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Chapter 4

Clinical-Pathologic Approach to Diffuse Infiltrative Lung Disease*

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Clinicians recognize a group of chronic lung diseases with several features in common. Clinically, dyspnea is the predominant symptom, and on examination frequently the only finding is "dry rales." Radiographs generally show a diffuse "infiltration" by irregular lines, small nodules, or "ground glass" shadows. Physiologically, the abnormalities primarily affect oxygen exchange and result in hypoxemia, whereas the mechanics of breathing are little impaired. None of the names used to designate this group is entirely accurate. "Diffuse lung disease" does not exclude the much more common obstructive disorders which are also "diffuse" yet specifically excluded here. The term "interstitial" is misleading because most of these disorders also have intra-alveolar abnormalities, and in some the latter actually predominate. Finally, "alveolar-capillary block" does not correspond to recent interpretation of the pathophysiologic process involved. We believe that the term "chronic diffuse infiltrative" is the most appropriate, although it must be acknowledged that sometimes the disease is more or less localized and sometimes the distinction between "acute" and "chronic" is uncertain.

This group of disorders has received increasing attention in recent years, perhaps because of more liberal use of lung biopsy with the opportunity to study early and active rather than nonspecific end-stage disease. A growing interest in environmental lung disease and in immunologic disorders also may have focused attention on infiltrative lung disease. Finally, an increasing therapeutic armamentarium, including effective antibiotics, antiinflammatory agents, immunosuppressive drugs and pulmonary lavage, has stimulated a search for more precise diagnosis and a study of the natural history of these diseases. The proportion of these disorders among all of our referrals has increased each year, and the 1,234 cases now on file represent 21.2% of all referrals seen during the last 25 years (Table 1). Most likely, this experience has been weighted by our special interests.

This review will focus primarily on the diagnostic approach; and, in this context,

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TABLE 1. DIFFUSE INFILTRATIVE LUNG DISEASE

	Total no.	With biopsy
Infections (3.2%)		
miliary tuberculosis	15	5
fungal and amoebic	10	2
viral*	14	2
"Allergic" reactions (3.1%)		
chronic eosinophilic pneumonia	30	21
asthma with infiltration and drug reactions	8	1
Malignant neoplasms (2.4%)		
leukemia and lymphoma	9	3
bronchoalveolar carcinoma	4	4
carcinomatosis, metastatic	16	7
Environmental diseases (24.8%)		
allergic alveolitis	15	5
silicosis, coal and graphite	65	21
asbestosis (excluding survey cases)	115	58
other silicates	17	4
berylliosis	63	16
toxic gases (NO_2, SO_2, Br, Cl) and "smoke"	31	2
Connective tissue disorders (7.9%)		
progressive systemic sclerosis	43	10
lupus erythematosus	26	2
rheumatoid lung	22	4
other or combined	7	2
Sarcoidosis (20.8%)	257	65
Interstitial pneumonias (12.8%)		
acute	7	6
usual	76	61
usual, due to radiation	24	6
desquamative	47	45
lymphocytic	4	4
Unusual specific disorders (3.8%)		
Wegener's granulomatosis	6	5
idiopathic hemosiderosis	3	3
Goodpasture's syndrome	5	5
pulmonary alveolar proteinosis	13	13
pulmonary alveolar microlithiasis	1	1
eosinophilic granuloma	15	15
tuberous sclerosis	1	1
lymphangioleiomyomatosis	3	3
Pulmonary vascular diseases (6.4%)		
arteriolitis	3	2
veno-occlusive	3	3
multiple emboli and idiopathic hypertension	73	12
Chronic passive congestion (1.9%)	23	7
Nonspecific reactions (5.8%)		
honeycombing, etiology?	18	16
focal fibrosis	22	20
primarily small airways disease	12	12
cystic fibrosis	10	2
primarily emphysema	3	3
aspiration (oil, blood, food)	4	4
normal lung	2	2
No diagnosis (7.2%)	89	5
	1,234	490

it will emphasize the expectations of the clinician with regard to histologic examination and the needs of the pathologist with regard to clinical information that may be helpful, indeed may be essential, to correct histologic interpretation.

