roentgenographic correlates of early disease are recent onset of symptoms and a ground glass or acinar pattern. Additionally, young patients respond best to treatment. In contrast, advanced interstitial disease, with minimal alveolitis and advanced fibrosis, does not respond to treatment with corticosteroids. There is no agreement on the dose of corticosteroids or the duration of treatment. Until more sensitive means to monitor the disease activity are developed, most experts recommend a regimen of high-dose prednisone (1 mg/kg/day) for four to six weeks, followed by a slow taper to 15 to 20 mg/day for a minimum of six months to one year.[1,3] Immunosuppressive therapy has been recommended as an alternative or an adjunct in the treatment of idiopathic pulmonary fibrosis; controlled data, however, do not support this.[1]

The treatment of pulmonary sarcoidosis is controversial. Patients with stage 1 sarcoidosis should not be treated, since more than 90 percent resolve spontaneously.[1,4] In contrast, patients with progressive disease or multiple-organ dysfunction should be treated. Many experts recommend alternate-day corticosteroid therapy in sarcoidosis. There are, however, no concrete data to indicate that corticosteroid treatment is more effective than symptomatic treatment of sarcoidosis.

In general, the chronic interstitial diseases associated with the collagen-vascular disorders have a good prognosis.[1] Patients with aggressive disease are generally managed in the same manner as patients with idiopathic pulmonary fibrosis, although some experts recommend the use of immunosuppressive therapy on an individual basis.

The pulmonary vasculitides represent an important group of patients. Data support the use of corticosteroids and immunosuppressive or cytotoxic agents in these diseases.[1,5] The Churg-Strauss syndrome may respond well to corticosteroids; unresponsive cases may respond to cytotoxic agents. Additionally, patients with Henoch-Schönlein syndrome or disseminated leukocytolastic vasculitis respond to corticosteroid treatment. Clearly, cyclophosphamide is the treatment of choice for

Wegener's granulomatosis.[5] Recent data also support the use of cyclophosphamide in the treatment of overlap vasculitis.[5] In contrast, the treatment of lymphomatoid granulomatosis is controversial, but most experts recommend early use of cytotoxic agents.

Plasmapheresis in conjunction with immunosuppressive therapy appears to be emerging as the therapy of choice for pulmonary hemorrhage associated with Goodpasture's syndrome and immune complex disease.[1]

Lung biopsy specimen examination is the best estimate of disease activity, but once the decision is made to treat patients, an objective means to monitor response to therapy is needed.[1-4] Traditionally, the chest roentgenogram and pulmonary function studies have been used to monitor patients' conditions. While these studies have enormous value when used serially, current data indicate that they are a relatively insensitive means of monitoring the disease.[1,3,4] Two new tests show promise as monitors of disease activity—bronchoalveolar lavage cellular analysis and ^{67}Ga lung scanning.[1-4] Several major centers have shown that bronchoalveolar lavage cell analysis accurately samples the inflammatory cells (alveolitis) as judged by lung biopsy specimen analysis. Additionally, a semiquantitative analysis of the uptake of ^{67}Ga in lung has been demonstrated to correlate well with the degree of alveolitis in lung biopsy specimens.[3,4] Both bronchoalveolar lavage cellular analysis and ^{67}Ga lung scanning are being intensively investigated as monitors of interstitial disease. However, further studies are needed before they can be recommended for routine management.

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Pneumoconioses and Their Masqueraders

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It has been traditional that if an adequate occupational history is obtained in workers exposed to harmful dusts, the chest x-ray is the main diagnostic tool. In recent years, however, it has been noted that in most all occupations of these types, there may be marked variation in individual susceptibility to developing a pneumoconiosis without necessarily showing a constant dose relationship. It has also been recognized that there is no occupation in which the worker is immune to nonoccupational diseases. It is not too infrequent that the usual diagnostic studies will not be sufficient to differentiate between masquerading diseases unrelated to the employment and diseases caused by the known hazards of certain employment. Some patients need more than just the usual work history, routine tests, and chest x-rays to differentiate occupational from nonoccupational diffuse lung disease. In my experience, additional tests, particularly lung biopsy, have found previously unsuspected pneumoconioses in an equal number of workers whose problems have been nonoccupational and masquerading as a dust disease of the lung. Thus both legal and medical requirements have been met.

