

Interstitial Lung Disease: Current Concepts of Pathogenesis, Staging and Therapy

RONALD G. CRYSTAL, M.D.

JAMES E. GADEK, M.D.

VICTOR J. FERRANS, M.D.

Bethesda, Maryland

JACK D. FULMER, M.D.

Birmingham, Alabama

BRUCE R. LINE, M.D.

GARY W. HUNNINGHAKE, M.D.

Bethesda, Maryland

The interstitial lung diseases are a group of chronic disorders that involve the entire lung parenchyma as well as the alveolar interstitium. Although fibrosis of the alveolar interstitium is a process common to all, the interstitial lung diseases are also distinguished by the presence of a chronic alveolitis that produces a derangement of the alveolar structures and ultimately leads to loss of functional gas exchange units ("end stage lung"). Studies of the cellular constituents of the alveolitis obtained by bronchoalveolar lavage strongly suggest that they may be categorized on the basis of the cell type relevant to the pathologic process involved. The central pathogenetic mechanisms operative in these diseases are those that relate to a maintenance of this alveolitis. The alveolitis in these disorders appears to be maintained by the local production of specific cell-derived chemotactic factors that recruit inflammatory cells from the blood into the alveolar interstitium with resultant disordering of the lung's connective tissue skeleton ("fibrosis") and injury of the parenchymal cell populations.

Although examination of tissue obtained by open lung biopsy provides a definitive means of assessing the alveolitis, this approach cannot be employed serially during the course of the disease. However, recovery of alveolar cells and relevant proteins by bronchoalveolar lavage and $^{67}\text{gallium}$ scintigraphy provide a safe, reliable means to monitor the activity and character of the alveolitis underlying these interstitial lung diseases. Analysis of lavage cells provides an accurate reflection of the inflammatory and immune cells populating the alveolar structure, and can provide the serial information necessary to determine the prognosis and to gauge the effects of therapy. $^{67}\text{Gallium}$ scintigraphy complements lavage cell analysis in that it is sensitive and specific for the alveolitis and may also be employed serially to assess disease activity. Although definitive therapy of the interstitial lung diseases awaits description of the precise etiologic factors involved, corticosteroid and cytotoxic therapy directed at the potentially reversible alveolitis promise more effective clinical control of these diseases when the results can be monitored by bronchoalveolar lavage and $^{67}\text{gallium}$ scanning in conjunction with conventional roentgenographic and physiologic studies.

From the Pulmonary Branch, and the Pathology Branch, National Heart, Lung and Blood Institute, Bethesda, Maryland; the Pulmonary Division, Department of Medicine, University of Alabama, Birmingham, Alabama; and the Clinical Center, Laboratory of Applied Studies, Division of Computer Research and Technology, National Institutes of Health, Bethesda, Maryland. Requests for reprints should be addressed to Dr. Ronald G. Crystal, Building 10, Room 6D06, National Institutes of Health, Bethesda, Maryland 20205. Manuscript accepted October 16, 1980.

The interstitial lung diseases are a group of heterogeneous, often fatal, disorders that diffusely involve the lung parenchyma [1-7]. The term "interstitial" was originally applied to these disorders because they are associated with thickening of the alveolar septum. In a sense, however, the term "interstitial" is a misnomer, since the interstitial lung

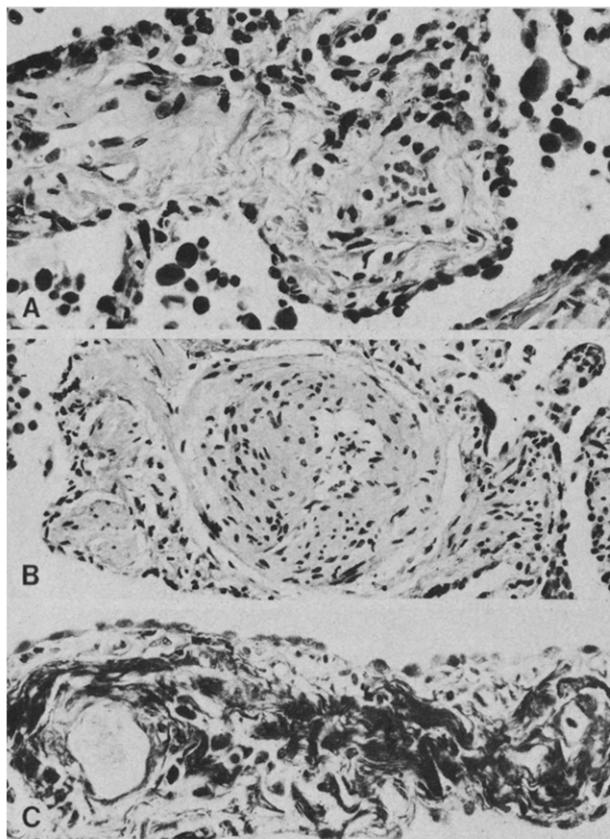


Figure 1. Idiopathic pulmonary fibrosis. **A**, high power view of the alveolar wall showing derangements of the interstitium and epithelial cells; the interstitium is thickened by fibrosis and the normal epithelium has been replaced by cuboidal cells. Hematoxylin and eosin stain, magnification $\times 250$. **B**, wall of small pulmonary artery in area of fibrotic interstitium is thickened by proliferation of smooth muscle cells. Hematoxylin and eosin stain, magnification $\times 160$. **C**, fibrotic alveolar septum contains numerous darkly stained collagen bundles. Masson trichrome stain; magnification $\times 250$, reduced by 39 percent.

disorders are not confined to the alveolar interstitium,* but generally involve alveolar epithelial and endothelial cells as well (**Figure 1A**). In addition, although these diseases primarily attack the alveolar structures, many also involve airways, arteries and veins (**Figure 1B**).

Although interstitial lung disease has diverse forms, one common denominator is the presence of fibrosis of

* Anatomically the "interstitium" is that part of the alveolar structures bounded by the alveolar epithelial and endothelial basement membranes [5]. The normal alveolar interstitium is composed of connective tissue components (collagen, elastic fibers, proteoglycans, and fibronectin [8-9], mesenchymal cells (fibroblasts, pericytes and rare smooth muscle cells) [10], and inflammatory and immune effector cells (monocytes/macrophages and lymphocytes [11]).

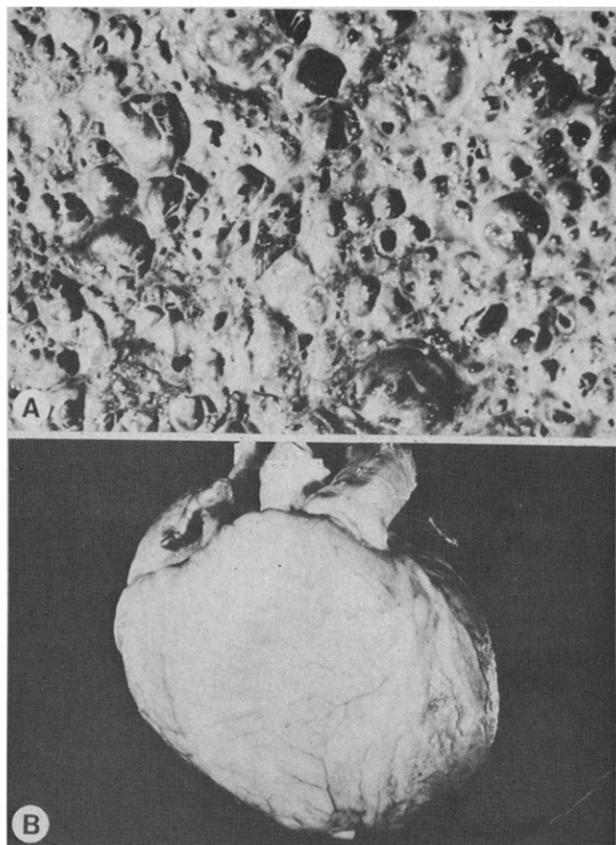


Figure 2. Idiopathic pulmonary fibrosis. **A**, photograph of the surface of lung from patient with idiopathic pulmonary fibrosis, showing multiple cystic areas and diffuse fibrosis. Histologic sections revealed "end-stage" lung. **B**, photograph of heart from patient with idiopathic pulmonary fibrosis, showing marked right ventricular enlargement (cor pulmonale).

the alveolar interstitium (**Figure 1C**). Thus, the terms "fibrotic lung disease" and "interstitial lung disease" are used interchangeably.

Once considered relatively rare, it is now known that interstitial lung disease is quite common. The 1972 Task Force Report on Lung Disease estimated that, outside of the infectious disorders, interstitial lung disease represents 15 percent of the diseases in all patients seen by pulmonary physicians in the United States [12]. Recent statistics bear this out; evaluation of inpatient records of 40 percent of all hospital cases in 1977 suggested that in the United States, 89,000 inpatients per year have chronic interstitial fibrosis [13].

A typical patient with interstitial lung disease presents with the insidious onset of breathlessness, occasionally associated with nonproductive cough [1,2,6,7]. On physical examination, the most common finding is bibasilar end-inspiratory dry rales [14], often associated with clubbing of the fingers and sometimes the toes [1,2,6,7]. Although there is a wide variation in the

TABLE I Interstitial Lung Diseases of Known Etiology*

| Occupational and Environmental Inhalants | |
|--|---|
| Inorganic dusts | Organic dusts cont'd |
| Silica (variants of silicon dioxide) | Chemical sources |
| Silicates | Synthetic-fiber lung |
| Asbestos (hydrated sodium, iron, calcium and magnesium silicates) | Bakelite worker's lung |
| Talc (hydrated magnesium silicates) | |
| Kaolin ("China clay," hydrated aluminum silicate) | |
| Sillimanite (anhydrous aluminum silicate) | |
| Diatomaceous earth ("Fuller's earth, aluminum silicate with iron and magnesium) | |
| Nepheline (hard rock containing mixed silicates) | |
| Mica (potassium and magnesium aluminum silicates) | |
| Aluminum | |
| Powdered aluminum | |
| Bauxite ("Shaver's disease," aluminum oxide) | |
| Antimony (oxides and alloys) | |
| Carbon (with or without silica) | |
| Coal dust | |
| Graphite | |
| Beryllium | |
| Mixed dusts (predominantly oxides of iron with silica, silicates, and other inorganic compounds) | |
| Hard metal dusts | |
| Titanium oxide | |
| Tungsten, titanium, hafnium, and niobium carbides | |
| Cadmium | |
| Organic dusts | |
| Living sources | |
| Farmer's lung | |
| Bagassosis | |
| Mushroom worker's lung | |
| Humidifier lung, air conditioner lung | |
| Maple bark stripper's lung | |
| Cheese worker's lung | |
| Malt worker's lung | |
| Sequoiosis | |
| Paprika splitter's lung | |
| Wheat weevil disease | |
| Suberosis | |
| Bird breeder's lung | |
| Chicken handler's disease | |
| Aspergillosis | |
| Pituitary snuff lung | |
| Turkey handler's lung | |
| Duck fever | |
| Wood-pulp worker's disease | |
| Sauna-taker's disease | |
| Detergent worker's lung | |
| Lycoperdonosis | |
| Wood-dust worker's disease | |
| Coffee worker's lung | |
| Furrier's lung | |
| New Guinea lung | |
| Coptic disease | |
| Japanese "summer type" | |
| | Drugs |
| | Chemotherapeutic agents |
| | Busulfan |
| | Bleomycin |
| | Cyclophosphamide |
| | Methotrexate |
| | Nitrosoureas (BCNU) |
| | Procarbazine |
| | Mitomycin |
| | Antibiotics |
| | Nitrofurantoin |
| | Sulfonamides |
| | Penicillin |
| | Others |
| | Diphenylhydantoin |
| | Drugs inducing lupus-like syndrome |
| | Gold salts |
| | Hexamethonium |
| | Mecamylamine |
| | Methysergide |
| | Pentolinium |
| | Propranolol |
| | Carbamazepine |
| | Poisons |
| | Paraquat |
| | Radiation |
| | External |
| | Inhaled |
| | Infectious agents |
| | Residue of active infection of any type |
| | Interstitial disease caused by disorders of organs other than lung |
| | Chronic pulmonary edema |
| | Chronic uremia |

* See [1] for details; new additions to the list of interstitial lung diseases of known etiology include Japanese "summer type" organic dust disease [17], mitomycin [18] and carbamazepine [19].

TABLE II Interstitial Lung Disease of Unknown Etiology*

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

* See [1] for details; new additions to the list of interstitial lung diseases of unknown etiology include Whipple's disease [20], Weber-Christian disease [21] and the Hermansky-Pudlak syndrome (a ceroid storage disorder associated with bleeding and albinism) [22].

roentgenographic appearance of these disorders, typically there is a diffuse reticulonodular infiltrate throughout the lung fields [1,15]. Functionally, on initial presentation, a typical patient will have mildly reduced lung volumes, reduced diffusing capacity, normal forced expiratory volume in 1 second/forced expiratory volume, mild resting hypoxemia, mild hyperventilation and a compensated respiratory alkalosis [1,2,6,7].

Untreated, most interstitial lung diseases are progressive and the patient's condition deteriorates as they irreversibly lose alveolar-capillary units. Of those in whom the disease progresses, the result is so-called "end-stage lung" in which there is almost complete loss of alveolar-capillary units and the lung takes on a cystic appearance interspersed with thick bands of fibrosis (**Figure 2A**) [16]. As the right side of the heart attempts to deal with the progressive loss of vascular bed, it hypertrophies in a vain attempt to maintain cardiac output and eventually fails with resulting cor pulmonale (**Figure 2B**). Of those patients with progression to end-stage lung, death is usually secondary to general respiratory insufficiency or decreased oxygen delivery to vital tissues such as heart and brain.

Faced with a patient with clinical, roentgenographic and physiologic findings compatible with interstitial lung disease, the physician must attempt to make a specific diagnosis. To do so, he should be aware of the more than 130 defined interstitial lung diseases. Conventionally, these disorders are grouped depending on whether the etiology is known or unknown (**Tables I and II**) [1]. In our present state of knowledge, the etiology can be identified in approximately 35 percent of all patients

[12]. Presumably, the remaining 65 percent are classified as having diseases of "unknown" etiology only because of our ignorance; eventually, the etiology of many of these disorders will be defined. That is not to say, however, that the interstitial lung diseases of unknown etiology are a loosely defined group of syndromes. Rather, most represent specific disorders that are identified by characteristic clinical, roentgenographic, physiologic, morphologic, scintigraphic and bronchoalveolar lavage features and thus are as much "specific diseases" as are atherosclerosis, diabetes or peptic ulcer disease.

MORPHOLOGY OF THE INTERSTITIAL LUNG DISEASES

Evaluation of lung biopsy specimens from patients with a variety of interstitial diseases reveals that, in general, all have some common histologic features [1,2-5,7,16,23,24]. The most important of these are (1) alveolitis; (2) derangement of the alveolar structures; and (3) "end-stage," i.e., destroyed areas. In order to develop a unifying concept of the pathogenesis of these disorders, it is important to consider each of these histologic features in detail.

The alveolitis of the interstitial lung disorders is defined as the chronic accumulation of inflammatory and immune effector cells within the alveolar structures. Normally, the inflammatory and immune effector cell populations of the lung parenchyma comprise less than 7 percent of the total cells present [25]; in the interstitial lung disorders there is a marked increase in the relative proportion of these effector cells compared to the actual

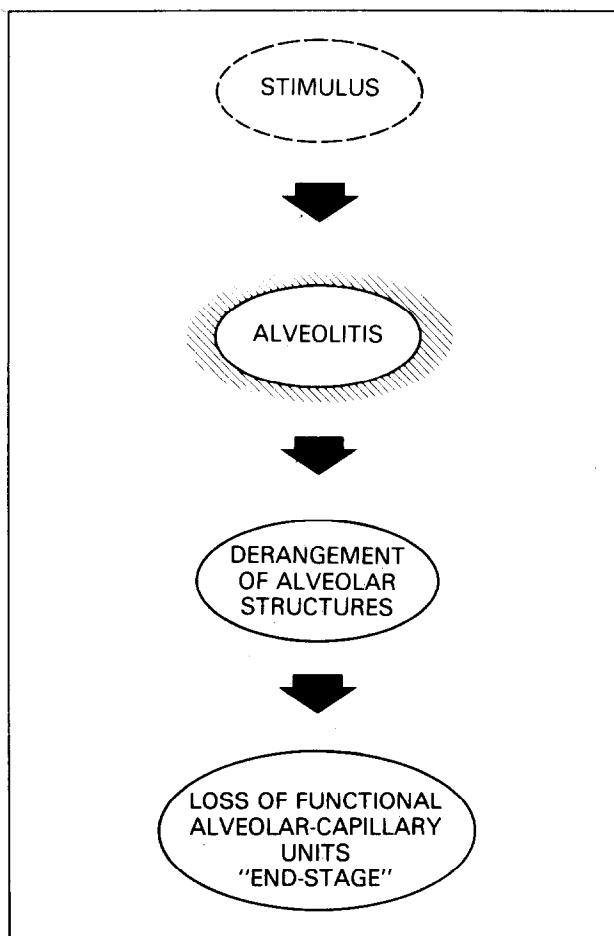


Figure 3. Current concepts of the pathogenesis of interstitial lung disease. Independent of whether the stimulus is known or unknown, the initial manifestation of these disorders is the alveolitis, an accumulation of inflammatory and immune effector cells within the alveolar structures. It is generally accepted that it is the alveolitis that causes derangement of alveolar structures and eventual loss of functional alveolar-capillary units, i.e., "end-stage lung."

cells comprising the parenchymal structure [1-5,7,16,23,24]. In addition, the alveolitis of these disorders is characterized by a shift in the relative proportions of those inflammatory and immune effector cells present. As we will see, it is this shift in the effector cell populations that is a key to the pathogenesis of these disorders.

The derangement of the alveolar structures seen in the interstitial lung diseases is defined as an alteration in the number, form, and location of the cellular and noncellular constituents of the normal alveolar structures [1,5,25]. In contrast to destructive lung disease, such as panacinar emphysema, the derangement of the alveolar structures in the interstitial lung disorders initially preserves the general form of the lung parenchyma. In some interstitial lung disorders such as idiopathic pulmonary fibrosis and asbestosis, this de-

rangement takes the form of changes in parenchymal cell populations together with interstitial fibrosis [1-5,7,23,24]. In other disorders, such as sarcoidosis and hypersensitivity pneumonitis, the derangement of alveolar structures is also characterized by the presence of granulomas, and collections of inflammatory and immune effector cells that distort the normal alveolar structures by their physical bulk [1-5,26-29].