The spectrum of disorders included in chronic diffuse infiltrative lung disease is very large and constantly growing. An alphabetic listing is not useful, and, therefore, for some years we followed an etiologic grouping suggested by Buechner.[4] With clarification of certain etiologies, description of new histologic patterns, characterization of allergic and immunologically mediated disorders, and the growing list of environmental lung diseases, we have recently used a classification based upon our experience (Table 1). This may form a useful framework for the following discussion although we will not specifically deal with the clinical and histologic features of each "entity" nor even of each major category.

DIAGNOSTIC APPROACH

In most instances the disease is discovered as the result of a chest roentgenogram obtained because of respiratory symptoms. Discovery was incidental to routine examination or because of symptoms suggestive of a systemic disorder in about 20% of cases.[14] The chief complaint in over one-half of our cases was dyspnea, sometimes with cough, expectoration, and weight loss, and less frequently with fever, night sweats, or other evidence of toxicity. Joint pains, with or without swelling and redness, was the only other relatively common chief complaint, occurring in about 6%, prominently in sarcoidosis and quite often in the interstitial pneumonias.[5]

The history is by far the most productive part of the examination and, in our earlier experience, has led to a diagnosis in 32% of all cases.[14] Apart from the conventional present, past, and family history, the most important aspect concerns environmental and occupational review. This should account for all materials worked on and for the tools and any intermediary compound used to facilitate the job, for example cutting oils, graphite, or talc.[13, 29, 30] Similar symptoms in other workers, the availability of masks, and frequent state inspections are important clues to potentially dangerous exposure. A review of recreational activities, hobbies, and geographic locations must be included here. The following case illustrates the importance of an occupational history accounting for every job, however brief, and also the importance of special stains.

Case 1: This 40-year-old policeman in a small town was first seen locally because of cough and dyspnea progressive for seven or eight years. Except for this, and some problems with a duodenal ulcer, he had been well and had worked for the police department since graduation from high school. Examination revealed diffuse dry rales with a close-to-the-ear sound and finger clubbing. Routine laboratory studies were all normal. The chest roentgenogram revealed the lungs to be somewhat reduced in volume. Additionally, there were fine irregular or linear markings at both bases, and the cardiac silhouette was indistinct (Fig. 1). A lung biopsy was interpreted as usual interstitial pneumonia (UIP) with honeycombing, and this diagnosis was confirmed by an authority on lung pathology.

About two years later the patient's physician attended our seminar on environmental lung disease. We mentioned a paper plant where, many years ago, cigarette filter paper had been made by mixing in a carding machine 85% acetate with 15% "Cape Blue" asbestos. Since then there has been a high prevalence of asbestosis among these workers even after brief exposure. The physician then recalled that this policeman had actually worked for 3 months at that same paper plant 17 years previously, but he had always worn a mask. Upon referral to us, this history was confirmed. Lung function studies showed marked lung volume restriction, slight impairment of flow attributed to a long smoking

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FIG. 1. Chest roentgenogram of patient #1. The lung volume is somewhat reduced and there is a fine linear or irregular infiltration causing the cardiac outline to become indistinct. Note the largely basal distribution of lesions and also the discrepancy between the relatively slight radiographic opacities and the marked functional (Table 2) and severe pathologic alterations (Fig. 2).

history, marked hypoxemia during slight exercise and a single breath diffusing capacity reduced to 46% of predicted (Table 2). The sections of lung tissue were reviewed. A chronic interstitial pneumonia of the usual pattern and some regions of endstage honeycombing were indeed present (Fig. 2). A moderate number of asbestos bodies were readily identified on recut sections stained for iron (Fig. 2, *inset*), although they were more difficult to find on sections stained with hematoxylin and eosin.

As this case illustrates, historical information is as important to the pathologist as it is to the clinician, since there are many ways in which the lung can be injured, but only a few stereotyped ways in which it can react. A few of these tissue reactions, such as the dust macule with or without fibrosis, are diagnostic of an environmental insult, especially when they contain abundant dust. Virtually all other lung reactions may or may not be related to the environment. For example, the sarcoid reaction may be "idiopathic" or it may result from exposure to beryllium; UIP may be "cryptogenic" (Case 4) or it may be caused by exposure to fibrous silicates (Fig. 2); and bronchiolitis obliterans may be the consequence of a viral pneumonia or it may result from acute or chronic exposure to oxides of nitrogen. Sometimes the pathologist is more familiar with the causes of occupational lung injury than the clinician, and then direct questions or those implied

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TABLE 2 LUNG FUNCTION STUDIES OF PATIENTS #1-#5*