This article will primarily be one in which the roentgenogram has been the main point of differential diagnosis.

A personal classification of pneumoconioses and of hypersensitivity occupational reactions of the lungs is shown in Table 1.

Masqueraders of silicosis as shown by roentgenography are listed in Table 2. An example of such is a man who worked in a glass industry for 30 years. He developed a cough and some shortness of breath and a roentgenogram of his chest showed diffuse generalized nodulation which was interpreted as silicosis (Fig 1). A more detailed analysis of this man's work history with the company, however, indicated that he had had a minimal exposure to free crystalline silica. A surgical lung biopsy specimen (Fig 2) showed the nodules to be due to hematogenous metastases from a signet ring cell type of carcinoma most compatible with a primary stomach neoplasm. Further roentgenographic studies confirmed the presence of an asymptomatic gastric neoplasm and

Table 1. — Pneumoconioses Classification.

A. Those that are nondisabling (so-called "benign", due to inert nonfibrogenic dusts):
   1. Siderosis
   2. Stannosis
   3. Baritosis
   4. Antimony Pneumoconiosis

B. Those that are usually nondisabling and usually reversible (occupational lung disorders of hypersensitivity):
   1. Byssinosis
   2. Bagassosis
   3. Farmer's Lung
   4. Maple Bark Disease
   5. Mushroom Picker's Disease
   6. Pigeon Breeder's Disease
   7. Saqueiosis
   8. Furrier's Lung
   9. Coffee Worker's Lung
   10. Vineyard Sprayer's Lung
   11. Paprika Splitter's Lung
   12. Cheese Worker's Lung
   13. Malt Worker's Lung
   14. Suberosis

C. Those which may be disabling and even fatal:
   1. Silicosis
   2. Asbestosis
   3. Beryllosis
   4. Coal Worker's Pneumoconiosis
   5. Shaver's Disease
   6. Talcosis
   7. Cristobalite Silicosis
   8. Diatomaceous Earth Pneumoconiosis

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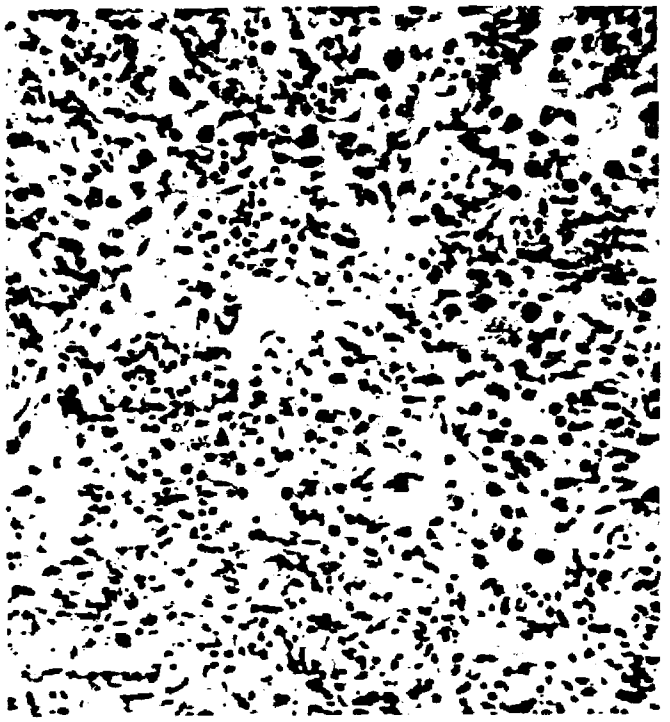

Fig 4. — Histologic study which showed the picture of fibrosing interstitial pneumonitis of the Hamman-Rich syndrome instead of asbestosis.

tern along with reduced clarity of the heart borders so often seen in asbestosis. The man had experienced respiratory symptoms of cough and progressive shortness of breath less than one year. A biopsy specimen of the lung revealed fibrosing interstitial pneumonitis of the Hamman-Rich syndrome, with no histologic signs of asbestosis (Fig 4).