When the derangement of the lung parenchyma is such that alveolar structures are no longer recognizable, the derangement is generally termed "end-stage" [16]. At this point, the alveolar structures are replaced by cystic spaces separated by thick bands of connective tissue interspersed with inflammatory and immune effector cells. Although these regions are well vascularized, they are not thought to be functional as gas exchange units.

PATHOGENESIS OF THE INTERSTITIAL LUNG DISEASES

The common histologic features of the interstitial diseases can be considered as stages in the pathogenesis of the interstitial lung disorders (**Figure 3**). Independent of whether the etiology is known or unknown, each of the interstitial disorders seems to follow the same general scheme of pathogenesis through stages of alveolitis, derangement of alveolar-capillary units and "end-stage."

The validity of considering the alveolitis as the predecessor of the derangement of the alveolar structures comes from several considerations: (1) biopsy of patients with early interstitial lung disease reveals alveolitis without derangement [1,3,4,7,23,24,26,28-33]; (2) in those cases in which serial histologic observations have been made, the alveolitis precedes the derangement [33-35]; (3) in experimental animal models of interstitial lung disease, the alveolitis precedes other abnormalities [36-42]; and, (4) most important, the cells comprising the alveolitis have a broad armamentarium of inflammatory and immune mediators that clearly have the potential to derange the alveolar structures (**Tables III and IV**). Thus, the alveolitis of the interstitial lung disorders is likely the controlling factor in the pathogenesis of the interstitial lung diseases; the rate, form and extent of the derangement caused by the alveolitis appear to be a function of the number, type and state of activation of the effector cells comprising it.

Reversibility of the interstitial lung disorders seems to be controlled by the relative permanence of the derangement caused by the alveolitis [5]. This permanence appears to be modulated, at least in part, by the relative integrity of the epithelial and endothelial basement membranes [43]. Current evidence suggests that, independent of the type of injury, the derangement of the alveolar structures can be restored to normal as long as the remaining epithelial and endothelial cells have the normal basement membrane scaffolding to direct the

TABLE III Alterations in Inflammatory and Immune Effector Cells Characteristic of the Alveolitis Associated with Some Interstitial Diseases*

| Inflammatory and Immune Effector Cell Type | Normal | Types of Alveolitis Observed in Interstitial Disorders | |
|--|-------------------------------|--|-----------------|
| | | Lymphocyte Type | Neutrophil Type |
| Total cells | 2.53 × 10 ⁹ /lung† | ↑ | ↑ |
| Relative proportions of each cell type | | | |
| Macrophages | 93 ± 3% | ↓ | ↓ |
| Lymphocytes | 7 ± 1% | ↑ | ↔ |
| T lymphocytes‡ | 73 ± 4% | ↑ | ↔ |
| Activated- | | | |
| T lymphocytes‡ | 6 ± 2% | ↑ | ↔ |
| B lymphocytes‡ | 8 ± 3% | ↔ | ↔ |
| Neutrophils | <1% | ↔ | ↑ |
| Eosinophils | <1% | ↔ | ± ↑ |
| Basophils | <1% | ↔ | ↔ |

* See [11] for a more detailed discussion and literature review.

† Total inflammatory and immune effector cells in the normal human lung parenchyma was estimated from the data of Barry et al. [25].

‡ Lymphocyte subpopulations are quantitated as percent of total lymphocytes.

placement of new parenchymal cells during the repair process. This concept helps to define the end-stage, i.e., that stage of injury at which the alveolar structures can no longer be restored to normal.

The Alveolitis of the Interstitial Lung Disorders. The end-stage appearance of the interstitial lung disorders is often similar from disease to disease, but the alveolitis stage is remarkably different; the disorders are distinguished by the types of inflammatory and immune effector cells that are present. To understand the significance of the number and types of cells comprising the alveolitis of these disorders, it is necessary to first consider the inflammatory and immune effector cells within the normal alveolar structures.

Normally, the inflammatory and immune effector cell populations of the lung parenchyma are dominated by the alveolar macrophage, a cell that generally comprises at least 90 percent of the effector cells present (Table III) [11,44]. Macrophages are found both on the alveolar epithelial surface and within the interstitium, but are relatively more abundant on the epithelial surface [45]. Alveolar macrophages are ultimately derived from blood monocytes [46], but can replicate *in situ* [47], likely from a reservoir of cells within the interstitium [48]. Although macrophages are generally easy to identify by light microscopy, some immature forms are difficult to distinguish from blood monocytes. For convenience, however, the term "macrophage" is generally used to refer to the spectrum of mature macrophages and their precursors within the alveolar structures. The resting alveolar macrophage appears to be a relatively innoc-

uous cell, with little effector function [11]. However, this cell is capable of interacting with a variety of inflammatory and immune stimuli, including immunoglobulins, complement, proteases, microorganisms and noninfectious particulates, all of which have been implicated as possible inciting agents for the interstitial lung disorders [11,44,49,50]. Once activated, the macrophage has a wide armamentarium of effector functions including regulation of lymphocyte responses, secretion of a variety of factors including enzymes and cellular cytotoxicity (Table IV).

After the macrophage, the lymphocyte is the next most populous effector cell of the lower respiratory tract. Normally comprising less than 10 percent of the inflammatory and immune effector cells present, lymphocytes tend to be more prevalent within the interstitium than on the epithelial surface [51]. In the normal subject, the lymphocyte subpopulations within the alveolar structures are almost identical to those found in

TABLE IV Effector Functions of Inflammatory and Immune Cells Comprising the Alveolitis of Some of the Interstitial Lung Disorders

| Cell Type | Effector Function |
|--------------|---|
| Macrophage | <p>Releases mediators of inflammation Superoxide radical [88], hydroxyl radical [89], complement components [90], prostaglandins [91], collagenase [92,93], elastase [94], neutral protease [93], plasminogen activator [95], β-glucuronidase [96], angiogenesis factor [97], fibroblast growth factor [98]</p> <p>Modulates lymphocyte function [99,100]</p> <p>Mediates antibody-dependent cellular cytotoxicity [44,101]</p> <p>Modulates inflammatory cell traffic Colony stimulating factor [102]</p> <p>Neutrophil chemotactic factor [49,76–81]</p> <p>Lymphocyte chemotactic factor [103]</p> |
| T lymphocyte | <p>Releases mediators of inflammatory cell function ("lymphokines") Macrophage migration inhibition factor [104]</p> <p>Leukocyte inhibitory factor [104]</p> <p>Monocyte chemotactic factor [105–107]</p> <p>Macrophage activating factor [108]</p> <p>Modulates B-lymphocyte function [109]</p> <p>Produces immunoglobulins [54–56]</p> |
| B lymphocyte | <p>Releases mediators of inflammation Superoxide radical [110], hydroxyl radical [111], myeloperoxidase [112], collagenase [113–115], elastase [116], cathepsins D and G [117], β-glucuronidase [118]</p> <p>Activates various humoral inflammatory pathways Complement system [119]</p> <p>Intrinsic coagulation pathway [120]</p> <p>Mediates cellular cytotoxicity [121]</p> |
| Neutrophil | |

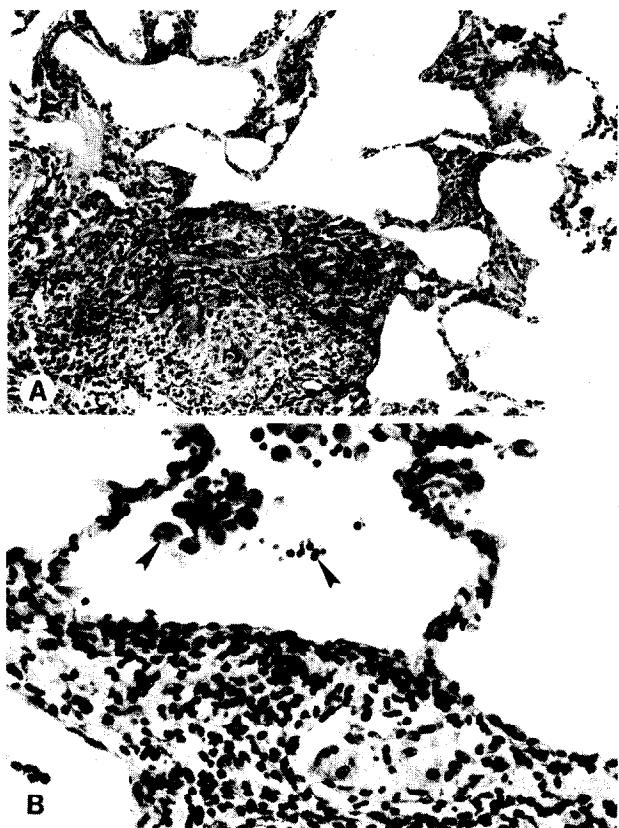


Figure 4. Pulmonary sarcoidosis. **A**, histologic section of lung from patient with pulmonary sarcoidosis shows areas of granuloma formation, with multinucleate giant cells, and areas of alveolitis (upper right) containing lymphocytes and monocytes/macrophages. Hematoxylin and eosin stain, magnification $\times 100$. **B**, high power view of the area of alveolitis. Although giant cells are seen within this area, this lesion is not organized like a granuloma and is characterized by large numbers of lymphocytes and monocytes/macrophages. Numerous lymphocytes and alveolar macrophages are seen within the alveolar lumen (arrowheads). Hematoxylin and eosin stain; magnification $\times 250$, reduced by 39 percent.

peripheral blood [11,51–53]. Approximately 73 percent are T lymphocytes, of which 6 percent are activated [53]. Activated T lymphocytes are of importance, as they secrete lymphokines (e.g., macrophage migration inhibition factor, leukocyte inhibitory factor, monocyte chemotactic factor) which regulate the traffic and function of other inflammatory and immune effector cells (Table IV). Eight percent are B lymphocytes; of these B lymphocytes, 0.1 to 0.3 percent are actively secreting immunoglobulin G (IgG), immunoglobulin A (IgA) or immunoglobulin M (IgM) [54–56]. The remaining lymphocytes do not have recognizable surface markers and are referred to as “null” cells [11,57].

In contrast to the complement of mononuclear cells resident within the alveolar structures, normal non-

smoking subjects have very few cells of the granulocytic series within their lung parenchyma (Table III). Smokers differ in that 2 to 3 percent of their total alveolar inflammatory and immune effector cells may be polymorphonuclear leukocytes, principally neutrophils [58,59]. The fact that polymorphonuclear leukocytes are rare in the alveolar structures is an important concept regarding the normal maintenance of lung homeostasis; these cells are capable of releasing a variety of mediators that have the potential to markedly derange the alveolar structures (Table IV). In this regard, the neutrophil is the best studied; it can release collagenase, elastase, neutral protease (cathepsin G), acid protease (cathepsin D), β -glucuronidase and various oxidants, all of which are hazardous to the cellular and noncellular constituents of the lung parenchyma.

As described previously, the alveolitis of the interstitial lung disorders is characterized by both an increase in the numbers of inflammatory and immune effector cells within the alveolar structures as well as by shifts in the relative proportions of these cells [7,11,53,60]. In order to simplify our discussion we will concentrate on two “types” of alveolitis that are commonly found in the interstitial lung disorders: the macrophage-lymphocyte type and the macrophage-lymphocyte-neutrophil type (Table III). The macrophage-lymphocyte type is characterized by relatively more lymphocytes than macrophages and is generally found in association with granulomas, e.g., sarcoidosis and hypersensitivity pneumonitis (Figure 4) [11,53,60]. For convenience, this type of alveolitis is termed a “lymphocyte alveolitis.” In contrast, the macrophage-lymphocyte-neutrophil type of alveolitis is dominated by the macrophage but is most remarkable for the chronic presence of neutrophils, e.g., idiopathic pulmonary fibrosis (Figure 5) [7,11,60]. Because the presence of neutrophils is so important to the pathogenesis of these disorders, this type of alveolitis is commonly called a “neutrophil alveolitis.”

Although the lymphocyte type of alveolitis is found in those disorders associated with granulomas, there is excellent evidence that the alveolitis precedes the granulomas and, as we will see, is likely responsible for granuloma formation (Figure 4) [26,29,30,61,62]. In both sarcoidosis and hypersensitivity pneumonitis, there is not only an increased proportion of lymphocytes within the alveolar structures, but there is also a shift in lymphocyte subpopulations toward increased numbers of T lymphocytes [53,60,63,64]. In addition, in the case of sarcoidosis, it is likely that these T lymphocytes are activated as determined by the observations that increased proportions of these cells have surface markers indicative of an activated state and are secreting lymphokines [53,62,65,66]. Both sarcoidosis and hypersensitivity pneumonitis are excellent examples of the fact that the peripheral blood cannot be relied upon to reflect ongoing inflammatory and immune processes within the alveolar structures: both diseases are associated with

increased proportions of T lymphocytes within the lung yet the proportion of T lymphocytes in the peripheral blood is either normal or decreased [53,60,67–69].

Conventional hematoxylin and eosin-stained sections of lungs obtained from patients with idiopathic pulmonary fibrosis often do not reveal the presence of neutrophils within the alveolar structures. However, when 0.5 µm toluidine blue-stained thin sections are examined, the neutrophils are easier to recognize and are observed to be a prominent component of the alveolitis of this disease (Figure 5A). When evaluated by electron microscopy, it is clear that these cells are intimately associated with parenchymal lung cells as well as interstitial connective tissue elements (Figure 5B). In contrast to the lymphocyte alveolitis of sarcoidosis and hypersensitivity pneumonitis, the proportion of T lymphocytes in idiopathic pulmonary fibrosis appears to be normal as is the fraction of T lymphocytes that is activated (Table III) [11,53,65]. B lymphocytes, however, may be turned-on; the proportion of immunoglobulin-secreting lymphocytes is markedly increased in the idiopathic pulmonary fibrosis lung compared to the lymphocytes found in normal lung [55]. Another characteristic feature of the alveolitis of idiopathic pulmonary fibrosis is the functional state of the macrophage; compared to normal persons, the macrophage of patients with idiopathic pulmonary fibrosis appears to have been stimulated by immune complexes [70–72]. Thus, the majority of the inflammatory and immune effector cells comprising the alveolitis of idiopathic pulmonary fibrosis are capable of deranging the alveolar structures: the macrophages are functionally altered, the B lymphocytes are actively secreting immunoglobulin, and neutrophils are present with their large stores of pre-formed mediators.

Maintenance of the Alveolitis of the Interstitial Lung Disorders. Alterations in the inflammatory and immune effector cells of the lower respiratory tract are not confined to the interstitial lung disorders; a classic example is the marked accumulation of neutrophils in association with pneumococcal pneumonia. However, the interstitial lung disorders are unique among lung diseases in that the alterations in the inflammatory and immune effector cells of the alveolar structures are chronic alterations. Although neutrophils accumulate for days in the bacterial pneumonias, the effector cell population of the lower respiratory tract soon returns to normal. By contrast, in diseases like idiopathic pulmonary fibrosis, the characteristic neutrophil alveolitis is present for years [7,60,73] and in sarcoidosis, the lymphocyte alveolitis persists for long periods [74]. The chronicity of the alveolitis is central to the current concepts of the pathogenesis of these diseases. In the acute lung disorders, the amount of inflammation may be the same, for a short period of time, as in the interstitial lung disorders, but apparently it is not present for a long enough period to significantly damage the alveolar

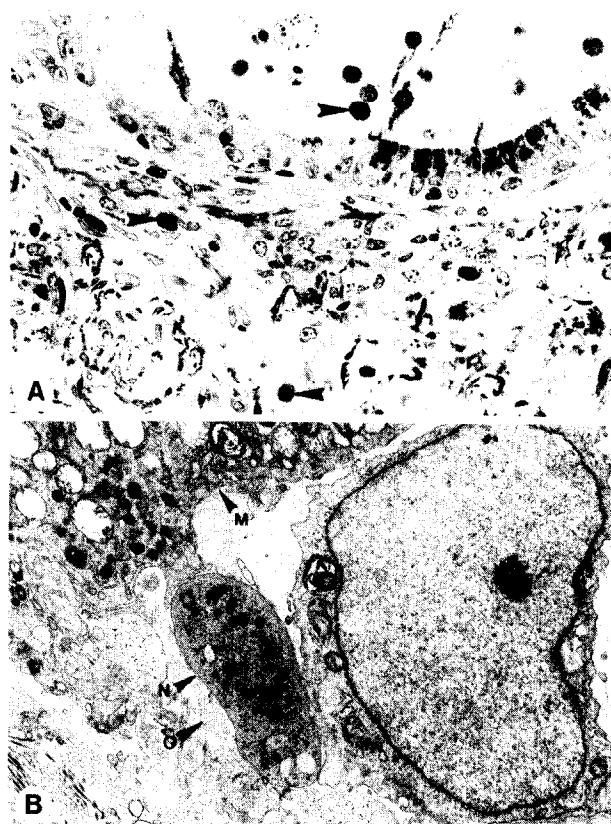


Figure 5. Idiopathic pulmonary fibrosis. **A**, half-micron-thick section of plastic-embedded tissue, showing neutrophils (arrowheads) within the interstitium and in the airspace. Alkaline toluidine blue stain, $\times 600$. **B**, electron micrograph showing part of a neutrophil in the interstitium (arrowheads) subjacent to alveolar epithelial cell. The alveolar lumen is at the far right. Note the loss of the basal lamina of the epithelial cell, the bundles of collagen (C) and a macrophage (M) adjacent to the neutrophil (N).

structures. In contrast, the chronic alveolitis of the interstitial lung disorders presents a continual burden of immunoglobulins, oxidants and/or proteolytic enzymes that overcomes the protective measures of the lower respiratory tract.

The fact that the alveolitis of the interstitial lung disorders is chronic suggests that mechanisms that maintain this alveolitis must be central to the pathogenesis of these disorders. For example, once present in tissues, the neutrophil has a half-life which is measured in hours [75]. Thus, to account for the persistence of neutrophils within the alveolar structures of the idiopathic pulmonary fibrosis lung, mechanisms must be operating to ensure that neutrophils constantly travel from blood into lung.