	Case # 4/72		Case #2 4/75		Case #3					Case #4			Case #5 11/76	
					3/70	8/71	5/74	9/73		12/74	9/75 Rx	8/76 Rx		
FVC, % predicted	47		68		66	81	62	89		83	68	69	90	
FEV_1/FVC, %	70		75		87	81	62	86		86	87	89	85	
FEF 25-75, % predicted	26		35		117	97	94	114		132	111	114	97	
MVV, % predicted	50		85		116	122	111	61		72	65	81	110	
RV, % predicted	78		87		54	64	58	49		46	42	44	85	
TLC, % predicted	53		77		71	87	67	94		85	81	69	91	
RV/TLC, %	36		38		23	23	28	27		31	28	30	24	
Dsb, % predicted	42		37		39	53	40	64		55	41	46	69	
	Rest	Ex.	Rest	Ex.	Rest	Rest	Rest	Rest	Ex.				Rest	Ex.
$P(A\text{-}a)O_2$, torr	28	50	48	61				72	61				28	25
Pao_2, torr	81	60	64	46	70	76	78	42	65				80	89
$Paco_2$, torr	34	35	35	35	45	38	34	36	27				33	34
Des, ml/min/torr	10	16	7	7				10	9				13	16

* Pulmonary terms and symbols from: A Report of the ACCP-ATS Joint Committee on Pulmonary Nomenclature, B. Burrows, Chairman, *Chest* 67 583-593, 1975. FVC, forced vital capacity; FEV_1 forced expiratory volume in 1 second, FEV_1/FVC, FEV_1 expressed as a percentage of the FVC, FEF 25-75, forced expiratory flow rate between 25 and 75% of FVC, MVV, maximum voluntary ventilation, RV, residual volume, TLC, total lung capacity, RV/TLC, residual volume expressed as a percentage of total lung capacity, Dsb, single breath diffusing capacity, $P(A\text{-}a)O_2$, alveolar arterial oxygen gradient, Pao_2, partial pressure of oxygen in arterial blood, $Paco_2$, partial pressure of carbon dioxide in arterial blood, Dss, steady state diffusing capacity

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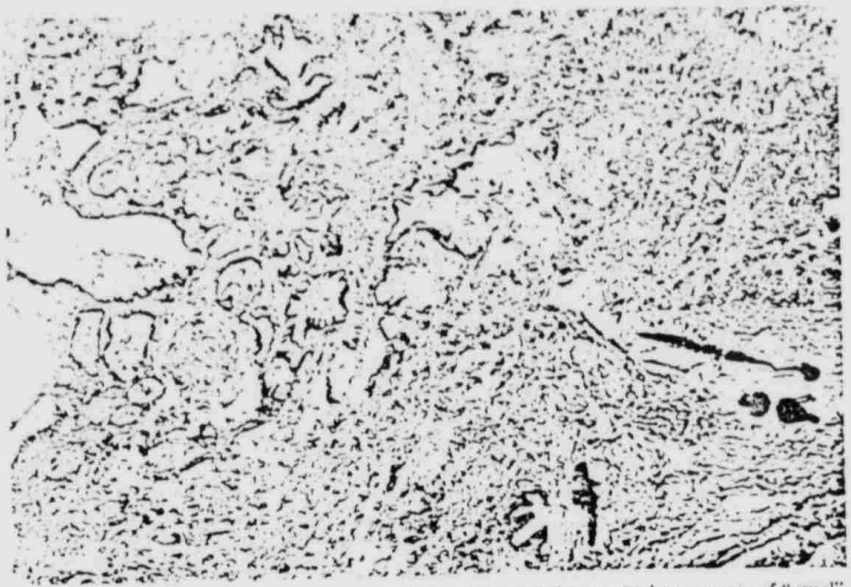


FIG. 2 Open lung biopsy from patient #1. Typical variegated interstitial pneumonia of "usual" pattern with changes ranging from cellular infiltrates to end-stage honeycombing. There is pooling of mucus in the large air spaces, and there is proteinaceous debris in some of the alveoli whose walls are infiltrated by a mixture of round cells. *Inset:* A few of the asbestos bodies, readily identified on recut sections, stained with a Prussian blue stain for iron.

by the tentative diagnoses may be of great help both in focusing the investigation and in stimulating renewed efforts when the original history was inadequate. Such questions are especially important when there is only a little dust in the lung tissue (Case 1) or when the histologic pattern is compatible with an environmental insult and there is no pathognomonic dust (Figs. 4 and 5). In such cases, the correct diagnosis can be made only with the aid of epidemiologic data.