Some of the roentgenographic masqueraders of berylliosis are shown in Table 4. The earliest roentgenographic changes in

Table 4. — Radiologic Masqueraders of Berylliosis.

Sarcoidosis
Miliary Tuberculosis
Lymphangitic Metastases
Pulmonary Alveolar Microlithiasis
Miliary Coccidiomycosis
Periarteritis Nodosa
Hematogenous Metastases
Scleroderma
Rheumatoid Lung
Desquamative Interstitial Pneumonitis
Hemosiderosis secondary to Mitral Stenosis
Psittacosis Pneumonia
Measles Pneumonia
Chicken Pox Pneumonia

Table 5. — Radiologic Masqueraders of Shaver's Disease.

Bullous Emphysema
Cystic Fibrosis
Aspergillosis
Cryptococcosis
Histiocytosis
Amyloidosis

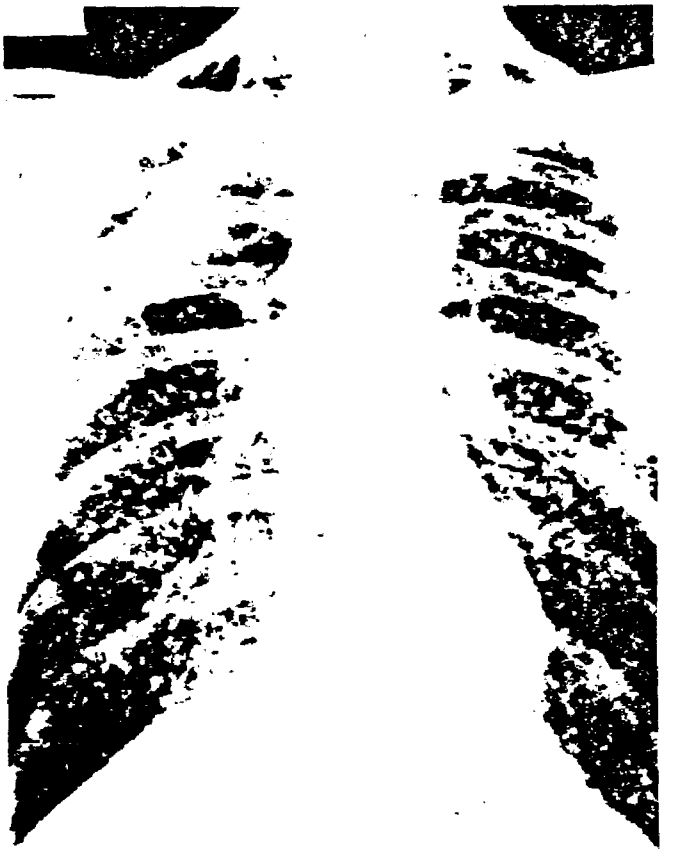

Fig 5. — Roentgenogram of a beryllium worker with 20 years in a basic industry where beryllium compounds were extracted from the ore, beryl. The minimal hilar adenopathy and diffuse fine sand-like nodulation in this roentgenogram had been interpreted as chronic berylliosis. Diagnostic studies indicated, however, that this was a problem of sarcoidosis.

Fig 6. — Roentgenogram of a bituminous coal miner who for most of 20 years had worked at operations at or near the face. The films were interpreted as suggestive of simple CWP.

Table 6. — Radiologic Masqueraders of Coal Worker's Pneumoconiosis (CWP).

Miliary Tuberculosis
Miliary Metastatic Carcinoma
Sarcoidosis
Lymphocytic Interstitial Pneumonitis
Desquamative Interstitial Pneumonitis
Hemosiderosis secondary to Mitral Stenosis
Chicken Pox Pneumonia
Miliary Coccidiomycosis
Pulmonary Alveolar Microlithiasis
Retained Lipoidol
Thesaurosis
Periarteritis Nodosa
Scleroderma

Fig 11. — Roentgenogram in a worker involved in the calcining process of diatomaceous earth. It was believed that he had diatomaceous earth pneumoconiosis.