Recent studies have demonstrated that, when normal resident macrophages and/or lymphocytes are stimulated, they can significantly influence the traffic of circulating inflammatory cells into the lung parenchyma

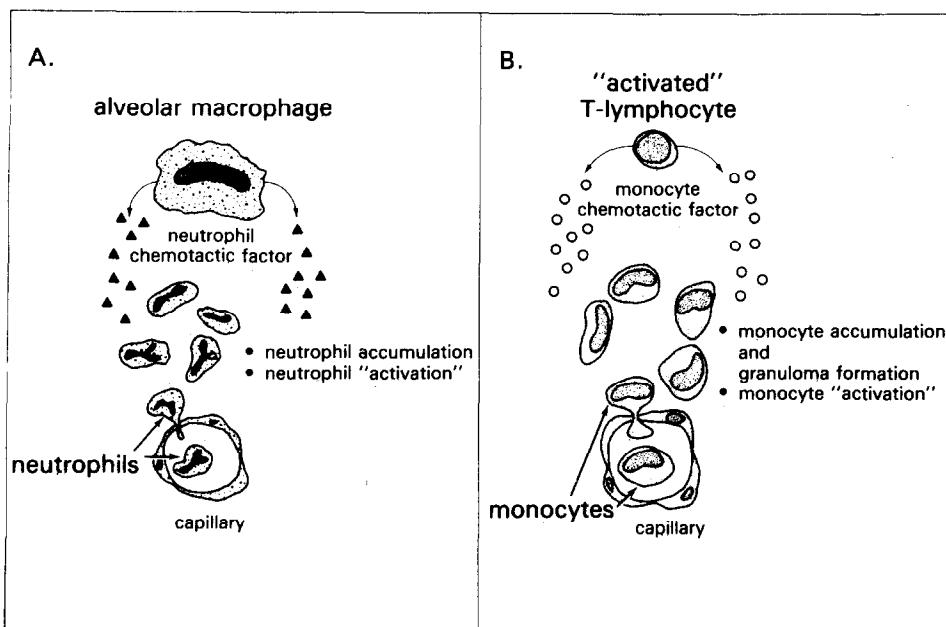


Figure 6. Mechanisms of maintenance of the alveolitis in some of the interstitial lung disorders. **A**, in those disorders associated with accumulation of neutrophils within the alveolar structures, the alveolar macrophage plays a key role by producing a chemotactic factor for neutrophils. This factor not only attracts neutrophils to the lower respiratory tract but also "activates" these cells. **B**, in those interstitial disorders associated with accumulation of monocytes and granulomas, it is likely that the activated T lymphocyte helps to maintain the alveolitis by releasing a chemotactic factor for monocytes. The "activation" of the monocytes is critical for subsequent granuloma formation.

[49,53,62,76-79]. It is probable, therefore, that the characteristics of the alveolitis of various interstitial diseases reflects the differential effect of the resident cell populations on the recruitment of specific populations of circulating leukocytes.

In idiopathic pulmonary fibrosis, the resident cell that regulates neutrophil traffic is likely the alveolar macrophage (Figure 6A) [70-72]. When subjected to appropriate stimuli, the alveolar macrophage releases a low molecular weight factor, at least partially lipid in nature, that is preferentially chemotactic for neutrophils [49,76-81]. In contrast to alveolar macrophages retrieved from normal subjects, alveolar macrophages obtained from patients with idiopathic pulmonary fibrosis are actively releasing this chemotactic factor [70-72]. Since IgG antigen-antibody complexes are among the agents that stimulate macrophages to release this neutrophil chemotactic factor [49,78], one possible mechanism for the initiation and maintenance of the alveolitis of idiopathic pulmonary fibrosis is the persistent presence of such immune complexes within the alveolar structures [70-72]. In this context, immune complexes have been found in the serum and lung of these patients, and immune complexes are present on their alveolar macrophages [70-72]. Although the antigen comprising the immune complexes is unknown, the fact that increased numbers of lung B lymphocytes from patients with idiopathic pulmonary fibrosis are producing immuno-

globulins [55] is consistent with the concept that the immune complexes are produced within the lung rather than external to the lung. In addition to attracting the circulating neutrophil to the alveolar structures, the alveolar macrophage derived chemotactic factor also "activates" these neutrophils so that the neutrophil releases its array of preformed mediators [82,83]. The relationship of this mechanism to the pathogenesis of idiopathic pulmonary fibrosis is supported by the observation that active collagenase (one of the preformed enzymes found in the neutrophil) can be found in the lower respiratory tract of 70 percent of the patients with this disease [84]. Since alterations in interstitial collagen play an important role in the pathophysiology of these patients [23], the presence of an active collagenase in the alveolar structures may be a critical factor in the pathogenesis of this disease. In addition, the activated macrophage of the idiopathic pulmonary fibrosis lung can stimulate the neutrophil to destroy parenchymal cells in the lung [85], further contributing to the derangement of alveolar structures that is characteristic of this disease.

Preliminary evidence suggests that there are important parallels between the pathogenic mechanisms operative in asbestosis and those outlined for idiopathic pulmonary fibrosis [86,87]. Bignon et al. [86] have demonstrated that, like idiopathic pulmonary fibrosis, the alveolitis of asbestosis is of the neutrophil type. Since

Schoenberger et al. [88] have shown that the ingestion of asbestos particulates stimulates the alveolar macrophage to release neutrophil chemotactic factor, the pathogenesis of asbestosis may be similar to idiopathic pulmonary fibrosis even though the initiating stimuli are quite different.

In contrast to the chronic neutrophil alveolitis associated with idiopathic pulmonary fibrosis and asbestosis, the pathogenetic mechanisms operative in sarcoidosis and chronic hypersensitivity pneumonitis are those which control the initiation and propagation of the intense mononuclear infiltrate and contribute to the formation of noncaseating granulomas within the alveolar structures. In pulmonary sarcoidosis, recent studies have demonstrated that it is the T lymphocyte [53,62], rather than the alveolar macrophage, which exerts the critical influence on inflammatory cell traffic within the alveolar structures (**Figure 6B**). These T-lymphocytes, when recovered from sarcoid lung, have been shown to release a soluble chemotactic factor preferentially directed at the circulating monocyte [62]. Resident alveolar macrophages may also play an accessory role in modulating the migration of blood monocytes to the lung since it is likely that the presence of these cells is required for optimal activation of lung T lymphocytes. This mechanism is likely important to the accumulation of mononuclear phagocytes within the pulmonary interstitium and may also contribute to the formation of granulomas within the alveolar structures. In addition to destroying the alveolar structures by their bulk, these granulomas may subserve a pathogenetic role in pulmonary sarcoidosis analogous to the role of the neutrophil in idiopathic pulmonary fibrosis. If the granulomas of the sarcoid lung have functional characteristics similar to experimentally-induced granulomas [61], the cells comprising the granulomas likely provide a source of mediators that injure parenchymal cells and interstitial connective tissue.

Pathophysiologic mechanisms similar to those outlined for sarcoidosis may also be operative in the alveolitis of chronic hypersensitivity pneumonitis. In this group of diseases, the inhalation of a complex, proteinaceous antigen is associated with the localization of T lymphocytes within the alveolar structures [39,60]. Although the precise events linking these phenomena remain undefined, these lymphocytes have been shown to release antigen-specific lymphokines that have the potential to regulate the traffic of mononuclear phagocytes within the alveolar structures [66], thus contributing to the formation of the granuloma that is characteristic of this disease. As in the case of pulmonary sarcoidosis, the interstitial granulomas likely provide a source of mediators capable of inducing the parenchymal derangement observed in the disease.

The mechanisms just outlined are not meant to be extended to all the interstitial lung disorders. However, it is clear from these observations, that the numbers, type

and state of activation of the inflammatory and immune effector cells within the alveolar structures can have a major influence on the structure, and hence function, of the lower respiratory tract. Although the precise initiating mechanisms are unknown in most of the interstitial lung disorders, it is likely that the normal effector cells present within the alveolar structures play a critical early role in propagating the alveolitis of the disease by producing chemotactic factors that regulate the traffic of blood inflammatory cells into the parenchyma of the lung. Once there, these inflammatory cells define the alveolitis that is characteristic of each disease and likely produce the mediators that effect the derangement, and eventual destruction, of the alveolar structures (Table IV [89-121]).

CLINICAL EVALUATION OF THE INTERSTITIAL DISORDERS

If the earliest manifestation of each interstitial disorder is a chronic inflammatory process within the alveolar structures, from the clinician's viewpoint, evaluation of the alveolitis is of critical importance. Since it is the chronic alveolitis that effects disordering of the alveolar structures, decisions as to prognosis and therapy can only be made with knowledge as to the character and intensity of the alveolitis. For the optimal management of these patients, therefore, it is necessary to have methods available that can be used to repeatedly assess inflammation within the alveolar structures.

Traditionally, four methods have been used to serve this purpose: lung biopsy, blood studies, chest roentgenograms and pulmonary function studies. More recently, two additional methods have become available: scintigraphic scanning with gallium-67 citrate and fiberoptic bronchoscopy with bronchoalveolar lavage.

The Use of the Lung Biopsy in Staging Alveolitis. The open lung biopsy is presently the best method available to initially stage the alveolitis of the interstitial disorders [1,122-125]. Since these diseases are generally diffuse throughout all lobes, histologic evaluation of a 2 by 2 cm² section of lung from any lobe usually gives a broad overview of the general type and intensity of the alveolitis of the disease. Unfortunately, however, because of discomfort, risk and cost, the open biopsy is usually used only once in the patient's course, and thus is not useful as a means to sequentially assess the alveolitis and follow its response to therapy.

In recent years, there has been increasing interest in substituting the transbronchial biopsy for the open biopsy in the evaluation of the interstitial disorders [126-133]. There is no question, however, that the open biopsy is superior to the transbronchial biopsy as a means for staging the alveolitis. Although the interstitial diseases affect all lobes, they can be very heterogeneous at the 2 to 4 mm level (**Figure 7**). Since this is approximately the size of tissue obtained with transbronchial forceps (usually 1 by 2 mm), biopsy specimens obtained



Figure 7. Pulmonary sarcoidosis. Low magnification of open lung biopsy specimen from patient with pulmonary sarcoidosis. There is considerable heterogeneity in the tissue, with discrete areas of granuloma formation, alveolitis and normal lung. It is easy to visualize how a biopsy specimen obtained by the transbronchial method might not be representative of the over-all intensity of the alveolitis. Hematoxylin and eosin stain; magnification X12, reduced by 40 percent.

by the transbronchial method often are not representative of the extent or intensity of the alveolitis present. In comparison, this microheterogeneity of the alveolitis at the 2 to 4 mm level tends to be less important if considered at the 1 to 2 cm level, i.e., with a section the size obtained by open biopsy, the observer can appreciate the over-all alveolitis of the disease. In addition, there is clear evidence that cigarette smokers can have localized collections of inflammatory and immune effector cells within the alveolar structures [134,135]. Over-all, such inflammation is different in extent and character than that associated with the interstitial disorders. However, with only small fragments of lung to visualize, the clinician relying on the transbronchial biopsy may get a false impression of the type and intensity of the alveolitis present.

The Use of Blood Studies in Staging Alveolitis. A number of blood studies have been recommended as "monitors" of the alveolitis of the interstitial disorders

[1,7,72,136-149]. It is apparent, however, that inflammatory and immune processes within the alveolar structures can behave quite independently of the rest of the body, and thus chronic lung inflammation is not necessarily reflected systemically [1,7,11,53,60]. Thus, although many patients with interstitial lung disorders will have an increased sedimentation rate or elevated immunoglobulin levels, there is little evidence that these values correlate closely with the activity of the lung disease itself [7,55]. Although parameters such as circulating immune complexes will roughly correlate with disease activity in idiopathic pulmonary fibrosis [72], and sarcoidosis [146-149], recent evidence suggests that such immune complexes may be "spillover" from immune complexes formed within the lung [55,70,71] and, thus, may not be as sensitive a monitor of the disease as direct assessment of the lung itself. Likewise, even though significant proportions of patients with "active" sarcoidosis have elevated serum levels of angiotensin converting enzyme [136-149], no study has correlated elevated serum angiotensin converting enzyme levels with a direct assessment of the alveolitis of this disorder.

The Use of the Chest Film in Staging the Alveolitis. Evaluation of serial chest roentgenograms taken over the course of an interstitial lung disease suggests a general pattern of evolution [7]. The earliest manifestation is thought to be a ground-glass pattern; as the disease progresses, that evolves into a nodular, reticular or reticulonodular pattern. This gradually changes into a coarser pattern with cystic areas, and finally, a honeycomb appearance [7]. In some of the interstitial diseases, however, a ground-glass pattern is not seen, and the earliest roentgenographic pattern is that of a reticular, nodular or reticulonodular pattern [150-153].

It is attractive to hypothesize that there would be a reasonable correlation between a ground-glass pattern and the alveolitis of interstitial disease, and the nodular, reticular or reticulonodular patterns and alveolar derangement, and roentgenographic-morphologic correlative studies of the interstitial diseases have been performed. Unfortunately, current data indicate that, in general, the chest roentgenogram is neither a sensitive nor a specific monitor of the alveolitis of these diseases.

Although the exact frequency of normal chest roentgenograms among patients with various types of interstitial lung disease is not known, up to 30 percent of the patients with biopsy-proved disease have chest films that show no abnormalities [154].

Additionally, in a review of over 1,200 patients with interstitial lung disease, of whom 490 had a lung biopsy, Carrington and Gaensler [155] showed that the severity of the roentgenographic infiltration correlated poorly with the morphologic estimate of the severity of the disease. Other studies of the interstitial diseases have come to the same conclusion. Although the morphology

of advanced idiopathic pulmonary fibrosis* correlates somewhat with the chest film, early to mid-stage idiopathic pulmonary fibrosis correlates poorly [156]. In a comparative study of lung morphology and the chest roentgenogram of 49 patients with sarcoidosis, Carrington et al. [31] found no correlation between the roentgenographic estimate and a semiquantitative estimate of the severity of the alveolitis. Although fewer patients were studied, these investigators also found no correlation between these parameters among patients with berylliosis or hypersensitivity pneumonitis [31]. Likewise, in inorganic dust disease, there is no correlation between the roentgenographic patterns and the over-all histologic estimates of the disease [157]. In addition to being nonspecific for the presence and the severity of interstitial disease, there is so much interobserver variability in reading chest roentgenograms in the interstitial disorders [158] that the chest film has little value in staging patients with these diseases.

Coarsely reticular, cystic and honeycomb patterns are generally associated with end-stage disease [7,159,160]. However, although most often this pattern does indicate advanced alveolar derangement and fibrosis, it may mask areas of significant alveolitis and normal parenchyma; histologic evaluation of lung biopsy specimens from patients with a honeycomb pattern often show areas of near normal to minimally deranged alveoli with alveolitis [16]. Thus, the presence of a honeycomb pattern may not be specific for the absence of concomitant, potentially reversible, alveolitis.

The Use of Physiologic Tests to Stage the Alveolitis. The classic physiologic findings in the interstitial lung disorders include a reduction in lung volumes (vital capacity; total lung capacity), a reduction in carbon monoxide diffusing capacity (DL_{CO}), normal airways mechanics and hypoxemia that worsens with exercise [1]. In addition, a number of other sophisticated functional tests of airways, pulmonary circulation, volume-pressure relationships and ventilation-perfusion relationships have been utilized to evaluate these patients.

Although it seems reasonable to assume that tests which assess the integrity and function of alveolar structures would be sensitive to the accumulation of inflammatory and immune effector cells, the available data are quite variable and seem to depend on the physiologic tests used.

Studies in early idiopathic pulmonary fibrosis and sarcoidosis indicate that lung volumes can be insensitive to the disease process. Of 40 patients with early idiopathic pulmonary fibrosis, the average vital capacity was 93 percent of the predicted value [161]. Similarly in a

study of sarcoidosis, only 20 percent of the patients with stage II disease had an abnormal vital capacity [162]. In contrast to lung volumes, however, DL_{CO} and gas exchange studies appear to be more sensitive detectors of alveolitis in both idiopathic pulmonary fibrosis and sarcoidosis [162]. In idiopathic pulmonary fibrosis, gas exchange studies are more sensitive to the presence of alveolitis than diffusing capacity [163].

Although some physiologic tests are sensitive to the accumulation of inflammatory and immune effector cells in the alveolar structures, the evidence is overwhelming that they are not specific for the alveolitis. The reasons for this are undoubtedly complex but are likely related to the fact that most tests primarily detect structural derangement rather than the alveolitis which may also modulate these tests to some degree.

In a study of over 400 patients with a variety of interstitial lung disorders, Gaensler et al. [164] used an "over-all histologic index" (which included alveolitis as one parameter) to evaluate specificity of various functional tests for the extent of parenchymal involvement. There were rough correlates between functional impairment and this histologic index, but there was little specificity. For example, an alveolar-arterial difference in oxygen tension ($A-aDO_2$) of 25 mm Hg was found in patients with nearly all degrees of histologic severity. In a similar study of 25 patients with different interstitial lung disorders, Green et al. [165] came to the same conclusion, i.e., functional changes do not agree closely with interstitial inflammatory cell infiltration. Thus, for interstitial disease in general, there is tremendous overlap in the significance of an abnormal functional finding relative to the actual amount of disease.

Even when the interstitial lung disorders are examined as individual disorders, there is still little evidence that functional tests give specific information concerning the extent of the inflammatory process [31,153]. In an attempt to tighten the association between functional testing and the alveolitis, Carrington et al. [31] used an index of functional impairment which includes lung volumes, diffusing capacity, gas exchange data and subjective parameters. However, although the over-all index gave a better correlation of the alveolitis than did the individual parameters, there was still a wide variation in the assessment of the inflammation of sarcoidosis. For example, moderate functional impairment was associated with patients who had mild cellularity as well as those with the most severe cellularity.

In idiopathic pulmonary fibrosis, it is clear that the abnormalities detected by most physiologic parameters bear little relationship to the alveolitis of the disease [156,165].

The Use of Gallium-67 Scanning in Staging Alveolitis. Gallium-67 is a cyclotron-produced radionuclide with a half-life of 78 hours. In the early 1970s, gallium-67 localization was observed in sites of acute and chronic inflammation [166-169]; since that time gallium-67 has

* Some investigators use the term "desquamative interstitial pneumonitis" (DIP) to refer to early idiopathic pulmonary fibrosis and the term "usual interstitial pneumonitis" (UIP) to refer to late idiopathic pulmonary fibrosis [1].

been widely used to detect abdominal abscesses and to evaluate sources of occult fever. Gallium-67 does not localize in normal lung tissue (**Figure 8A**). Thus, it has been possible to utilize gallium-67 scanning to detect and quantify the chronic alveolitis of many interstitial lung diseases.