The chest roentgenogram by definition should be abnormal. However, the pathologist consulted about a possible lung biopsy should be aware that the roentgenogram may be normal even when there is severe interstitial lung disease. This was true in 7.7% of our 508 patients who had lung biopsy, including patients with UIP, desquamative interstitial pneumonia (DIP), sarcoidosis, bronchiolitis obliterans, allergic alveolitis, asbestosis, and lymphangioleiomyomatosis.[11] As a corollary, in our experience the severity of radiographic infiltration correlates poorly both with physiologic abnormalities and with pathologic estimates of severity.[6, 17, 18] The following patient illustrates such a discrepancy in that the roentgenogram was always normal while there were a severe impairment of gas exchange and impressive lesions microscopically. This patient, like the first (Case 1), also illustrates the importance of taking a detailed environmental history, with noxious exposure here unrelated to occupation.

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Case 2. This 46-year-old secretary and accountant saw her physician because of exertional dyspnea, a dry cough, and fatigue of two years' duration. Her symptoms improved during the summer and worsened each winter. Her history apparently was noncontributory; examination was not revealing; and the chest roentgenogram was normal. Nevertheless she was placed on corticosteroids and her condition improved. She discontinued therapy after one month because of depression and other side effects. Severe symptoms recurred during the next winter, and in March 1975 she saw her physician once more, now unable to perform simple household tasks or to walk more than 1 block without resting. Again examination and the roentgenograms were normal, but the Pa_{O_2} was only 44 torr at rest. When referred to us because of dyspnea and hypoxemia of unknown etiology, she confirmed that she had always been a secretary, had confined her activities to home and office and had never worked in a factory. Her chest roentgenogram was normal once more (Fig. 3), and clinical examination was not remarkable. Laboratory tests revealed a diffuse hyperglobulinemia and a rheumatoid factor titer of 1:2,560. Lung function studies revealed slight lung volume restriction, no obstructive impairment, and a screening diffusing capacity was reduced to 37% of predicted. Furthermore, she had severe hypoxemia with a Pa_{O_2} of only 46 torr during slight exercise (Table 2). Her open lung biopsy initially was interpreted as compatible with sarcoidosis. However, the fact that the miliary granulomata were randomly scattered rather than clustered along lymphatic vessels, and that an extensive interstitial infiltrate rich in plasma cells (Fig. 4), and an intense bronchiolitis were present (Fig. 5), suggested that a biologic dust sensitivity reaction should also be strongly considered.