Table 7. — Radiologic Masqueraders of Talcosis.

Bronchiolar-alveolar Carcinoma
Scleroderma
Rheumatoid Lung
Lymphangitic Metastases
Hematogenous Metastases
Lymphocytic Interstitial Pneumonitis
Miliary Coccidiomycosis
Desquamative Interstitial Pneumonitis
Sarcoidosis
Histoplasmosis
Chicken Pox Pneumonia
Hamman-Rich Syndrome
Pneumocystis Carinii
Chemical Pneumonias
Measles Pneumonia

Fig 12. — Photograph of a trephine drill lung biopsy specimen which showed diffuse lymphocytic lymphoma instead of diatomaceous earth pneumoconiosis.

Table 8. — Radiologic Masqueraders of Diatomaceous Earth Pneumoconioses.

Bronchiolar-alveolar Carcinoma
Scleroderma
Rheumatoid Lung
Lymphangitic Metastases
Hematogenous Metastases
Lymphocytic Interstitial Pneumonitis
Miliary Coccidiomycosis
Desquamative Interstitial Pneumonitis
Sarcoidosis
Histoplasmosis
Chicken Pox Pneumonia
Hamman-Rich Syndrome
Pneumocystis Carinii
Chemical Pneumonias
Measles Pneumonia
Diffuse Pulmonary Lymphoma

Table 9. — Radiologic Masqueraders of the Immunologic Occupational Lung Disorders (Farmer's Lung, Etc.).

Sarcoidosis
Alveolar Proteinosis
Pulmonary Edema
Tropical Eosinophilia
Drug Infiltrates
Chemical Pneumonias
Thesaurosis
Pneumocystes Carinii
Adult Respiratory Distress Syndrome
Inclusion Body Pneumonia
Scleroderma
Pseudolymphoma
Lipid Pneumonia
Rheumatoid Lung
Bronchiectasis Universalis

earth pneumoconioses are shown in Table 8. It is generally believed that this pneumoconiosis results from the heat calcining process with the basic fibrogenic dust being crystobalite. Figure 11 is a roentgenogram of a man who had worked for several years in this occupation: diatomaceous earth pneumoconiosis was suspected. A needle biopsy (of the trephine drill type), however, showed his diffuse lung involvement to be lymphocytic lymphoma (Fig 12).

Roentgenographic masqueraders of the immunologic occupational lung disorders are shown in Table 9. Figure 13 shows bilateral lower lung field infiltrates in a farmer who was experiencing intermittent cough and wheezing which he felt at times might be worse after working in his hay barn. The histologic study, however, as shown in Fig 14, established the diagnosis of tropical eosinophilia instead of farmer's lung (even though he had never been out of his home state of Pennsylvania other than coming to the Cleveland Clinic for diagnostic study). He promptly responded to arsenical therapy as shown in Fig 15. He had no recurrence of his problem.

In summary, just as it has been found that certain unusual roentgenograms can be due to a specific occupational disease and histologically proven so, in contrast it is also known that there is no occupation which allows a worker to be immune to nonoccupational diseases which can mimic roentgenographically the specific fibrogenic dust entity or forms of immunologic occupational diseases. This article presents a personal classification of the pneumoconioses and also tables and examples of masqueraders of them. Not too infrequently, the differential diagnostic tool of most importance is the microscope. In these modern times, biopsies can be obtained through various ways and usually adequately to obtain the proper final answer. These biopsies include those obtained through fiberoptic bronchoscopy, the various types of percutaneous needle lung biopsies, and lung biopsy specimens obtained at a minor surgical procedure.