Abnormal gallium uptake in the lung is found in a variety of pulmonary disorders with different pathogenesis including bleomycin toxicity [170], asbestos [169], silicosis [167–169], systemic lupus erythematosus [171], sarcoidosis [166–168,171], idiopathic pulmonary fibrosis [172], Wegener's granulomatosis [172], histiocytosis X [173], and a variety of infectious and neoplastic disorders of the lung [167,168]. Thus, by itself, a positive gallium scan of the lung is not diagnostic for any particular disease entity. Most categories of interstitial lung disease have been associated with positive gallium scans. In some of these disorders, e.g., idiopathic pulmonary fibrosis and sarcoidosis, positive gallium scans are the rule. In other diseases, such as histiocytosis X, pulmonary uptake of gallium-67 is only occasionally observed. The reason for this wide spectrum in the sensitivity of the gallium scan is not entirely clear, but it is likely associated with the type, intensity and duration of the alveolitis of each disease.

The most common pattern observed in gallium scans of patients with interstitial lung disease is diffuse, but mixed diffuse and focal patterns are occasionally seen. For example, a patient with Wegener's granulomatosis shows a focal uptake in the upper lobe of the left lung and a diffuse accumulation in the lower zone of the right lung (**Figure 8B**). A patient with silicosis (**Figure 8C**) shows an example of a mixed pattern with medium intensity, diffuse uptake in the lower lobes and more focal uptake in the lateral chest fields. In contrast, a diffuse pattern is seen in a posterior gallium-67 scan of a patient with bleomycin toxicity (**Figure 8D**). High intensity uptake is present in the mid and lower lung zones with slightly less intense uptake near the apices.

Since an abnormal gallium-67 scan of a patient with interstitial lung disease likely results from the alveolitis of the disease, it is natural to consider the use of the gallium scan as a means to assess the intensity of this alveolitis. With a suitable means of quantifying the pulmonary uptake of gallium-67, the scan could provide a noninvasive means of following the course of the alveolitis and its response to therapy. Unfortunately, the usual interpretations of gallium-67 scans are qualitative and, thus, not very useful for assessing the degree of alveolitis or for making serial comparisons of the status of the chronic inflammation.

To circumvent this problem, an estimate (called the “⁶⁷Ga-index”) can be made of the degree of gallium-67 uptake by the lung. The ⁶⁷Ga-index is a semiquantitative measure which minimizes the effects of body morphology, imaging technique and interpretation subjectivity [172]. The posterior gallium-67 scans are used to determine the ⁶⁷Ga-index because they are less sensitive

to differences in patient size, sex and body habitus than anterior scans. To calculate the ⁶⁷Ga-index from a gallium-67 scan, each region of the lung showing increased ⁶⁷Ga accumulation is characterized by its image area and intensity.* The uptake area is estimated as a percentage of the total lung area; this adjusts for differences in image size between patient studies. The highest possible ⁶⁷Ga-index is 400 U; gallium lung scans are considered “positive” if they are found to have an uptake equivalent to more than 50 ⁶⁷Ga-index units.

The widest experience in the use of ⁶⁷Ga-index has been in patients with sarcoidosis and idiopathic pulmonary fibrosis (**Figures 8E and 8F**). Nearly two thirds of the untreated patients with sarcoidosis have gallium scans with gallium-67 uptake greater than 50 ⁶⁷Ga-index units. In comparison, scans of patients with idiopathic pulmonary fibrosis indicate that in 70 percent gallium-67 uptake is greater than 50 U. Gallium-67 scans in patients with idiopathic pulmonary fibrosis show two main differences from studies in patients with sarcoidosis. First, nodal uptake is never seen in scans of patients with idiopathic pulmonary fibrosis, but it is common in patients with sarcoidosis. Second, the gallium-67 uptake of patients with idiopathic pulmonary fibrosis tends to be less intense on the average than the uptake in patients with sarcoidosis [172,173].

There is increasing evidence that the gallium-67 scan is sensitive to, and specific for, the alveolitis of the interstitial disorders. For example, in some people in whom interstitial disease develops secondary to bleomycin administration, the gallium scan has been noted to be positive before any abnormality could be detected on the chest film [170]. When the administration of bleomycin was discontinued, the gallium scan returned to normal before the roentgenogram. In addition to such case reports, there are direct correlative studies demonstrating the association between pulmonary gallium-67 uptake and the degree of alveolitis. Most of this information concerns sarcoidosis and idiopathic pulmonary fibrosis. However, in both sarcoidosis and idiopathic pulmonary fibrosis, there is a strong correlation between the magnitude of the ⁶⁷Ga-index and the intensity of the alveolitis, despite the fact that the type of alveolitis in the two disorders is markedly different [172].

In sarcoidosis, there is significant association of gallium uptake and the accumulation of T lymphocytes within the alveolar structures [172]. Since lymphocytes, and more specifically T lymphocytes, are important in the alveolitis of sarcoidosis, this finding strongly suggests that gallium uptake reflects the degree of alveolitis in this disease. Consistent with this concept, Merz et al. [174] have shown that activated T lymphocytes accu-

* The ⁶⁷Ga-index estimates the “equivalent tracer volume” of gallium-67 from the area and intensity (concentration X depth) of each uptake [172].

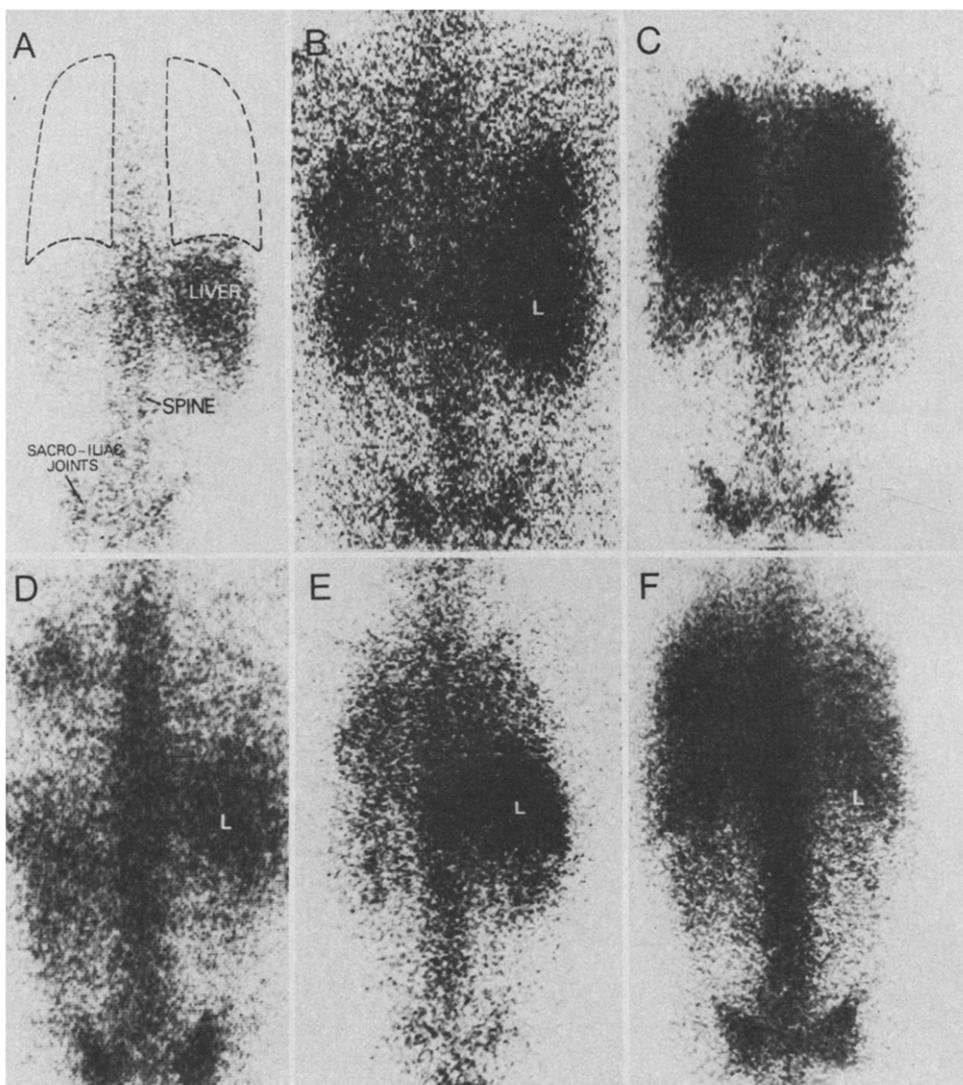


Figure 8. Posterior thorax and abdominal gallium-67 rectilinear scans from a normal patient and five patients with interstitial lung disease. **A**, normal person showing physiologic accumulation of gallium-67 in spine, pelvis, liver (L) and spleen. Low intensity uptake in lower lung fields is associated with rib localization. **B**, gallium-67 scan of uptake in 45 year old white man with silicosis. Diffuse uptake in the lower part of the lung is associated with more intense accumulations in lateral basal lung regions (^{67}Ga -index = 135 U). **C**, diffuse, high intensity lung uptake in 56 year old white woman with bleomycin lung toxicity. Pulmonary localization is more intense than hepatic uptake (^{67}Ga -index = 360 U). **D**, thirty-five year old white man with Wegener's granulomatosis showing focal uptake in the upper lobe of the left lung and diffuse uptake in the lower lobe of the right lung (^{67}Ga -index = 55 U). Focal uptake corresponds to pulmonary infiltrate with cavitation on the chest roentgenogram. Two older cavities in right lung did not localize gallium-67. **E**, gallium-67 scan of a 55 year old white woman with idiopathic pulmonary fibrosis. Diffuse uptake of moderate intensity in the mid and lower lung zone with no focal prominence (^{67}Ga -index = 155 U). **F**, diffuse gallium-67 uptake with prominence of right mid lung in 28 year old black man with sarcoidosis (^{67}Ga -index = 220).

mulate greater quantities of gallium-67 than do normal lymphocytes. Further evidence in favor of the usefulness of gallium-67 scanning in assessing the activity of the inflammatory process in sarcoidosis is provided by the studies of Niden et al. [171] who noted good agreement between a qualitative assessment of scan uptake and the presence of active inflammation in lung biopsy tissue. Thus, although the mechanism by which the activated T lymphocytes (and possibly other cells com-

prising the alveolitis) in the sarcoid lung take up gallium is not known, the correlative data suggest that patients with low ^{67}Ga -indices are those with relatively little alveolitis whereas those with high ^{67}Ga -indices have significant degrees of parenchymal inflammation.

In contrast to the T lymphocyte alveolitis of sarcoidosis, the alveolitis of idiopathic pulmonary fibrosis is associated with a chronic accumulation of neutrophils within the alveolar structures. It is known that neutro-

phils are involved in the localization of gallium-67 in sites of acute inflammation [7,172], and thus it is reasonable to assume that the uptake of gallium in the lungs of patients with idiopathic pulmonary fibrosis is associated with the neutrophil alveolitis of this disease. Correlative studies suggest this is the case; there is a significant association between the level of the ^{67}Ga -index and the degree of alveolitis of patients with idiopathic pulmonary fibrosis, particularly with the proportion of neutrophils present [172].

In summary, although not diagnostically specific, the gallium-67 scan can be used to characterize the severity and anatomic location of regions of alveolitis and hence is capable of giving a longitudinal assessment of the degree of inflammation in the parenchyma as a whole. Gallium-67 scanning is widely available, noninvasive and involves low radiation exposures; it should thus prove useful in assessing the alveolitis of the interstitial diseases and the efficacy of therapy protocols.

The Use of Bronchoalveolar Lavage in Staging Alveolitis. One means to characterize and quantitate the alveolitis of the interstitial disorders is to recover the inflammatory and immune effector cells and related proteins which comprise the alveolitis by lavaging the lower respiratory tract of these patients through the fiberoptic bronchoscope [11,44,53,58,60,69,175,176]. The validity of this procedure rests on the concept that the cells and proteins derived from the alveolar epithelial surface are similar in type, proportion and function to the effector components within the alveolar interstitium. In this regard, comparisons of inflammatory and immune effector cells in lavage fluid and from open lung biopsies of patients with interstitial lung diseases have demonstrated that, at least for these disorders, lavage fluid cells accurately reflect the effector cells present within the alveolar structures [65,177]. Since bronchoalveolar lavage can be performed multiple times during the course of a patient's disease, this technique is a valuable clinical tool which permits specific, quantitative assessment of the ongoing alveolitis.

Technique of Bronchoalveolar Lavage. Bronchoalveolar lavage of normal volunteer subjects and those with interstitial lung disease is associated with minimal discomfort, little morbidity and no mortality [11,44,53,58,60,69,175,176]. In terms of patient selection, it is important to recognize that in the lavage process, the fluid must pass by medium and small bronchi en route to, and returning from, the alveoli [11]. It is imperative, therefore, that there is no evidence of inflammatory airway disease. If airway disease is present, it is impossible to determine the relative contribution of airways and alveoli to the recovered cells and proteins. In addition, we do not lavage patients with a forced expiratory volume in 1 second of less than 0.8 liters; even though only a small volume of fluid is left in the lung after the lavage procedure, this criterion insures patient safety.

The method we utilize is essentially that devised by Reynolds et al. [11,58].

For the typical patient with interstitial disease, the recovery of instilled fluid is approximately 50 percent; usually this fluid contains approximately 10^7 cells and 1 to 10 mg protein [11,44,53,58,60,65,69,175,178]. The recoveries are less in those patients who have lost airway support from alveolar destruction (e.g., histiocytosis X, neurofibromatosis, lymphangioleiomyomatosis); in these cases the airways tend to collapse when the suction is applied.

Because the recovered fluid contains a variable mixture of alveolar epithelial fluid and the saline solution used for lavage, it is difficult to make use of the absolute amounts of recovered cells and proteins for quantitative purposes [11,44,53,58,60,69,175]. For example, the fact that lavage fluid from patient A contains 8×10^6 cells whereas fluid from patient B contains 12×10^6 cells has little significance; it may simply reflect "stickiness" of patient A's cells to the alveolar epithelial surface. For quantitative purposes, therefore, lavage cellular analyses are usually discussed in proportional terms (i.e., percent neutrophils) and lavage protein analyses are expressed relative to albumin (i.e., milligrams of a specific protein detected in lavage fluid per milligram albumin in lavage fluid). These concepts are detailed in several recent studies [11,58,60,69,175,176].

Bronchoalveolar Lavage of Normal Individuals. The significance of the inflammatory and immune effector cells and proteins recovered by lavage of patients with interstitial disease [1,7,11,20,23,24,31,49,53,58,60,65,69,175–183] can only be recognized by comparison with the cells and proteins recovered by lavage of the normal lung. Most of the cells found in bronchoalveolar lavage of normal people are alveolar macrophages; however, a small number of lymphocytes are also present (Figure 9A). In nonsmoking normal people, $93 \pm 5^*$ percent of the cells are alveolar macrophages and 7 ± 1 percent are lymphocytes [53]. Of the lymphocytes that are normally present, 73 ± 4 percent are T lymphocytes and 8 ± 3 percent are B lymphocytes [53]; 19 ± 5 percent of the cells do not have surface markers identifying them as either T or B lymphocytes and thus are designated as "null" cells [11,44,53]. Less than 1 percent of the cells present in lavage fluid of normal subjects are neutrophils, eosinophils or basophils. In people who smoke cigarettes, the percentages of each of these cell types are similar to those in nonsmokers except that small numbers of neutrophils are also present [11,184].

Lavage fluid of normal persons also contains various proteins which are potentially important components of various inflammatory and immune processes in the lung [5,11,23,58,60,69,175,176]. Of the major immuno-

* All data are presented as mean \pm standard error of the mean.

globulins, IgC [58,175,180,181,185–188], IgA [58,175,180,186,187,189] and IgE [60] are routinely present; IgM is detected in less than 5 percent of the normal subjects [58,175,176,180,181,186,187]. The complement proteins C4 and C6 [58] and α 1-antiproteinase [190,191] are also present in normal alveolar epithelial fluid; however, α 2-macroglobulin is usually not present [58,187,191]. Collagenase and elastase, the major proteases capable of disrupting the architecture of the lung are not found in normal lung [84,192].

Characterization of Interstitial Lung Disease by Bronchoalveolar Lavage. As characterized by bronchoalveolar lavage, the cell populations of several of the interstitial disorders varies from studies of normal subjects and there are differences between the individual clinical entities (**Table V**). The alveolitis of idiopathic pulmonary fibrosis is characterized by the presence of neutrophils (**Figure 9B**) [11,53,60,65,69,177] but with normal proportions of lymphocytes and lymphocyte subpopulations in lavage fluid [11,53,65,177]. Small numbers of neutrophils are also components of the alveolitis of patients with interstitial lung disease associated with the collagen-vascular disorders and histiocytosis X [11,60,69]. The alveolitis of patients with histiocytosis X is further characterized by the presence of so-called "Langerhans' cells" (**Figure 9C**); these cells, when visualized by transmission electron microscopy, have characteristics cytoplasmic inclusion bodies termed "X-bodies" [183,193]. "Langerhans"-like cells are present in the lung parenchyma of patients with other interstitial disorders, such as idiopathic pulmonary fibrosis [194] but in much smaller numbers compared to histiocytosis X. Although the function of the Langerhans' cell within the lung is unknown, it is probably derived from the monocyte-macrophage series of effector cells [183].

Analysis of the effector cells recovered by bronchoalveolar lavage of patients with chronic hypersensitivity pneumonitis and sarcoidosis clearly demonstrates that the alveolitis of these disorders significantly differs from the alveolitis of the disorders such as idiopathic pulmonary fibrosis (**Figure 9D, E** and **Table V**) [11,44,53,60,65,69,175,176]. The inflammatory and immune effector cells present in lavage fluid of people with chronic hypersensitivity pneumonitis and sarcoidosis are characterized by the presence of increased numbers of lymphocytes, particularly T lymphocytes [11,53,65,69]. Neutrophils are rarely present in lavage fluid of nonsmokers with these diseases [11,53].