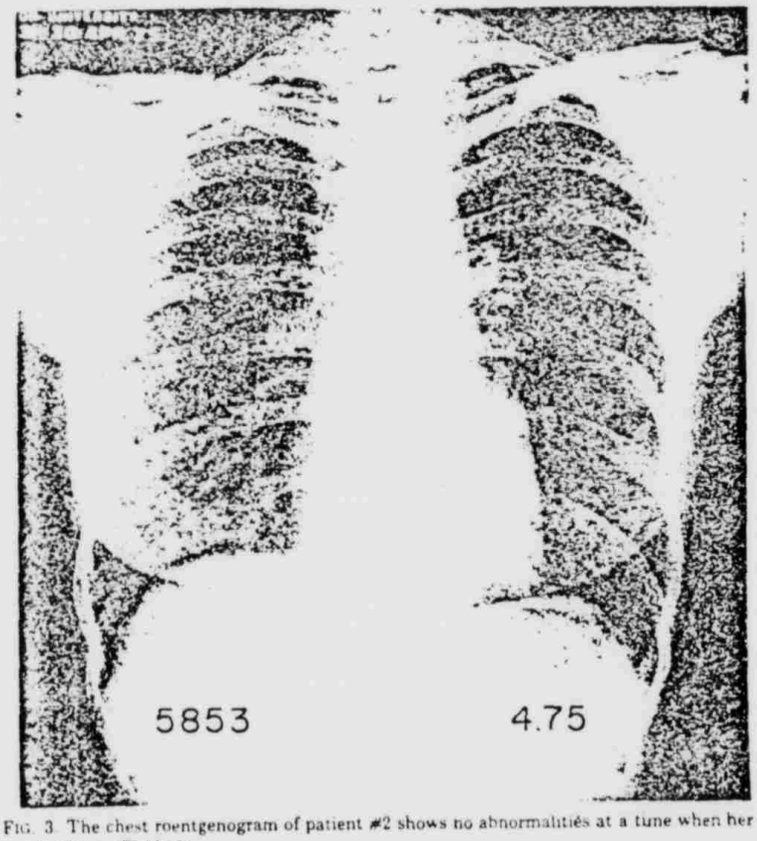


FIG. 3. The chest roentgenogram of patient #2 shows no abnormalities at a time when her Pa_{O_2} was only 48 torr (Table 2).

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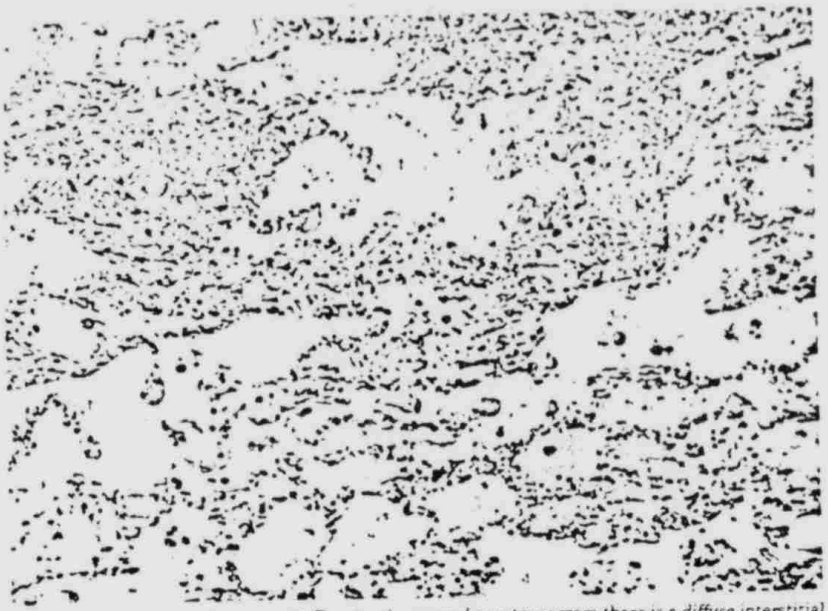


FIG. 4. Open biopsy of patient #2. Despite the normal roentgenogram there is a diffuse interstitial pneumonia rich in plasma cells. This somewhat overshadows the small granuloma.



FIG. 5. Open biopsy of patient #2. There is an intense infiltration of this bronchiole by lymphocytes and plasma cells. The combination of a diffuse interstitial pneumonia, bronchiolitis, and miliary granulomata is suggestive of a biologic dust reaction although it is also compatible with idiopathic sarcoidosis.

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As a result we reviewed her environmental history. She disliked animals and birds and had never done any farm or outdoor work. However, she minded the dryness of her home during the winter and therefore had had two humidifiers installed in series in the forced air heating system of her home. Culture of the humidifier water grew thermoactinomyces, *Penicillium cladosporium*, yeasts, and 6 unidentified fungi. The patient had positive serum precipitins to *Thermoactinomyces vulgaris*, *Micropolyspora faeni*, and Cladosporium, and double gel diffusion showed the strongest bands against the humidifier water. The diagnosis of allergic alveolitis was now confirmed, and dramatic improvement during the succeeding summer was sustained during the next winter, when the humidification system was removed. Indeed, her diffusing capacity more than doubled without specific therapy (Table 2).

This case also illustrates the nonspecificity of some tissue reactions. Nevertheless, the way in which the biopsy findings redirected the clinical investigation towards an environmental cause emphasizes the value of close collaboration between the clinician and the pathologist.

Radiographic opacities may consist of the linear or irregular markings[7] that are most often seen in interstitial pneumonias (Figs. 1, 12, and 14). Alternatively, they may be rounded, as in silicosis,[22] or "reticulo-nodular"—perhaps a combination of linear and rounded opacities—as is seen most often in granulomatous disorders.[7] Additionally, and most importantly, the entire lungs or parts thereof may have a "ground glass" appearance.[18] Such opacities have been referred to as "alveolar pattern" or "airlessness" and may indeed result from displacement of alveolar gas by cellular or amorphous debris, as in pulmonary edema, or from patchy or diffuse atelectasis. However, a similar ground glass pattern also may be seen when the alveoli are smaller than normal, as in full expiration, or, more pertinent, when all alveolar walls are diffusely thickened by cells and/or scars. Finally, a honeycomb pattern has been well described both from the radiologic[19] and from the pathologic standpoint;[20, 27] the significance of this "end-stage lung" is discussed below.