Medical Responsibilities and Rights

It is said that the right to excellent health care, unlike the freedom of speech and other guarantees derived from the Bill of Rights, is going to make much greater demands on our national resources and ought not to be considered in the same light. Yet we are determined that there shall be equal access; like other human rights, it cannot be guaranteed to future generations unless defended and protected against decay by the *responsible* actions of those now benefited. The process of continuous growth and renewal of biomedical knowledge, as well as the cultivation of professional skills, cannot benefit the next generation without the help of the patients of today. We have resolved that this burden shall no longer be borne chiefly by the poor, the ignorant and the wards of the state. If we take an egalitarian view of the *rights* of the patient, should we take any other view of his *responsibilities?*

Nevertheless, in practice these responsibilities are not universally accepted by patients and their families. Though the majority play their part in good grace, some of them make it clear that they consider their involvement an unforeseen indignity. Others simply refuse, and one hears, for example:

"I don't want to be a guinea pig."

"The medical student (or even the intern) can learn on someone else."

"I don't think her brother is strong enough to donate blood, and besides he's too busy to come."

"If you have doubts about the effectiveness of the new treatment, call me when you feel more sure."

— From "Sounding Board" by Thomas P. Almy, M.D. in *The New England Journal of Medicine*, July 21, 1977

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Crackles in the Early Detection of Asbestosis[1,2]

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SUMMARY We studied 386 workers exposed to asbestos to assess the value of chest auscultation by a trained technician in detecting asbestosis as defined by previously reported clinical, physiologic, and roentgenologic criteria. The presence and degree of crackles were assessed at preselected basilar lung sites by a technician whose performance was validated by comparison with computer-generated time-expanded waveforms of tape recordings of lung sounds. Asbestosis was present in only 2.8% of the total population, but it was present in 8.6% of those with over 25 yr or more of employment. The technician correctly identified all the workers in whom the diagnosis was most certain, that is, those with all criteria positive. The overall true positive rate was 88%. The majority (94.8%) of those with no abnormal criteria were correctly classified. Auscultation by an objectively validated technician can be a useful noninvasive method for screening industrial populations exposed to asbestos.

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Introduction

Minimal interstitial pulmonary fibrosis caused by the inhalation of asbestos can be difficult to detect (1, 2). Symptomatology is subjective and pulmonary function studies are often nonspecific. Roentgenographic manifestations of early interstitial disease are often difficult to distinguish from normal shadows (1-3), and observer variability in interpretation of radiographs is also a problem. Discontinuous adventitious lung sounds (crackles, rales) have been recognized as prominent features of pulmonary asbestosis (4-6) and are thought to be an early finding (7-9). Although chest auscultation is regarded as highly subjective, recently developed technology has brought the promise of objective quantification of lung sounds. One such method, called time-expanded waveform (TEW) analysis, consists of tape recordings of sounds for analysis by a computer. Amplitude is then plotted versus time, with a time axis of 800 mm/s or more, allowing visualization of minute details of pulmonary sounds (10). Because TEW analysis provides documentation of the presence of crackles, it can be used to train technicians in auscultation (11). Monitoring of exposed workers by auscultation is attractive because it is noninvasive and inexpensive. The purpose of this investigation was to quantify the relationship between the prevalence of crackles assessed by a technician, whose performance had been objectively validated, to other criteria for asbestosis in exposed workers.

Methods

The 386 workers included in this study were exposed to asbestos during the manufacture of paper and insulation materials and in a shipyard. Lung sounds were recorded at 4 preselected basilar sites during breathing with the mouth open while the worker was in a sitting position. Workers were asked to breathe slightly more deeply than the usual tidal breathing as in standard clinical practice. These sites were the right and left bases in the midscapsular line, the right midclavicular line, and the left anterior axillary line. The number of crackles was estimated at each auscultation site using a scale ranging from 0 (none) to 3.0 (indicating many), and a weighted crackle score (WCS) was then calculated. Scores from the right and left bases posteriorly were doubled and added to the scores from the anterior sites. The resulting WCS ranged from 0 to 18. Lung sounds were recorded at the time of auscultation, and selected tape recordings were analyzed for frequency content and TEW analysis with and without 800-Hz filtered sound. These were compared with the independent observations of a trained technician.