Since analysis of the effector cell populations recovered by lavage closely mirrors that of the alveolitis of the interstitial disorders [11,175,178], it is apparent that lavage analyses can be used diagnostically. When significant proportions of neutrophils (i.e., >10 percent) are found in lavage fluid of a patient with roentgenographic and physiologic findings consistent with interstitial disease, it is likely that the patient has a disorder like

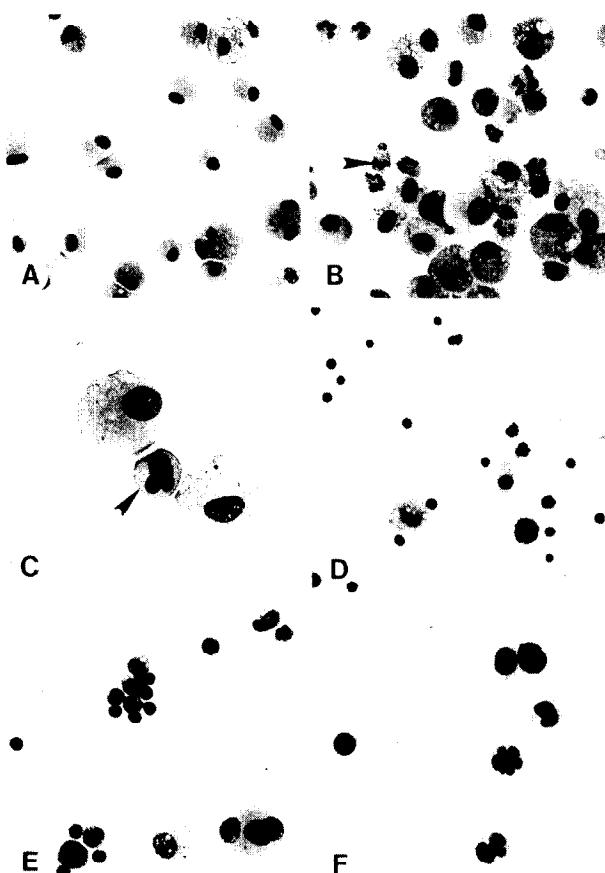


Figure 9. Cyt centrifuge preparations of cells obtained by bronchoalveolar lavage of patients with various disorders (Wright-Giemsa stain). **A**, normal subject; most of these cells are alveolar macrophages. **B**, patient with idiopathic pulmonary fibrosis; these cells consist of a mixture of neutrophils (arrowheads), macrophages and small numbers of lymphocytes. **C**, patient with histiocytosis X, showing a cell (arrowhead) of the type thought to contain the cytoplasmic rod-shaped structures (so-called "X bodies") characteristic of this disease. **D**, patient with hypersensitivity pneumonitis, showing macrophages and a predominance of lymphocytes. **E**, patient with pulmonary sarcoidosis, also showing a predominance of lymphocytes. **F**, patient with a T-cell lymphoma involving the lung; note large atypical lymphocytes (blast forms) with multilobulated nuclei.

idiopathic pulmonary fibrosis or asbestosis [11,175,176]. Likewise, when large proportions (i.e., >15 percent) of lymphocytes are noted, the patient probably has a disease such as sarcoidosis or hypersensitivity pneumonitis [11,175]. But, as with all other diagnostic tests, a word of caution in interpreting lavage findings is necessary. Occult inflammatory airway disease must be ruled out (i.e., as a source of neutrophils). In addition, as more diseases are studied by lavage, more exceptions will be found to these general guidelines. For example, recent studies have demonstrated increased proportions of

TABLE V Bronchoalveolar Lavage in Interstitial Lung Disease*

| Parameter | Idiopathic Pulmonary Fibrosis† | Familial Pulmonary Fibrosis† | Asbestosis† | CILD-CV‡ | Histiocytosis-X§ | Hypersensitivity Pneumonitis† | Sarcoidosis† |
|-----------------------------|--------------------------------|------------------------------|-------------|----------|------------------|-------------------------------|--------------|
| Cells* | | | | | | | |
| Neutrophils | ↑↑ | ↑ | ↑ | + | + | 0 | 0 |
| Lymphocytes | ↔↔ | ↔↔ | ↔↔ | ↔↔ | ↔↔ | ↑** | ↑** |
| T lymphocytes†† | ↔↔ | ↔↔ | ? | ↔↔ | ↔↔ | | |
| B lymphocytes‡‡ | ↔↔ | ↔↔ | ? | ↔↔ | ↔↔ | | |
| Macrophages with "X-bodies" | + | ? | ? | ? | ↑ | ? | ? |
| Proteins | | | | | | | |
| Immunoglobulins | | | | | | | |
| IgG | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ |
| IgM§§ | 0 | 0 | 0 | 0 | 0 | + | 0 |
| IgA | ↔↔ | ↔↔ | ↔↔ | ↔↔ | ↔↔ | ↔↔ | ↔↔ |
| IgE | ↔↔ | ? | ? | ↔↔ | ? | ↔↔ | ↔↔ |
| Complement | | | | | | | |
| C4 | ↔↔ | ? | ? | ? | ? | ↔↔ | ↔↔ |
| C6 | ↔↔ | ? | ? | ? | ? | ↔↔ | ↔↔ |
| Antiproteases | | | | | | | |
| α1AP | ↔↔ | ? | ? | ? | ? | ? | ↔↔ |
| α2M | 0 | ? | ? | ? | ? | ? | 0 |
| Proteases | | | | | | | |
| E'ase | 0 | ? | ? | ? | ? | ? | 0 |
| C'ase | + | ? | ? | ? | ? | ? | 0 |

NOTE: "X-bodies" = characteristic 42 nm club shaped cytoplasmic inclusions [183,193]; α1AP = α1 antiproteinase; α2M = α2 macro-globulin; E'ase = elastase assayed using a labeled insoluble elastin substrate; C'ase = collagenase assayed using a labeled type 1 soluble lung collagen substrate; CILD = chronic interstitial lung disease associated with collagen vascular disorders.

* The cellular content of bronchoalveolar lavage fluid is a valid representation of the status of inflammatory and immune effector cells in alveolar structures only when no inflammatory airway disease is present. The classification given is for nonsmokers; smokers will generally have variably higher proportions of neutrophils in the cell differential.

† Patients with active disease.

‡ Only patients with chronic disease have been evaluated. These data include patients with rheumatoid arthritis, progressive systemic sclerosis, systemic lupus erythematosus and the overlap syndrome.

§ Patients with stable disease.

¶ ↑ = proportion increased compared to normals; ↓ = proportion decreased compared to normals; ↔↔ = proportion similar to normals; 0 = evaluated but absent; + = present but not in large numbers; ? = not evaluated.

** Increased lymphocytes have also been noted in patients with pulmonary tuberculosis and pulmonary lymphomas [195].

†† Proportion of total lymphocytes capable of rosetting with neuraminidase-treated sheep red blood cells at 4°C.

‡‡ Proportion of total lymphocytes with stable surface immunoglobulin; detected with a F(ab')₂ goat antihuman immunoglobulin reagent.

§§ IgM is rarely found in normal people (<5 percent); in patients with idiopathic pulmonary fibrosis it is barely detected in 15 percent; in chronic hypersensitivity pneumonitis it is detected in most patients [5].

|| In normal people, epithelial fluid IgA is 91 percent dimeric, 9 monomeric; in patients with idiopathic pulmonary fibrosis 75 percent is dimeric and 25 percent monomeric [58,60].

||| Rare people (<5 percent) have α2-macroglobulin in lavage fluid [58,175,187,191].

lymphocytes as well as T lymphocytes in lavage fluid of patients with pulmonary lymphoma (Figure 9F) [195] and active tuberculosis [195,196].

In general, analysis of the inflammatory and immune related proteins of lavage fluid has not been as useful in characterizing the alveolitis of the interstitial lung diseases as has evaluation of the recovered cells. For example, all of the interstitial disorders that have been evaluated are characterized by increased levels of IgG and normal levels of IgA, IgE and the complement proteins C4 and C6 [11,69]. However, some characteristic alterations in lavage proteins have been noted. Calvanico et al. [196] recently showed that in pigeon breeders with chronic hypersensitivity pneumonitis, the elevated levels of lavage IgG are of the IgG₄ subclass, suggesting some disease specificity. Likewise, in contrast

to normal subjects and in patients with other interstitial disorders, IgM is routinely detected in the lavage fluid of patients with hypersensitivity pneumonitis [69]. In addition, free collagenase is routinely detected in lavage fluid of patients with idiopathic pulmonary fibrosis [84]. The presence of this enzyme within the alveolar structures may account, in part, for the disorganization of collagen fibers that is characteristic of this disorder.

Prognostic Use of Bronchoalveolar Lavage. Bronchoalveolar lavage is a useful method to gauge the intensity of the alveolitis of the interstitial lung diseases and thereby the prognosis of these disorders. In this regard, most clinical experience has been concerned with the use of cellular analyses of lavage fluid to stage patients with idiopathic pulmonary fibrosis and sarcoidosis.

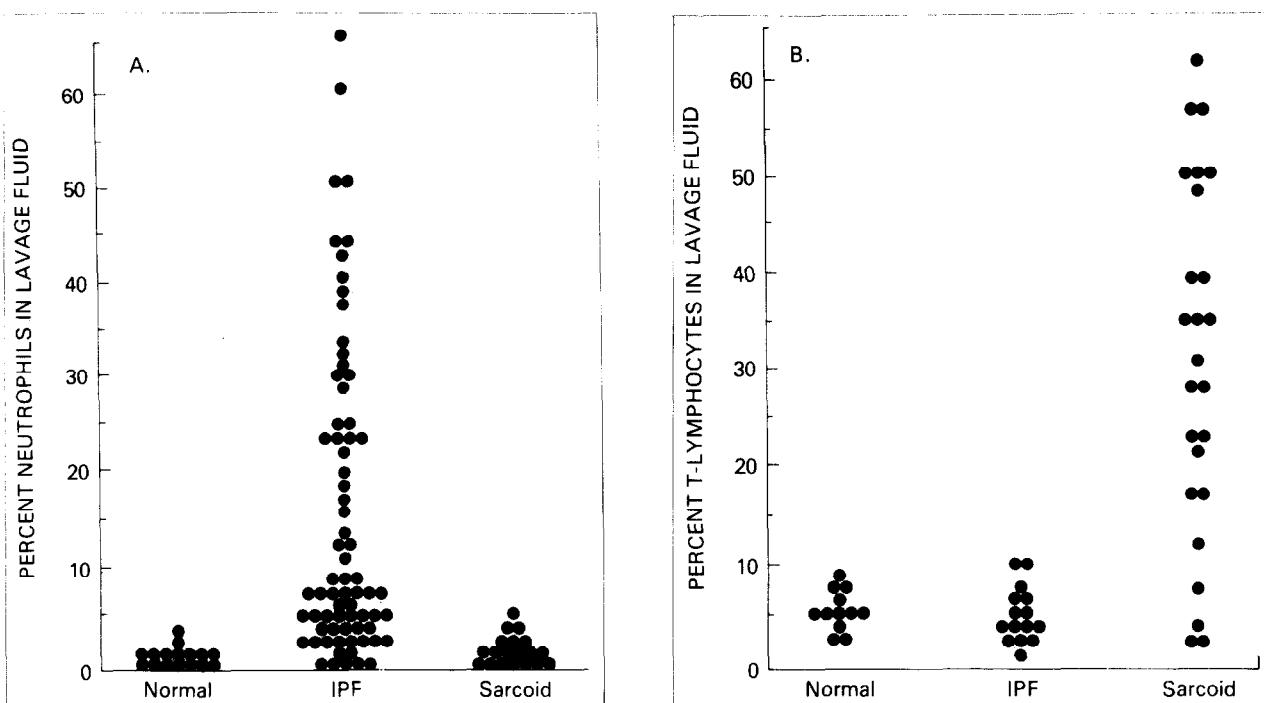


Figure 10. Proportions of neutrophils and T lymphocytes in lavage fluid of normal subjects and patients with idiopathic pulmonary fibrosis (IPF) and sarcoidosis. The percentage of cells is on the ordinate and the source of the cells is indicated on the abscissa. **A**, percentages of bronchoalveolar cells that are neutrophils. **B**, percentages of bronchoalveolar cells that are T lymphocytes.

Idiopathic pulmonary fibrosis is a disorder associated with neutrophil accumulation in the lung. Based on this observation, it has been hypothesized that if neutrophils are an important determinant of parenchymal injury in idiopathic pulmonary fibrosis, the prognosis of this disorder should be related to the levels of neutrophil accumulation in the alveolar structures. The percentages of neutrophils in lavage fluid of patients with idiopathic pulmonary fibrosis vary widely from very low levels to as high as 65 percent (Figure 10A). Studies of Rust et al. [73] have demonstrated that, in general, there is no correlation between the percentages of neutrophils in the lavage fluid of patients with idiopathic pulmonary fibrosis and various clinical parameters, blood tests or pulmonary function studies of these patients. Male patients with idiopathic pulmonary fibrosis tend to have more neutrophils in lavage fluid than do female patients; this correlation is not explained by smoking history or differences in duration of symptoms. Independent of the sex of the patient, there is a strong correlation between the percentages of neutrophils in the lavage fluid of these patients and the prognosis of their disease [73]. To illustrate this phenomenon, patients with idiopathic pulmonary fibrosis were followed for one year with various pulmonary function studies including lung volumes, diffusing capacity, and arterial blood gases at rest and with exercise. After the one year of observation

and independent of the therapy that they received, they were classified by the intensity of their alveolitis. Patients were defined as having a high intensity alveolitis if there were >10 percent neutrophils in their lavage fluid at the end of the study period; conversely, they were classified as having a low intensity alveolitis if there were ≤10 percent neutrophils in their lavage fluid after one year of follow-up. In the group with low intensity alveolitis, only 7 percent of the patients showed deterioration in two or more pulmonary function parameters over one year. In contrast, 45 percent of patients with a high intensity alveolitis showed deterioration in two or more of these pulmonary functions during the same period. The differences between these two groups were significant at the 1 percent level, strongly suggesting an association between the intensity of the alveolitis and the prognosis of this disease.

In contrast to the neutrophil alveolitis characterizing idiopathic pulmonary fibrosis, sarcoidosis is a disorder associated with a lymphocyte alveolitis. As in idiopathic pulmonary fibrosis, it has been hypothesized that if the alveolitis is an important determinant of lung parenchymal injury in sarcoidosis, then the prognosis of this disorder should be related to the intensity of the alveolitis. The alveolitis of sarcoidosis can be followed by quantifying the proportions of T lymphocytes in bronchoalveolar lavage fluid [11,44,53,65,197] and by

quantifying ^{67}G uptake in the lung parenchyma.

Untreated patients with sarcoidosis have a wide spectrum of lymphocytic alveolitis: their ^{67}G indices range from 10 to 350 and the percent of T lymphocytes in their bronchoalveolar lavage range from 8 to 60 percent (**Figure 10B**). As an initial approach to using these parameters in a prognostic fashion, Keogh et al. [197] have grouped patients with sarcoidosis as those with high intensity alveolitis (^{67}G index $>50 \text{ U} +$ percent lavage T lymphocytes >28 percent of total cells) and those with low intensity alveolitis (^{67}G index $>50 \text{ U}$ and/or percent lavage T lymphocytes ≤ 28 percent). These patients were followed with a variety of pulmonary function studies over a period of six months as described for the patients with idiopathic pulmonary fibrosis. The results of these studies were striking: in the group with low intensity alveolitis, 69 percent of the patients either showed improvement or no change in their pulmonary functions; in marked contrast, all those in the group with high intensity alveolitis showed deterioration in one or more pulmonary function parameters over the study period.

These observations suggest that bronchoalveolar lavage is a useful method to obtain inflammatory and immune effector cells from the alveolar structures and to characterize the type of alveolitis that is present in the interstitial lung diseases. Lavage can be used to help place the patient into a general diagnostic group. In addition, lavage is a useful means by which to stage the intensity of the alveolitis and thus determine the prognosis of the interstitial lung disorders. This specificity for the alveolitis should prove particularly useful in gauging the effect of therapy in these diseases.

Principals of Therapy. Even though the interstitial disorders comprise a heterogeneous group of diseases with different etiologies, presentations and clinical courses, there are certain basic principals of therapy that can be applied to all patients:

(1) Although the etiology is known in only approximately 35 percent of the cases [1,12], it is critical that known etiologic agents be identified and the patient permanently removed from future exposure.

(2) The basic approach to the pharmacologic therapy of all interstitial lung disorders is to attack the alveolitis before it causes irreversible derangement of alveolar-capillary units. The adult human lung cannot replenish destroyed alveolar-capillary units; when lost, these units are lost forever [198]. Since the derangement of alveolar structures is likely initiated by the alveolitis, a rational approach to therapy demands the use of agents that interrupt interactions between the inflammatory and immune effector systems and the alveolar structures.

(3) Therapy directed against the alveolitis must be aggressive and life-long, unless it is clear that the alveolitis within most alveolar-capillary units is of low intensity. If the alveolitis is intense, the therapy against it must be sufficient to halt its effect on the alveolar structures. In addition, it is important to appreciate that all alveolar-capillary units do not go through the stages of alveolitis \rightarrow derangement \rightarrow end-stage together; rather, small groups of units pass through these stages at different rates and different times leading to the marked microheterogeneity found within each open lung biopsy specimen. Thus, within the approximately 300×10^6 alveoli in the normal adult human lung, a patient with early interstitial lung disease will have some alveoli that are normal, some that are affected with alveolitis only, and some that have evidence of derangement. Over a period of time, as the alveolitis continues to derange more and more units, the number of alveoli in each stage will shift, with relatively fewer normal alveoli and increased numbers of deranged and/or "end-stage" alveolar-capillary units. Even though a person may have large numbers of alveolar capillary units that are irreversibly deranged, other units may be simultaneously in the alveolitis stage and should be treated. Otherwise, those remaining units will also become deranged, and the lung will eventually no longer be able to fill its role as a gas exchanging organ.

Staging the Alveolitis for Therapy Decisions. From the principals discussed, it is apparent that a major problem in treating these patients is how to accurately and specifically stage the intensity of the ongoing alveolitis (**Table VI**). There is little evidence that blood, roentgenographic or physiologic parameters are sensitive to, or specific for, chronic inflammatory processes within the lung parenchyma and thus, these test results bear little relationship to those processes within the lung that actually define disease "activity." However, both ^{67}G scans and bronchoalveolar lavage are very specific for the alveolitis process and are not significantly influenced by the extent or type of derangement of alveolar structures. These tests, therefore, represent methods by which the clinician may follow the intensity of the alveolitis and thus make rational decisions relating to the administration of therapies directed toward inflammatory and immune effector processes within the alveolar structures.

Current Therapeutic Approaches to Interstitial Lung Disease. The standard therapy for the interstitial lung diseases is corticosteroids, a group of agents that clearly modulate inflammatory and immune effector processes [199–208]. Corticosteroids are known to interfere with various inflammatory cell functions including chemotaxis [209] and secretion of proteolytic enzymes [210]. Thus, corticosteroids have a rational place in the therapy

TABLE VI Clinical Usefulness of Various Tests for the Evaluation of the Alveolitis of the Interstitial Lung Disorders

| Parameter | Sensitivity to Alveolitis | Specificity for Alveolitis | Comments |
|---|---------------------------|----------------------------|---|
| Chest roentgenogram | Fair | Poor | Although the most widely used method for following patients, there is little evidence that it is useful in evaluating relative disease activity |
| Pulmonary function tests Open lung biopsy* | Fair Excellent | Poor Excellent | See text for details concerning each test Generally, can only be used once during the disease course; not very useful for quantitating subtypes or function of immune and inflammatory cells |
| Blood studies | Poor | Poor | The lung can significantly alter its inflammatory and immune processes with little or no reflection in peripheral blood |
| Gallium scan | Good | Excellent | Gallium scans are not as sensitive as lavage in detecting alveolitis because of problems distinguishing high normal from low positive scans; this is likely due to the background radioactivity from overlying ribs |
| Bronchoalveolar lavage | Excellent | Excellent | For lavage to be useful in evaluating alveolitis, the patient must not have inflammatory airway disease |

* Transbronchial biopsy specimens do not necessarily reflect the alveolitis of these disorders; see text for details.

of interstitial disorders in which the chronic accumulation of neutrophils within the alveolar structures play an important pathogenic role (e.g., idiopathic pulmonary fibrosis). Corticosteroids also influence T lymphocyte function, either by direct action or by their effect on macrophages, whose function is critical for normal T lymphocyte responses [201,203]. In human subjects, conventional doses of corticosteroids impair T lymphocyte proliferation [204] and T-cell effector functions [200,202,204,206]. The latter effect may also be secondary to a redistribution of immune effector cells caused by these agents [205,207]. Since the pathogenesis of disorders such as sarcoidosis and chronic hypersensitivity pneumonitis are closely linked to the presence of activated T lymphocytes within the alveolar structures, the usefulness of corticosteroids in these disorders may result from action of such agents on these cells.

It is important to realize that, however rational the use of corticosteroids may be for the treatment of interstitial disease, there are only a few interstitial disorders in which the administration of corticosteroids is of proved efficacy. Probably the best example of their proved usefulness is in the treatment of idiopathic pulmonary fibrosis. This is a generally fatal disorder with rare spontaneous remissions [161,211]. However, if given early (when there is mostly alveolitis and little derangement of alveolar-capillary units), corticosteroid therapy slows the progression of the disease and occasionally reverses it [156,161,211-214]. Although often the subject of debate, most clinicians agree that corticosteroids also help some people with sarcoidosis, even though for most patients, the long-term survival appears to be unaffected by therapy [215-222]. In contrast to idiopathic pulmonary fibrosis and sarcoidosis, little attention has been given to use of corticosteroids in the treatment of chronic interstitial disease associated with rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis/polymyositis or the overlap syndrome.

Although corticosteroids are generally the first therapy used [1,223] their efficacy has not been evaluated in any systematic fashion.

There are some interstitial lung disorders in which it is generally accepted that corticosteroids are not efficacious. In general, these are disorders in which the alveolitis is of very low intensity (e.g., progressive systemic sclerosis) [224-226] or in which the alveolitis is apparently comprised of effector cells that are not influenced by the actions of corticosteroids (e.g., histiocytosis X) [152].

Although there are many forms of corticosteroids, the conventional therapy of interstitial lung disease is with oral agents, usually prednisone. This is not to suggest that prednisone is any more effective than other oral corticosteroid preparations; no comparative studies have been attempted.

In general, prednisone is given to patients with interstitial lung disease in a single daily dose. Alternate day therapy is rarely used and anecdotal reports suggest this form of therapy is not as effective. This is consistent with the general concept that alternate day therapy is not useful in disorders associated with very aggressive inflammatory and immune processes [227,228].

The Pulmonary Branch, NHLBI, uses the following approach to corticosteroid therapy of interstitial lung disease. To satisfy the principles of attacking the alveolitis early and aggressively, we start therapy two to four weeks after open lung biopsy using prednisone at 1 mg/kg daily. This dose is continued for six weeks and then tapered at 2.5 mg each week until a daily maintenance dose of 0.25 mg/kg is reached. Long-term therapy decisions are then based on periodic evaluation of the alveolitis with 67-gallium scans and bronchoalveolar lavage. If the alveolitis disappears, the dose of prednisone is tapered to zero, and if the alveolitis remains stable, the maintenance dose is continued. However, if the alveolitis worsens, a high dose prednisone trial (1

mg/kg for six weeks, then taper as described) is again attempted; if necessary, this can be repeated several times throughout the patient's course.

With this approach, we have observed very few major problems resulting from the side effects of corticosteroids. Changes in body habitus, such as moon facies, striae and weight gain are common. In an occasional patient hypokalemia develops secondary to the mineralocorticoid effect of the drug, but this is easily treated with oral potassium preparations. In approximately 5 percent of the patients corticosteroid therapy must be stopped because of central nervous system effects (e.g., depression, impotence, hyperexcitability or frank psychosis) or collapse of multiple vertebrae. Occasionally, overt diabetes mellitus will develop, but this is easily controlled with insulin therapy. For those patients in whom the alveolitis disappears, tapering the daily dose of corticosteroids is usually accomplished with a 2 mg/week reduction from the maintenance dose until approximately 7 mg/day is reached; tapering is then done more slowly (1 mg/week or 1 mg/two weeks). Patients are cautioned about the symptoms of hypoadrenalinism, and the corticosteroid dose is transiently increased for any stressful activities. In those people in whom tapering is a problem, serum cortisol levels are evaluated and physiologic maintenance with corticosteroids is continued indefinitely if necessary.

Use of Agents Other Than Corticosteroids. Over the past 15 years several reports have suggested that agents such as azathioprine [211,229–233], penicillamine [211,231,234,235], cyclophosphamide [230,231,233,236], chlorambucil [231] or vincristine [236] (given alone or in combination with corticosteroids) may be efficacious in the therapy of idiopathic pulmonary fibrosis. One of the most detailed of these reports is the study by Winterbauer et al. [229] of 20 patients with biopsy proved disease who were treated with a combination of prednisone and azathioprine over a one year period. For the 16 patients who completed the study, there was a significant improvement in vital capacity as well as gas exchange at rest and exercise. Eight of the patients appeared to have a selective beneficial effect from azathioprine, but the numbers of patients were too small to prove this statistically. A longer study by Meier-Sydw et al. [211] of 11 patients with idiopathic pulmonary fibrosis treated with prednisone plus azathioprine showed that, over a two to eight year period, a larger number were alive than was predicted for patients treated with corticosteroids alone. However, in contrast to these encouraging studies, a double-blind, randomized trial of the usefulness of azathioprine as an adjunctive agent to corticosteroids in the therapy of idiopathic pulmonary fibrosis demonstrated no difference in the corticosteroid alone versus corticosteroid plus azathioprine groups studied over a one year period [232]. In addition, the use of azathioprine in the treatment of idiopathic pulmonary fibrosis can be associated with significant adverse reactions [229,232]. Cyclophosphamide and penicillamine are also associated

with major adverse reactions; in fact, both have been reported to cause interstitial lung disease as well as treat it [237–239]. In addition, the use of azathioprine, cyclophosphamide or chlorambucil for the long-term therapy of chronic disorders has also been associated with the development of hematologic malignancies [240].

There has been interest in the treatment of sarcoidosis with nonsteroidal anti-inflammatory drugs such as chloroquine [241] or oxyphenbutazone [242]. However, these agents appear to have no advantage over corticosteroids, and their use has been generally abandoned.

Probably the best evidence for the use of cytotoxic agents in the therapy of interstitial disease comes from the experience with cyclophosphamide in the treatment of Wegener's granulomatosis and lymphomatoid granulomatosis [243]. This does not mean, however, that cytotoxic agents are useful for all interstitial disorders; the dangers associated with the use of these drugs demand that randomized trials be conducted to prove their efficacy before they are accepted into the pharmacologic armamentarium directed against interstitial disease.

General Care of the Patient with Interstitial Lung Disease. Beyond a direct therapeutic attack on the alveolitis of interstitial lung disease, it is important to symptomatically treat the sequelae of the derangement of alveolar structures. Many patients with interstitial lung disease decrease their arterial oxygen tension (PaO₂) with exercise, and thus, even though they may have only mild hypoxemia at rest, they can have severe hypoxemia with even moderate exercise. This, together with the fact that they progressively lose alveolar-capillary units and thus soon begin to have limited cardiac output, means that oxygen delivery to vital organs such as heart and brain may be insufficient for proper function. It is important, therefore, to make oxygen available to patients with interstitial lung disease once they demonstrate decreases in PaO₂ with exercise to levels less than 50 mm Hg. There is no evidence that oxygen supplementation alters the course or ultimate survival of these patients, but, on an individual basis, these patients report an improved quality of their everyday life.

In addition, although interstitial lung diseases are primarily disorders of the alveoli, many are also associated with obstruction to airflow, either due to intrinsic disease or loss of airway support [244]. It is understandable, therefore, why in many patients with interstitial disease inflammatory airway disease and bacterial infection eventually develop. Thus, even though these people do not have reactive airway disease, bronchodilators, such as aminophylline, are often used in their therapeutic program. This, together with chest physiotherapy, appears to be useful in helping them clear secretions, particularly as they approach the "end-stage" and have few functioning alveoli. It is critical to be constantly vigilant for the development of infection, as even localized bacterial pneumonia can be fatal to such people.

REFERENCES

1. Fulmer JD, Crystal RG: Interstitial lung disease. In: Simmons DH, ed, *Current pulmonology*. Boston: Houghton Mifflin, 1979; 1: 1-65.
2. Scadding JG: Diffuse pulmonary alveolar fibrosis. *Thorax* 1974; 29: 271-281.
3. Spencer H: Pathology of the lung: vol 1, 2. Philadelphia: WB Saunders, 1977.
4. Spencer H: Interstitial pneumonia. *Ann Rev Med* 1967; 18: 423-442.
5. Weinberger SE, Crystal RG: Reactions of the interstitial space to injury. In: Fishman AP, ed. *Pulmonary diseases*. New York: McGraw Hill, 1979.
6. Fulmer JD, Crystal RG: The biochemical basis of pulmonary function. In: Crystal RG, ed. *The biochemical basis of pulmonary function*. New York: M Dekker, 1976; 419-466.
7. Crystal RG, Fulmer JD, Roberts WC, Moss ML, Line BR, Reynolds HY: Idiopathic pulmonary fibrosis: clinical, histologic, radiographic, physiologic, scintigraphic, cytologic, and biochemical aspects. *Ann Int Med* 1976; 85: 769-788.
8. Hance AJ, Crystal RG: The connective tissue of lung. *Am Rev Respir Dis* 1975; 112: 657-711.
9. Bray BA: Cold-insoluble globulin (fibronectin) in connective tissues of adult human lung and in trophoblast basement membrane. *J Clin Invest* 1978; 62: 745-752.
10. Bradley KH, Kawanami O, Ferrans VJ, Crystal RG: The fibroblast of the human alveolar structures: a differentiated cell with a major role in lung structure and function. *Human tissues and cells in biomedical research*. In: Harris C, Trump BF, Stoner GS, eds. *Methods and perspectives in cell biology*, vol 21. New York: Academic Press, 1980; 37-64.
11. Hunninghake GW, Gadek JE, Kawanami O, Ferrans VJ, Crystal RG: Inflammatory and immune processes in the human lung in health and disease: evaluation by bronchoalveolar lavage. *Am J Pathol* 1979; 97: 149-206.
12. Respiratory Diseases Task Force: Report on problems, research, approaches, and needs, Oct 1972. (DHEW publication no. [NIH]76-432).
13. The Hospital Record Study; Commission on Professional and Hospital Activities, 1968 Green Road, Ann Arbor, Mich: IMS American Ltd, Ambler, Pa, Jan-Dec, 1977.
14. Epler GR, Carrington CB, Gaensler EA: Crackles (rales) in the interstitial pulmonary diseases. *Chest* 1978; 73: 333-339.
15. Fraser RG, Pare JAP: *Diagnosis of diseases of the chest*, 2nd ed. Vol III. Philadelphia: WB Saunders, 1979.
16. Heppleston AG: The pathology of honeycomb lung. *Thorax* 1956; 11: 77-93.
17. Ochi T, Miyagawa T, Kikui M, et al.: A new type of hypersensitivity pneumonitis in Japan. VIII International Conference on Sarcoidosis and Other Granulomatous Diseases, Cardiff, Wales, September 11-15, 1978.
18. Orwoll ES, Kiessling PJ, Patterson JR: Interstitial pneumonia from mitomycin. *Ann Intern Med* 1978; 89: 352-355.
19. Stephen WC, Parks RD, Tempest B: Acute hypersensitivity pneumonitis associated with carbamazine therapy. *Chest* 1978; 74: 463-464.
20. Winberg CD, Rose ME, Rappaport H: Whipple's disease of the lung. *Am J Med* 1978; 65: 873-880.
21. Federman Q, Abrams RM, Lee T: Pulmonary radiographic findings in a case of febrile, relapsing, nonsuppurative panniculitis (Weber-Christian Disease). *Mt Sinai J Med* 1976; 43: 174-179.
22. Garay SM, Gardella JE, Fazzini EP, Goldring RM: Hermansky-Pudlak syndrome. Pulmonary manifestations of a ceroid storage disease. *Am J Med* 1979; 66: 737-749.
23. Crystal RG, Fulmer JD, Baum BJ, et al.: Cells, collagen and idiopathic pulmonary fibrosis. *Lung* 1978; 155: 199-224.
24. Brody AR, Craighead JE: Interstitial associations of cells lining air spaces in human pulmonary fibrosis. *Virchows Arch (Pathol Anat)* 1976; 372: 39-49.
25. Barry BE, Crapo JD, Gehr P, Bachofen M, Weibel ER: Population characteristics of the cells of the normal lung. *Am Rev Respir Dis* 1979; 119: 287A.
26. Rosen Y, Athanasiades TJ, Moon S, et al.: Nongranulomatous interstitial pneumonitis in sarcoidosis: relationship to the development of epithelioid granulomas. *Chest* 1978; 74: 122-125.
27. Roberts RC, Moore VL: Immunopathogenesis of hypersensitivity pneumonitis. *Am Rev Respir Dis* 1977; 116: 1075-1090.
28. Schlueter DP: Response of the lung to inhaled antigens. *Am J Med* 1974; 57: 476-492.
29. Takahashi M: Histopathology of sarcoidosis and its immunological basis. *Acta Pathol Jpn* 1970; 20: 171-182.
30. Teilum G: Morphogenesis and development of sarcoid lesions. Similarities to the group of collagenoses. *Acta Med Scand* 425 (suppl) 1964; 14-18.
31. Carrington CB, Gaensler EA, Milsus JP, Schachter AW, Burke GW, Goff AM: Structure and function in sarcoidosis. *Ann NY Acad Sci* 1976; 278: 265-282.
32. Barrowcliff DF, Arblaster PG: Farmer's lung: a study of an acute fatal case. *Thorax* 1968; 23: 490.
33. Ghose T, Landrigan P, Killeen R, Dill J: Immunopathological studies in patients with farmer's lung. *Clin Allergy* 1974; 4: 119-129.
34. Hinson KFW: Diffuse pulmonary fibrosis. *Hum Pathol* 1970; 1: 275-288.
35. Crystal RG, Fulmer JD, Ferrans V, Roberts W, Keogh B: Unpublished observations.
36. vanToorn DW: Experimental interstitial pulmonary fibrosis. *Pathol Europ* 1970; 5: 97-104.
37. Ryan SF: Experimental fibrosing alveolitis. *Am Rev Respir Dis* 1972; 105: 776-791.
38. Brentjens JR, O'Connell DW, Pawlowski IB, Hsu KC, Andres GA: Experimental immune complex disease of the lung. The pathogenesis of a laboratory model resembling certain human interstitial lung diseases. *J Exp Med* 1974; 104: 105.
39. Bernardo J, Hunninghake GW, Gadek JE, Ferrans VJ, Crystal RG: Acute hypersensitivity pneumonitis. Serial changes in lung lymphocyte subpopulations following exposure to antigen. *Am Rev Respir Dis* 1979; 120: 985-999.
40. Adamson IYR, Bowden DH: The pathogenesis of bleomycin-induced pulmonary fibrosis in mice. *Am J Pathol* 1974; 77: 185-190.
41. Sikic BI, Young DM, Mimnaugh EG, Gram TE: Quantification of bleomycin pulmonary toxicity in mice by changes in lung hydroxyproline content and morphometric histopathology. *Cancer Res* 1978; 38: 787-792.
42. Jennings FL, Arden A: Development of experimental radiation pneumonitis. *Arch Pathol Lab Med* 1961; 71: 437-446.
43. Vrako R: Significance of basal lamina for regeneration of injured lung. *Virchows Arch (Pathol Anat)* 1972; 355: 264-274.
44. Hunninghake GW, Gadek JE, Szapiel SV, et al.: The human alveolar macrophage. In: Harris CC, Trump BF, Stoner GD, eds. *Methods and perspectives in cell biology: cultured human cells and tissues in biomedical research*. Vol 21. New York: Academic Press, 1980; 95-112.
45. Brain JD, Godleski JL, Sorokin SP: Quantification, origin, and fate of pulmonary macrophages. In: Brain JD, Proctor DF, Reid LM, eds. *Respiratory defense mechanisms*. Vol II. New York: M Dekker 1977: 849-892.
46. Thomas ED, Ramberg RE, Gale GE, et al.: Direct evidence for a bone marrow origin of the alveolar macrophage in man. *Science* 1976; 192: 1016-1017.
47. Golde DW, Byers LD, Finley TN: Proliferative capacity of the human alveolar macrophage. *Nature* 1974; 247: 373-375.
48. Adamson IYR, Bowden DH: Role of monocytes and interstitial cells in the generation of alveolar macrophages. *Fed*