For this assessment, worker identification was masked by use of code numbers. Comparison of the WCS was made by 2 observers who interpreted the TEW analyses while simultaneously listening to the sounds. The technician's results were also compared with the pulmonary physician's listening during the surveys. The Kappa statistic was calculated according to the method of Fleiss (12). Kappa is a numerical method of separating agreement from chance association, and it varies from 0 (no agreement) to 1.0 (complete agreement). For interpretation of the intermediate values, we employed the criteria of Landis and Koch (13): a Kappa value of 0.81 to 1.0 indicates almost perfect agreement, 0.61 to 0.80 indicates substantial agreement, 0.41 to 0.60 indicates moderate agreement, and 0.4 and below indicates slight to poor agreement.

Other data were collected using a questionnaire on respiratory history and occupational exposure, a physical examination including independent observations on lung sounds by 2 or more chest physicians, chest roentgenographic readings according to the ILO scheme, and detailed pulmonary function testing (14). Asbestosis in these exposed workers was considered to be present when 3 or 4 of the following criteria were present: (*1*) radiograph showing irregular opacification of a profusion of 1/2 or more, (*2*) single-breath diffusing capacity less than 80% predicted, (*3*) vital capacity less than 80% predicted, and (*4*) crackles at 2 or more basilar sites.

Results

Asbestosis by our criteria was present in only 2.3% of the workers and did not occur in workers with less than 11 yr of exposure. In the 93 workers with over 25 yr of employment, 8.6% were considered to have asbestosis. The prevalence of abnormal findings in each of these criteria is shown in table 1. In general, the prevalence of these criteria increased both with exposure and with age, as is expected in populations wherein age and duration of exposure are closely correlated (figure 1). Pleural abnormalities also showed a similar relationship to duration of exposure and age (figure 2).

The relationship between the tech-

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crackles were distributed upwards from the base at the scapular level.

The belief that crackles are an early sign is also consistent with many published reports. Crackles have been regarded as a feature of pulmonary asbestosis for over 50 yr, and even in early reports were considered to be present with minimal disease (17). Clinical features of their nature and distribution on the chest were described in some detail by Smither (9). Mitchell and coworkers (20) found crackles more closely related to duration of exposure to heat-resistant and friction composites than was vital capacity, and they recommended that chest auscultation be included as a biologic monitor of the work environment. Reported rates vary, but about half of the persons considered to have asbestosis on clinical grounds are reported to have crackles (21–23). These represent selected cases. In order to understand the strength of an association between an exposure and a health effect, it is important to know the status of all persons exposed. If only patients are studied, the effects may appear more striking than if asymptomatic persons are also included. Population-based studies, therefore, allow more precise examination of the frequency of crackles in asbestos-exposed persons. These show prevalences ranging from about 10 to 20%. Such prevalences depend on a variety of factors including the method of auscultation, the severity and duration of exposure, the age of population, the prevalence of the diseases causing crackles, etc. Nevertheless, the association between crackles and asbestos exposure is clearly established by: (*1*) high frequency in diagnosed cases, (*2*) common occurrence in exposed populations, and (*3*) increased frequency with increased duration of exposure (24, 25). Furthermore, the prevalence in control populations is low (24–27).

The correct detection of those in whom the epidemiologic diagnosis of asbestosis was most certain suggests that a trained technician can screen a group of exposed workers to estimate the prevalence of asbestosis. Despite the high true positive rate there are errors in the method. In our study, 5 of the 7 workers with 3 of 4 positive criteria were missed (false negative). Although this may represent technician error, it is known that not all those with asbestosis have crackles. Indeed, Epler and coworkers (7) reported crackles in

TABLE 2

RELATIONSHIP OF AUSCULTATION BY A TECHNICIAN TO NUMBER OF ASBESTOS CRITERIA

Number of Positive Criteria per Worker of 4 Possible Asbestosis Criteria	Weighted Crackle Score 0	1	2	3+	Total
0	225	34	15	15	289
1	50	5	3	5	63
2	13	3	2	5	23
3	3	2	0	2	7
4	0	0	0	4	4
Total	291	44	20	31	386