- Proc 1979; 38: 1205.
49. Gadek JE, Hunninghake GW, Zimmerman R, Crystal RG: Regulation of release of the alveolar macrophage-derived chemotactic factor. *Am Rev Respir Dis* 1980; 121: 723-733.
 50. Miller K, Kagan E: The in vivo effects of quartz on alveolar macrophage membrane topography and the characteristics of intrapulmonary cell populations. *J Reticuloendothel Soc* 1977; 21: 307-316.
 51. Reynolds HY: The importance of lymphocytes in pulmonary health and disease. *Lung* 1978; 155: 225-242.
 52. Daniele RP, Altose MD, Rowlands DR: Immunocompetent cells from the lower respiratory tract of normal human lungs. *J Clin Invest* 1975; 56: 986-995.
 53. Hunninghake GW, Fulmer JD, Young RC, Gadek JE, Crystal RG: Localization of the immune response in sarcoidosis. *Am Rev Respir Dis* 1979; 120: 49-57.
 54. Lawrence EC, Blaese RM, Martin RR, Stephens PM: Immunoglobulin secreting cells in normal human bronchial lavage fluids. *J Clin Invest* 1978; 62: 832-835.
 55. Hunninghake GW, Schmit N, Rust M, et al.: Lung immunoglobulin production in chronic lung disease. *Clin Res* 1979; 27: 493A.
 56. Lawrence EC, Martin RR, Blaese RM, et al.: Increased bronchoalveolar IgG-secreting cells in interstitial lung diseases. *N Engl J Med* 1980; 302: 1186-1189.
 57. Winchester RJ, Fu SM, et al.: IgG on lymphocyte surfaces: technical problems and the significance of a third cell population. *J Immunol* 1975; 114: 1210-1218.
 58. Reynolds HY, Newball HH: Analysis of proteins and respiratory cells obtained from human lungs by bronchial lavage. *J Lab Clin Med* 1974; 84: 559-573.
 59. Hunninghake GW, Gadek JE, Crystal RG: Mechanisms by which cigarette smoke attracts polymorphonuclear leukocytes to lung. *Chest* 1980; 77 (suppl): 273.
 60. Reynolds HY, Fulmer JD, Kazmierowski JA, Roberts WC, Frank MM, Crystal RG: Analysis of bronchoalveolar lavage fluid from patients with idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis. *J Clin Invest* 1977; 59: 165-175.
 61. Boros OL: Granulomatous inflammations. *Prog Allergy* 1978; 24: 183-267.
 62. Hunninghake GW, Gadek JE, Young RC, Kawanami O, Ferrans VJ, Crystal RG: Maintenance of granuloma formation in pulmonary sarcoidosis by T-lymphocytes within the lung. *N Engl J Med* 1980; 303: 594-598.
 63. Rossman MD, Daniele RP, Dauber JH: Bronchoalveolar lymphocytes in sarcoidosis. *Am Rev Respir Dis* 1979; 119: 795.
 64. Daniele RP, Dauber JH, Rossman MD: Immunologic abnormalities in sarcoidosis. *Ann Intern Med* 1980; 92: 406-416.
 65. Hunninghake GW, Gadek JE, Weinberger S, et al.: Comparison of the alveolitis and idiopathic pulmonary fibrosis. *Chest* 1979; 75S: 226S-227S.
 66. Schuyler MR, Thigpen TP, Salvaggio JE: Local pulmonary immunity in pigeon breeder's disease. *Ann Intern Med* 1978; 88: 355-358.
 67. Ramachander K, Douglas SD, Siltzbach LE, et al.: Peripheral blood lymphocyte subpopulations in sarcoidosis. *Cell Immunol* 1975; 16: 422-426.
 68. Daniele RP, Rowlands DT: Lymphocyte subpopulations in sarcoidosis: correlation with disease activity and duration. *Ann Intern Med* 1976; 85: 593-600.
 69. Weinberger SE, Kelman JA, Elson NA, et al.: Bronchoalveolar lavage in interstitial lung disease. *Ann Intern Med* 1978; 89: 459-466.
 70. Hunninghake GW, Gadek JE, Lawley TJ, Crystal RG: Mechanisms of neutrophil accumulation in the lungs of patients with idiopathic pulmonary fibrosis. *J Clin Invest* 1981; (in press).
 71. Gadek JE, Hunninghake GW, Zimmerman R, Kelman J, Fulmer J, Crystal RG: Pathogenetic studies in idiopathic pulmonary fibrosis: control of neutrophil migration by immune complexes. *Chest* 1979; 75S: 264S-265S.
 72. Dreisen RB, Schwarz MI, Theofilopolous AN, Stanford RE: Circulating immune complexes in the idiopathic interstitial pneumonias. *N Engl J Med* 1978; 298: 353-357.
 73. Rust M, Hunninghake G, Keogh B, Fulmer JD, Crystal RG: Unpublished observations.
 74. Keogh B, Hunninghake G, Line B, et al.: Therapeutic decisions in sarcoidosis: prospective evaluation of the effect of corticosteroids on lavage lymphocytes and 67 Gallium scans. *Clin Res* 1979; 27: 400A.
 75. Cline MJ: The white cell. Cambridge, Mass: Harvard University Press, 1975.
 76. Kazmierowski JA, Gallin JI, Reynolds HY: Mechanisms for the inflammatory response in primate lungs; demonstration and partial characterization of an alveolar macrophage chemotactic factor with preferential activity for polymorphonuclear leukocytes. *J Clin Invest* 1977; 59: 273-281.
 77. Hunninghake GW, Gallin JI, Fauci AS: Immunologic reactivity of the lung. VI. The in vivo and in vitro generation of a neutrophil chemotactic factor by alveolar macrophages. *Am Rev Respir Dis* 1978; 117: 15-23.
 78. Hunninghake GW, Gadek JE, Crystal RG: Human alveolar macrophage chemotactic factor for neutrophils: stimuli and partial characterization. *J Clin Invest* 1980; 66: 473-483.
 79. Merrill WW, Naegel GP, Matthay RA, Reynolds HY: Alveolar macrophage-derived chemotactic factor. Kinetics of in vitro production and partial characterization. *J Clin Invest* 1980; 65: 269-276.
 80. Dauber JH, Daniele RP: Release of phagocyte and lymphocyte chemotactic factors by alveolar macrophages. *Am Rev Respir Dis* 1979; 119: 64.
 81. Valone FH, Franklin M, Goetzl EJ: Generation of a human polymorphonuclear leukocyte (PMN) chemotactic factor by the lipoxygenase pathway of alveolar macrophage (AM). *Clin Res* 1979; 27: 476A.
 82. Gadek JE, Fells J, Hunninghake GW, Zimmerman R, Crystal RG: Alveolar macrophage-neutrophil interaction: a role for inflammatory cell cooperation in the disruption of connective tissue. *Clin Res* 1979; 27: 397A.
 83. Gadek JE, Fells J, Hunninghake GW, Crystal RG: Interaction of the alveolar macrophage (AM) and the circulating neutrophil. AM-induced neutrophil activation. *Am Rev Respir Dis* 1979; 119: 66A.
 84. Gadek JE, Kelman JA, Fells GA, et al.: Collagenase in the lower respiratory tract of patients with idiopathic pulmonary fibrosis. *New Engl J Med* 1979; 301: 737-742.
 85. Hunninghake GW, Szapiel SV, Fulmer JD, Keogh B, Crystal RG: Neutrophil-mediated fibroblast destruction in idiopathic pulmonary fibrosis (IPF). *Am Rev Respir Dis* 1979; 119: 72A.
 86. Bignon J, Atassi K, Jaurand MC, Geslin P, Solle R: Cellular and protein content of bronchoalveolar lavage fluid from patients with idiopathic pulmonary fibrosis and asbestosis. *Am Rev Respir Dis* 1978; 117: 56.
 87. Gadek JE, Hunninghake GW, Schoenberger CI, Fells GA, Crystal RG: Idiopathic pulmonary fibrosis and asbestosis: pathogenetic parallels. *Chest* 1981; (in press).
 88. Schoenberger CI, Hunninghake GW, Gadek JE, Crystal RG: Inflammation and asbestosis. Characterization and maintenance of alveolitis following acute asbestos exposure. *Chest* 1981; (in press).
 89. Babior BM: Oxygen-dependent microbial killing by phagocytes. *N Engl J Med* 1978; 298: 659-668, 721-725.
 90. Colten HR: Biosynthesis of serum complement. In: Brent L, Holborow J, eds, *Progress in Immunology*, Vol. 2. Amsterdam: North Holland Publishing Company, 1974: 183-190.
 91. Hsueh W, Kuhn CS: Prostaglandin secretion in rabbit alveolar macrophages and its relationship to phagocytosis. *Chest* 1979; 75S: 249-251.
 92. Werb Z, Gordon S: Secretion of a specific collagenase by stimulated macrophages. *J Exp Med* 1975; 142: 346-360.
 93. Horowitz AL, Kelman JA, Crystal RG: Activation of alveolar macrophage collagenase by a neutral protease secreted

- by the same cell. *Nature* 1976; 264: 772-774.
94. Janoff A, Rosenberg R, Gladston M: Elastase-like esteroprotease activity in human and rabbit alveolar macrophage granules. *Proc Soc Exp Biol Med* 1971; 136: 1054-1058.
 95. Unkeless JC, Gordon S, Reich E: Secretion of plasminogen activator by stimulated macrophages. *J Exp Med* 1974; 139: 934-850.
 96. Davies P, Page RC, Allison AC: Changes in cellular enzyme levels and extracellular release of lysosomal acid hydrolases in macrophages exposed to group A streptococcal cell wall substance. *J Exp Med* 1974; 139: 1262-1282.
 97. Polverini PJ, Cotran RS, Cimbrow MA, Unanue ER: Activated macrophages induce vascular proliferation. *Nature* 1977; 269: 804-806.
 98. Bitterman PB, Crystal RG: Pulmonary macrophages release a factor that stimulates human lung fibroblasts to replicate. *Am Rev Respir Dis* 1980; 121: 58.
 99. Rosenthal AS, Lipsky PE, Shevack EM: Macrophage-lymphocyte interaction and lymphocyte recognition. *Fed Proc* 1975; 34: 1743-1748.
 100. Unanue ER: Secretory function of mononuclear phagocytes. *Am J Pathol* 1976; 83: 396-417.
 101. Evans R, Alexander P: Mechanisms of extracellular killing of nucleated mammalian cells by macrophages. In: Nelson DS, ed. *Immunobiology of the Macrophage*. New York: Academic Press, 1976: 535-576.
 102. Golde DW, Finley TN, Cline MJ: Production of colony-stimulating factor by human macrophages. *Lancet* 1972; 2: 1397-1399.
 103. Ward PA, Unanue ER, Goralnick SJ, Schreiner GF: Chemotaxis of rat lymphocytes. *J Immunol* 1977; 119: 416-421.
 104. Rocklin RE: Products of activated lymphocytes. Leukocyte inhibitory factor (LIF) distinct from migration inhibitory factory (MIF). *J Immunol* 1974; 112: 1461-1466.
 105. Ward PA, Remold HG, David JR: Leukocyte chemotactic factors produced by sensitized lymphocytes. *Science* 1969; 163: 1079-1081.
 106. Altman LC, Chassy B, Mackler BF: Physicochemical characterization of chemotactic lymphokines produced by human T and B lymphocytes. *J Immunol* 1975; 115: 18-21.
 107. Koopman WJ, Sandberg AL, Wahl SM, Mergenhagen SE: Interaction of soluble C3 fragments with guinea pig lymphocytes: comparison of effects of C3a, C3b, C3c, and C3d on lymphokine production and lymphocyte proliferation. *J Immunol* 1976; 117: 331-336.
 108. Blanden RV, Harpel AJ, Doherty PC, Zinkernagel RM: Lymphocyte-macrophage interactions and macrophage activation in the expression of antimicrobial immunity in vivo. In: Nelson DS, ed. *Immunobiology of the macrophage*. New York: Academic Press, 1976: 367-400.
 109. Waldmann H: Conditions determining the generation and expression of T helper cells. *Immunol Rev* 1977; 35: 121-145.
 110. Drath DB, Karnovsky ML: Superoxide production by phagocytic leukocytes. *J Exp Med* 1975; 141: 257-262.
 111. Weiss SJ, Rustagi PK, LoBuglio AF: Human granulocyte generation of hydroxyl radical. *J Exp Med* 1978; 147: 316-323.
 112. Klebanoff SJ: A peroxidase-mediated antimicrobial system in leukocytes. *J Clin Invest* 1967; 46: 1078.
 113. Lazarus ES, Brown RS, Daniels JR, et al.: Human granulocyte collagenase. *Science* 1968; 159: 1483-1485.
 114. Horowitz AL, Hance AJ, Crystal RG: Granulocyte collagenase: selective digestion of type I and type III collagen. *Proc Natl Acad Sci* 1977; 74: 897-901.
 115. Wright DG, Kelman JA, Gallin JI, Crystal RG: Extracellular release by human neutrophils (PMNs) of a latent collagenase stored in the specific (secondary) granules. *Clin Res* 1978; 26: 387A.
 116. Janoff A, Scherer J: Mediators of inflammation in leukocyte lysosomes. IX. Elastinolytic activity in granules of human polymorphonuclear leukocytes. *J Exp Med* 1968; 128: 1137-1155.
 117. Haveman K, Janoff A: Neutral proteases of human polymorphonuclear leukocytes. Baltimore-Munich: Urban & Schwarzenberg, 1978.
 118. Goldstein IM, Kaplan HB, Radin A, Frosch M: Independent effects of IgG and complement upon human polymorphonuclear leukocyte function. *J Immunol* 1976; 117: 1282-1287.
 119. Wright DG, Gallin JI: Functional differentiation of human neutrophil granules: generation of C5a by specific (secondary) and inactivation of C5a by azurophil (primary) granule contents. *J Immunol* 1977; 119: 1068-1076.
 120. Muhlfelder TW, Niemetz J, Kreutzer D, Beebe D, Ward PA, Rosenthal SI: C5 chemotactic factor induces leukocyte production of tissue factor activity. A link between complement and coagulation. *J Clin Invest* 1979; 63: 147-150.
 121. Sacks T, Moldow CF, Craddock PR, Bowers TK, Jacobs HS: Oxygen radicals mediate endothelial cell damage by complement-stimulated granulocytes: an in vitro model of immune vascular damage. *J Clin Invest* 1978; 67: 1161-1167.
 122. Klassen KP, Andyan AJ, Curtis GM: Biopsy of diffuse pulmonary lesions. *Arch Surg* 1949; 59: 694-704.
 123. Gaensler EA, Moister MVB, Hamm J: Open-lung biopsy in diffuse pulmonary disease. *N Engl J Med* 1964; 270: 1319-1331.
 124. Kent DC, Houk VN, Elliott RC, Sokolowski JW, Baker JH, Sorensen K: The definitive evaluation of sarcoidosis. *Am Rev Respir Dis* 1970; 101: 721-727.
 125. Ray JF III, Lawton BR, Myers WO, et al.: Open lung biopsy. Nineteen-year experience with 416 consecutive operations. *Chest* 1976; 69: 43-47.
 126. Koerner SK, Sakowitz AJ, Appleman RI, Becker NH, Schoenbaum SW: Transbronchial lung biopsy for the diagnosis of sarcoidosis. *N Engl J Med* 1975; 293: 268-270.
 127. Koontz C, Joyner LR, Nelson RA: Transbronchial lung biopsy via the fiberoptic bronchoscope in sarcoidosis. *Ann Intern Med* 1976; 85: 64-66.
 128. Smith CW, Murray GF, Wilcox BR, Starek PJK, Delany DJ: The role of transbronchial lung biopsy in diffuse pulmonary disease. *Ann Thoracic Surg* 1977; 24: 54-58.
 129. Whitcomb ME, Domby WR, Hawley PC, Kataria YP: The role of fiberoptic bronchoscopy in the diagnosis of sarcoidosis. *Chest* 1978; 74: 205-208.
 130. Wilson RK, Fechner RF, Greenberg SD, Estrada R, Stevens PM: Clinical implications of a "nonspecific" transbronchial biopsy. *Am J Med* 1978; 65: 252-256.
 131. Anderson HA: Transbronchial lung biopsy for diffuse pulmonary diseases. Results in 939 patients. *Chest* 1978; 73 (S): 734-736.
 132. Wall CP, Epler GR, Gaensler EA, Carrington CB: Comparison of transbronchial and open biopsy in chronic diffuse infiltrative lung disease. *Am Rev Respir Dis* 1979; 119(2): 180.
 133. Poe RH, Utell MJ, Israel RH, Hall WJ, Eshleman JD: Sensitivity and specificity of the nonspecific transbronchial lung biopsy. *Am Rev Respir Dis* 1979; 119: 25-31.
 134. Niewoehner DE, Klinerman J, Rice DB: Pathologic changes in the peripheral airways of young cigarette smokers. *N Engl J Med* 1974; 291: 755-758.
 135. Auerbach O, Garfinkel L, Hammond EC: Relation of smoking and age to findings in lung parenchyma: a microscopic study. *Chest* 1974; 65: 29-35.
 136. Lieberman J: Elevation of serum angiotensin-converting enzyme (ACE) level in sarcoidosis. *Am J Med* 1975; 59: 365-372.
 137. Lieberman J: The specificity and nature of serum-angiotensin-converting-enzyme (serum ACE) elevations in sarcoidosis. *Ann NY Acad Sci* 1976; 278: 488-497.
 138. Silverstein E, Friedland J, Lyons HA, Gourin A: Markedly elevated angiotensin converting enzyme in lymph nodes containing non-necrotizing granulomas in sarcoidosis. *Proc Natl Acad Sci* 1976; 73: 2137-2141.

139. Fanburg BL, Schoenberger MD, Bachus B, Snider GL: Elevated serum angiotensin I converting enzyme in sarcoidosis. *Am Rev Respir Dis* 1976; 114: 525-528.
140. Siltzbach LE, Krakoff L, Dorph D, Teirstein AS: Angiotensin converting enzyme (ACE) and lysozyme (L) levels in sera of patients with sarcoidosis (abstract). 8th International Conference on sarcoidosis and other granulomatous diseases (Abst), Cardiff, Wales, 1979, p 23-24.
141. Nasal A, Schleissner LA, Mishkin FS, Lieberman J: Angiotensin-I-converting enzyme and gallium scan in non-invasive evaluation of sarcoidosis. *Ann Intern Med* 1979; 90: 328-331.
142. Rohrbach MS, De Remee RA: Serum angiotensin converting enzyme activity in sarcoidosis as measured by a simple radiochemical assay. *Am Rev Respir Dis* 1979; 119: 761-767.
143. Pascual RS, Gee JBL, Finch SC: Usefulness of serum lysozyme measurement in diagnosis and evaluation of sarcoidosis. *N Engl J Med* 1973; 289: 1074-1076.
144. Klockers M, Selroos O: Serum lysozyme in sarcoidosis: evaluation of its usefulness in determination of disease activity. *Acta Pathol Microbiol Scand* 1977; 85: 169-173.
145. Turner-Warwick M, Doniach D: Auto-antibody studies in interstitial pulmonary fibrosis. *Br Med J* 1965; 1: 886-891.
146. Hedfors E, Norberg R: Evidence for circulating immune complexes in sarcoidosis. *Clin Exp Immunol* 1974; 16: 493-496.
147. Gupta RC, Kueppers F, De Remee RA, Huston KA, McDuffie FC: Pulmonary and extrapulmonary sarcoidosis in relation to circulating immune complexes. *Am Rev Respir Dis* 1977; 116: 261-266.
148. Verrier-Jones J, Cumming RH, Asplin CM, Laszlo G, White RJ: Circulating immune complexes in erythema nodosum and early sarcoidosis. *Lancet* 1976; 1: 153.
149. Daniele RP, Rowlands DT: Lymphocyte subpopulations in sarcoidosis: correlation with disease activity and duration. *Ann Intern Med* 1976; 85: 593-600.
150. Morgan WKC, Lapp NL: Respiratory disease in coal miners. *Am Rev Respir Dis* 1976; 113: 531-559.
151. Fraser RG, Pare JAP: Extrinsic allergic alveolitis. *Sem Roentgenol* 1975; 10: 31-42.
152. Bassett F, Corrin B, Spencer H, et al: Pulmonary histiocytosis X. *Am Rev Respir Dis* 1978; 118: 811-820.
153. Carrington CB, Cugell DW, Gaensler EA, et al: Lymphangiomyomatosis: physiologic-pathologic radiologic correlations. *Am Rev Respir Dis* 1977; 116: 977-996.
154. Epler GR, McLoud TC, Gaensler EA, Mikus JP, Carrington CB: Normal chest roentgenograms in chronic diffuse infiltrative lung disease. *N Engl J Med* 1978; 298: 934-939.
155. Carrington CB, Gaensler EA: Clinical-pathologic approach to diffuse infiltrative lung disease. In: Thurlbeck WM, Abell MR, eds. *The lung structure, function and disease*. Baltimore: Williams & Wilkins, 1978: 58-87.
156. Scadding JC, Hinson KFW: Diffuse fibrosing alveolitis (diffuse interstitial fibrosis of the lungs). *Thorax* 1967; 22: 291-304.
157. Naegele RL: Types of fibrosis in coal workers' pneumoconiosis. *Ann NY Acad Sci* 1972; 200: 381-400.
158. Theros EG: The value of radiologic-pathologic correlation in the education of the radiologist. *Am J Roentgenol* 1969; 107: 235-257.
159. Bohl H, Bristol LJ, Cartier PH, et al: UICC/Cincinnati classification of the radiographic appearances of the pneumoconioses. *Chest* 1970; 58: 57-67.
160. Genereux GP: The end-stage lung. *Radiology* 1975; 116: 279-289.
161. Carrington CB, Gaensler EA, Couture RE, Fitzgerald MX, Gupta RG: Natural history and treated course of usual and desquamative interstitial pneumonia. *N Engl J Med* 1978; 298: 801-809.
162. Miller A, Chuang M, Terstein AS, Siltzbach LE: Pulmonary function in stage I and II pulmonary fibrosis. *Ann NY Acad Sci* 1976; 278: 292-300.
163. Fulmer JD, Von Gal ER, Roberts WC, Crystal RG: Morphologic-physiologic correlates of the severity of fibrosis in idiopathic pulmonary fibrosis. *J Clin Invest* 1979; 63: 665-676.
164. Gaensler EA, Carrington CB, Couture RE, Fitzgerald MX: Radiographic pathologic correlations in interstitial pneumonias. In: Bassett F, Georges R, eds. *Alveolar interstitium of the lung. Pathological and physiological aspects. Progress in respiratory research Vol 8*. Basel: S Karger, 1974: 223-242.
165. Green GM, Graham WGB, Hanson JS, et al: Correlated studies of interstitial pulmonary disease. *Chest* 1976; 69 (suppl): 263.
166. Lavendar PJ, Lowe J, Barker JR, Burn JI, Chaudri MA: Gallium-67 citrate scanning in neoplastic and inflammatory lesions. *Br J Radiol* 1971; 44: 361-366.
167. Dige-Peterson H, Heckscher T, Hertz M: ^{67}Ga -scintigraphy in non-malignant lung diseases. *Scand J Resp Dis* 1972; 53: 314-319.
168. Higasi T, Nakayama Y, Murata A, et al: Clinical evaluation of ^{67}Ga -citrate scanning. *J Nucl Med* 1972; 13: 196-201.
169. Siemsen JK, Sargent EN, Grebe SF, Winsor DW, Wentz D, Jacobson G: Pulmonary concentration of ^{67}Ga in pneumoconiosis. *Radiology* 1974; 120: 815-820.
170. Richman SD, Levenson SM, Bunn PA, Flinn GS, Johnston GS, Devita VT: ^{67}Ga accumulation in pulmonary lesions associated with bleomycin toxicity. *Cancer* 1975; 36: 1966-1972.
171. Niden AH, Mishkin FS, Khurana ML: $^{67}\text{Gallium citrate}$ lung scans in interstitial lung disease. *Chest* 1976; 69: 266-268.
172. Line BR, Fulmer JD, Reynolds HY, et al: Gallium-67 citrate scanning in the staging of idiopathic pulmonary fibrosis. Correlation with physiological and morphologic features and bronchoalveolar lavage. *Am Rev Respir Dis* 1978; 118: 355-365.
173. Javaheri S, Levine BW, McKusick KA: Serial $^{67}\text{Gallium}$ lung scanning in pulmonary eosinophilic granuloma. *Thorax* 1979; 34: 822-823.
174. Merz T, Malmud L, McKusick K, Wagner HN: Mechanism of ^{67}Ga association with lymphocytes. *Cancer Res* 1974; 34: 2495-2499.
175. Reynolds HY, Newball HH: Fluid and cellular milieu of the human respiratory tract. In: Kirkpatrick CH, Reynolds HY: *Immunologic and infectious reactions in the lung*. New York and Basel: Marcel Dekker, Inc, 1976; 1: 3-27.
176. Reynolds HY, Merrill WM: Analysis of bronchoalveolar lavage in normal humans and patients with diffuse interstitial lung diseases. In: Biserte G, Chretien J, Woisin C: *Bronchoalveolar lavage in man*. Paris: INSERM, 1979; 227-249.
177. Hunnighake GW, Kawanami O, Ferrans VJ, Roberts WC, Crystal RG: Characterization of the inflammatory and immune effector cells in lung parenchyma of patients with interstitial lung disease. *Am Rev Respir Dis* 1981; (in press).
178. Reynolds HY: Assessment of bronchoalveolar lavage (BAL) analysis in the diagnosis of patients with interstitial lung diseases. *Bull Eur Physiopath Resp* 15: 28P, 1979.
179. Davis GS, Brody AR, Landis JN, Graham WGB, Craighead JE, Green GM: Quantitation of inflammatory activity in interstitial pneumonitis by bronchofiberscopic pulmonary lavage. *Chest* 1976; 69S: 265S-266S.
180. Jaurand MC, Bignon J, Magne L, Kaplan H: Enzymes in bronchoalveolar lavage fluid from patients with asbestos exposure. *Am Rev Respir Dis* 1978; 117: 243A.
181. Mandel MA, Dvorak J, Worman LW, DeCosse JJ: Immunoglobulin content in the bronchial washings of patients with benign and malignant pulmonary disease. *N Engl J Med* 1976; 295: 694-698.
182. Yeager H, Williams MC, Beekman JF, Bayly TC, Beaman BL, Hawley RJ: Sarcoidosis: analysis of cells obtained by bronchial lavage. *Am Rev Respir Dis* 1977; 116: 951-955.
183. Bassett F, Sulu P, Wyllie L, et al: Langerhans cells and lung interstitium. *Ann NY Acad Sci* 1976; 278: 599-611.

184. Hunninghake GW, Gadek JE, Crystal RG: Cigarette smoking and lung parenchymal injury: mechanisms by which cigarette smoke attracts polymorphonuclear leukocytes to lung. *Chest* 1980; 77 [suppl]: 273.
185. Clements JA, King RJ: Composition of the surface active material. In: Crystal RG, ed. *The biochemical basis of pulmonary function*. New York and Basel: Marcel Dekker, Inc. 1976; 363-387.
186. Falk GA, Odinaka AJ, Siskind GW: Immunoglobulins in the bronchial washings of patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1972; 105: 14-21.
187. Low RB, David GS, Giancola MS: Biochemical analyses of bronchoalveolar lavage fluids of healthy human volunteer smokers and nonsmokers. *Am Rev Respir Dis* 1978; 118: 863-875.
188. Patterson R, McKenna JM, Suszko IM, et al.: Living histamine containing cells from bronchial lumens of humans. Description and comparison of histamine content with cells of Rhesus monkeys. *J Clin Invest* 1977; 59: 217-225.
189. Goto T, Doi H, Ozaki T, Nakayama T, et al.: Immunoglobulin A system in the respiratory disease. *Am Rev Respir Dis* 1979; 119: 685.
190. Olsen GN, Harris JO, Castle JR, Waldmen RH, Karmgard HJ: Alpha-1-antitrypsin content in serum, alveolar macrophages, and alveolar lavage fluid of smoking and nonsmoking normal subjects. *J Clin Invest* 1975; 55: 427-430.
191. Gadek JE, Zimmerman RG, Fells GA, Crystal RG: The antielastases of the human alveolar structures: assessment of the $\alpha 1$ -antitrypsin hypothesis. Submitted.
192. Kelman J, Brin S, Horowitz A, et al.: Collagen synthesis and collagenase production by human lung fibroblasts. *Am Rev Respir Dis* 1977; 115: 343A.
193. Basset F, Soler P, Grandsargne M, et al.: Etude ultrastructurale des liquides de lavage broncho-alvéolaire (LBA) chez l'homme. *Bull Eur Physiopath Resp* 15: 34P-35P, 1979.
194. Hunninghake GW, Keogh BA, Line BR, Gadek JE, Kawamami O, Ferrans VJ, Crystal RG: Pulmonary sarcoidosis: Pathogenesis and therapy. In: Boros D, Yoshida T, eds. *Basic and clinical aspects of granulomatous diseases*. New York: Elsevier-North Holland 1980 (in press).
195. Hunninghake GW, Keogh BA, Gadek JE, Bitterman PB, Rennard SI, Crystal RG: Inflammatory and immune characteristics of idiopathic pulmonary fibrosis. In: R. Suskind, ed. *Immunologic mechanisms in pulmonary disease*, 1980 (in press).
196. Calvanico NJ, Ambegaonkar SP, Schlueter DP, Fink JN: Immunoglobulin levels in bronchoalveolar lavage fluid from pigeon breeders. Submitted.
197. Keogh B, Hunninghake G, Line B, Price D, Young R, Crystal R: Therapy decisions in sarcoidosis. Prospective use of bronchoalveolar lavage and gallium-67 scanning. *Am Rev Respir Dis* 1980; 121 [suppl]: 155.
198. Hodson WA, ed: *Development of the lung*. New York: M Dekker, 1977.
199. Claman HN: Corticosteroids and lymphoid cells. *N Engl J Med* 1972; 287: 388-396.
200. Fauci AS, Dale DC, Balow JE: Glucocorticosteroid therapy: mechanisms of action and clinical considerations. *Ann Intern Med* 1976; 84: 304-315.
201. Balow JE, Rosenthal AS: Glucocorticoid suppression of macrophage migration inhibitory factor. *J Exp Med* 1973; 137: 1031-1041.
202. Hedfors E: Influence of steroid treatment: response in sarcoidosis. *Clin Immunol Immunopathol* 1975; 4: 96-100.
203. Dimitriu A: Suppression of macrophage arming by corticosteroids. *Cellular Immunol* 1976; 21: 79-87.
204. Ilfeld DN, Krakauer RS, Blaese RM: Suppression of the human autologous mixed lymphocyte reaction by physiologic concentrations of hydrocortisone. *J Immunol* 1977; 119: 428-434.
205. Haynes BF, Fauci AS: The differential effect of in vivo hydrocortisone on the kinetics of subpopulations of human peripheral blood thymus-derived lymphocytes. *J Clin Invest* 1978; 61: 703-707.
206. Saxon A, Stevens RM, Ramer SJ, Clements PJ, Yu DTY: Glucocorticosteroids administered in vivo inhibit human suppressor T-lymphocyte function and diminish B-lymphocyte responsiveness in *in vitro* immunoglobulin synthesis. *J Clin Invest* 1978; 61: 922-930.
207. Parrillo JE, Fauci AS: Mechanisms of corticosteroid action on lymphocyte subpopulations. *Clin Exp Immunol* 1978; 31: 116-125.
208. Hunninghake GW, Fauci AS: Immunological reactivity of the lung. III. Effects of corticosteroids on alveolar macrophage cytotoxic effector cell function. *J Immunol* 1977; 118: 146-150.
209. Boggs DR, Athens JW, Cartwright GE, Wintrobe MM: The effect of adrenal glucocorticosteroids upon the cellular composition of inflammatory exudates. *J Appl Physiol* 1964; 44: 763-773.
210. Werb Z: Biochemical actions of glucocorticoids on macrophages in culture. Specific inhibition of elastase, collagenase and plasminogen activator secretion and effects on other metabolic functions. *J Exp Med* 1978; 147: 1695-1712.
211. Meier-Sydwor J, Rust M, Kronenberger H, Thiel C, Amthor M, Riemann H: Long-term follow-up of lung function parameters in patients with idiopathic pulmonary fibrosis treated with prednisone and azathioprine or D-penicillamine. *Prax Pneumol* 1979; 33: 680-688.
212. Reed J, Holland RAB: Treatment of the Hamman-Rich syndrome with cortisone. *Thorax* 1959; 14: 71-75.
213. Stack BHR, Choo-Kang YFJ, Heard BE: The prognosis of cryptogenic fibrosing alveolitis. *Thorax* 1972; 27: 535-542.
214. Gracey DR, Divertie MB: Corticosteroid treatment of diffuse interstitial pulmonary fibrosis. *JAMA* 1970; 211: 495-497.
215. Mitchell DN, Scadding JG: Sarcoidosis. *Am Rev Respir Dis* 1974; 110: 774-802.
216. Johns CJ, Zachary JB, Ball Jr. WC: A 10 year study of corticosteroid treatment of pulmonary sarcoidosis. *Hopkins Med J* 1974; 134: 271-83.
217. Stone DJ, Schwartz A: A long-term study of sarcoid and its modification by steroid therapy. *Am J Med* 1966; 41: 528-540.
218. Young RL, Harkleroad LE, Lordon RE, Weg JG: Pulmonary sarcoidosis: a prospective evaluation of glucocorticoid therapy. *Ann Intern Med* 1970; 73: 207-212.
219. Israel HL, Fouts DW, Beggs RA: A controlled trial of prednisone treatment of sarcoidosis. *Am Rev Respir Dis* 1973; 107: 609-614.
220. DeRemee RA: The present status of treatment of pulmonary sarcoidosis: a house divided. *Chest* 1977; 71: 388-393.
221. Johns CJ, MacGregor MI, Zachary JB, Ball WC: Extended experience in the long-term corticosteroid treatment of pulmonary sarcoidosis. *Ann NY Acad Sci* 1976; 278: 722-731.
222. Turiaf J, Johns CJ, Teirstein AS, Tsuji S, Wurm K: The problem of the treatment of sarcoidosis: report of the subcommittee on therapy. *Ann NY Acad Sci* 1976; 278: 743-751.
223. Hunninghake GW, Fauci AS: State of the art-pulmonary disorders associated with the collagen vascular diseases. *Am Rev Respir Dis* 1979; 119: 471-503.
224. Colp CR, Riker J, Williams MH Jr.: Serial changes in scleroderma and idiopathic interstitial lung disease. *Arch Intern Med* 1973; 132: 506-515.
225. Hughes DTD, Lee FI: Lung function in patients with systemic sclerosis. *Thorax* 1963; 18: 16-20.
226. Guleria JS, Pande JN, Malik SK, Bhutani LK: Lungs in progressive systemic sclerosis. *Br J Dis Chest* 1970; 64: 150-160.
227. Dale DC, Fauci AS, Wolff SM: Alternate-day prednisone. *N Engl J Med* 1974; 291: 1154-1158.
228. Fauci AS: Alternate-day corticosteroid therapy. *Am J Med*

- 1978; 64: 729-731.
229. Winterbauer RH, Hammar SP, Hallman KO, et al.: Diffuse interstitial pneumonitis. *Am J Med* 1978; 65: 661-672.
 230. Brown CH, Turner-Warwick M: The treatment of cryptogenic fibrosing alveolitis with immunosuppressant drugs. *Q J Med* 1971; 158: 289-302.
 231. Meier-Sydon J, Mitrou PS: Aspekte der therapie von autoimmunerkrankungen, unter besonderer berücksichtigung ihrer pulmonalen manifesten. *Prax Pneumol* 1979; 33: 333-340.
 232. Fulmer J, Elson N, Von Gal E, et al.: Treatment of idiopathic pulmonary fibrosis. *Clin Res* 1978; 26: 538A.
 233. Weese WC, Levine BW, Kazemi H: Interstitial lung disease resistant to corticosteroid therapy. *Chest* 1975; 67: 57-60.
 234. Goodman M, Turner-Warwick M: Pilot study of penicillamine therapy in corticosteroid failure patients with widespread pulmonary fibrosis. *Chest* 1978; 74: 338.
 235. Cegla UH, Kroidl RF, Meier-Sydon J, Thiel C, Czarnecki GV: Therapy of the idiopathic fibrosis of the lung. Experiences with three therapeutic principles: corticosteroids in combination with azathioprine, D-penicillamine and K-para-aminobenzoate. *Pneumonologie* 1975; 152: 75-92.
 236. Meuret G, Fueter R, Gloor F: Early stage of fulminant idio-
pathic pulmonary fibrosis cured by intense combination therapy using cyclophosphamide, vincristine, and prednisone. *Respiration* 1978; 36: 228-233.
 237. Topilow AA, Rothenberg SP, Cottrell TS: Interstitial pneumonia after prolonged treatment with cyclophosphamide. *Am Rev Respir Dis* 1973; 108: 114-117.
 238. Patel AR, Shah PC, Rhee HL, Sassoon H, Rao KP: Cyclophosphamide therapy and interstitial pulmonary fibrosis. *Cancer* 1976; 38: 1542-1549.
 239. Eastmond CJ: Diffuse alveolitis as complication of penicillamine treatment for rheumatoid arthritis. *Br Med J* 1976; 1: 1506.
 240. Casci o D, Scott JL: Acute leukemia following prolonged cytotoxic agent therapy. *Medicine (Baltimore)* 1979; 58: 32-47.
 241. Research Committee of the British Tuberculosis Association: Chloroquine in the treatment of sarcoidosis. *Tubercle (Lond)* 1967; 48: 257-272.
 242. James DG, Carstairs LS, Trowell J, Sharma OP: Treatment of sarcoidosis. *Lancet* 1967; 1: 526-528.
 243. Fauci AS, Wolff SM: Wegener's granulomatosis and related diseases. *Dis Month* 1977; 23: 1.
 244. Fulmer JD, Roberts WC, Von Gal ER, Crystal RG: Small airways in idiopathic pulmonary fibrosis: comparison of morphologic and physiologic observations. *J Clin Invest* 1977; 60: 595-610.