TABLE 3

TECHNICIAN VALIDATION: COMPARISON OF TECHNICIAN'S WEIGHTED CRACKLE SCORE MADE AT THE INDUSTRIAL SITE TO WAVEFORM INTERPRETATIONS OF THE SAME LUNG SOUNDS*

Waveform Interpretations	Weighted Crackle Score† 3 or More	Less than 3	Total
Positive for crackles	6	2	8
Negative for crackles	0	14	14
Total	6	16	22

* Kappa = 0.80; 20/22 = 90.9%.
† On-site tech observations.

TABLE 4

RELATIONSHIP OF ROENTGENOGRAPHIC EVIDENCE OF EMPHYSEMA AND SYMPTOMS OF CHRONIC BRONCHITIS TO ASBESTOSIS AND WEIGHTED CRACKLE SCORE

	Asbestosis* Yes	No	Total	Weighted Crackle Score Yes	No	Total
Emphysema†						
Yes	0	5	5	1	4	5
No	11	343	354	28	326	354
Total	11	348	359	29	330	359
Chronic bronchitis‡						
Yes	3	56	59	8	51	59
No	8	319	327	23	304	327
Total	11	375	386	31	355	386

* Asbestosis defined as 3 or 4 criteria positive.
† Emphysema defined by roentgenographic criteria.
‡ Chronic bronchitis defined by American Thoracic Society criteria.

TABLE 5

RELATIONSHIP OF SMOKING HISTORY TO WEIGHTED CRACKLE SCORE*

Smoking History (pack-years)	Weighted Crackle Score 0	1, 2	3+	Total
0–20	189 (153.4)†	27 (36.64)	12 (15.91)	208
21–40	52 (57.54)	20 (14.49)	6 (5.97)	78
41–60	32 (33.93)	9 (8.55)	5 (3.52)	46
61+	17 (25.08)	12 (6.32)	5 (2.60)	34
Total	270	68	28	366

* X^2 = 19.35, $p < 0.005$
† Numbers in parentheses refer to the expected value for that cell.

probable that those who develop severe asbestosis have roentgenographic progression from UICC grade 0/0 to 3/4 in a relatively orderly fashion. Our reluctance to regard the lesser UICC grades of small opacifications as prima facie evidence of an effect of asbestos is based on the reliability of such evidence. First, the early diagnosis of interstitial fibrosis has long been regarded as one of the most subjective in radiology (2, 3) (other causes for roentgenologically similar shadows include soft tissues, inadequate inspiration, etc.). Second, it is likely that a variety of other illnesses and exposures produce similar findings (previous pulmonary infection, other silicates, drugs, congestive heart failure, etc.). Third, in our studies, lesser grades of opacifications in asbestos workers could not be distinguished reliably from shadows seen on roentgenograms of the control subjects (10, 36). Decreasing the degree of disease required to classify an individual as a positive case in epidemiologic studies frequently leads to an increase in sensitivity. Unfortunately, this also often decreases the specificity or accuracy of the observation (13). The relative "earliness" of pulmonary function abnormalities, roentgenographic findings, and auscultation are all subject to this phenomenon. The relevant issue is which test or set of tests provides reliable monitoring of workers to assure, as far as practicable, their safety. In this regard, a significant advantage of auscultation is its noninvasiveness, as worker acceptance must also be considered. Roentgenograms offered by employers are frequently refused by workers because of the fear of exposure to radiation or personal considerations.

The results of these studies indicate that auscultation, by a properly trained and objectively validated technician, can be a useful method for screening industrial populations with exposure to asbestos. Although true positives may be underestimated, the false negative rate is low and the method is inexpensive. With the use of modern recording and analysis techniques, chest auscultation can be verified and permanent records can be made. Further studies of the sensitivity and specificity are warranted in view of the noninvasive nature of auscultation.

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