These various radiographic patterns, together with their predominant location, can be related statistically to certain pathologic entities, but in individual cases they are rarely diagnostic. A few exceptions include pulmonary alveolar microlithiasis, recognized by the sand-like appearance of the roentgenogram, or a ground glass pattern involving the lung periphery, which is virtually diagnostic for chronic eosinophilic pneumonia.[16] Other radiographic patterns may be diagnostic when supported by minimal clinical information, for example a reticulonodular pattern together with bilateral hilar adenopathy in young black persons represents a combination of findings diagnostic of sarcoidosis.

A review of previous radiographs often is the most revealing diagnostic procedure in the study of pulmonary disease. The pathologist should share in this information or ask for older films for an indication of the natural history of the disease. Most persons have had such roentgenograms during previous unrelated admissions, for insurance examinations or in connection with pre-employment screening. The time and expense involved in correspondence and travel to obtain such films is paltry compared to the alternatives of long hospitalization, extensive laboratory investigations, or, worse, discharge and later readmission with the hope of establishing the natural history prospectively. Recent films frequently enable differentiation of acute from chronic disease as discussed below; and films spanning many years often document the onset of diffuse lung disease many years

before the appearance of symptoms. This is because the pulmonary reserve is very large, and, unlike airways obstruction, restrictive lung disease initially does not greatly increase the work of breathing.

Physical examination does not often aid in diagnosis. Dry rales with a "close-to-the-ear" sound or "cellophane rales" may be heard early during the course of interstitial disease but are quite nonspecific. We recorded such adventitious sounds in about 60% of our patients with UIP and asbestosis and in 20% with sarcoidosis.[19] Digital clubbing, exercise cyanosis, and signs of cor pulmonale merely are indicative of advanced disease. More specific findings, such as hepatosplenomegaly, enlarged lymph nodes and especially signs suggesting connective tissue disorders, are important leads to further examination. Careful cardiac examination may reveal the diffuse lung disease to be a consequence of heart disease, most often mitral stenosis.

Routine laboratory studies may be of interest in regard to kidney disease or anemia. Polycythemia generally is secondary and nonspecific as is a reversed albumin:globulin ratio or an elevated sedimentation rate. Eosinophilia suggests an allergic disorder or the presence of parasites. However, such allergic reactions as chronic eosinophilic pneumonia may be seen without eosinophilia,[16] while this finding is not uncommon in infections such as tuberculosis or coccidioidomycosis. Additionally, our routine studies have included screening for connective tissue disorders, although the results more often than not have been confusing rather than enlightening. More recently we have screened for precipitating antibodies to various biologic dust antigens.

There are other routine examinations that can be done quickly, inexpensively and painlessly. They include skin testing for anergy, tuberculosis, and fungal infections and especially repeated examination of the sputum by aerobic and anaerobic culture for bacteria and fungi as well as multiple cytologic examinations. Occasionally, a search for asbestos bodies or alveolar casts may be useful.

Physiologic examination, particularly of respiratory gas exchange, is useful in detecting diffuse infiltrative lung disease, especially if the chest roentgenogram is normal (Cases 2 and 5). Furthermore, such studies characterize the severity of the disease much more accurately than either clinical examination or the chest roentgenogram. Therefore, pulmonary function tests are useful for monitoring the natural course of disease and for evaluating the results of therapy. They are, however, not helpful for specific diagnosis, because the type of physiologic derangement observed is common to virtually all of the disorders shown in Table 1. The type of pathophysiology has been well described.[3, 25] Generally, there is no overt obstruction, and restriction of lung volumes is variable and usually is seen only in advanced disease. The characteristic abnormalities consist of diminution of diffusing capacity and increased alveolar-arterial oxygen pressure difference ($P(A\text{-}a)O_2$) resulting in hypoxemia (Table 2, Fig. 16). This is accompanied by alveolar hyperventilation and a compensated respiratory alkalosis stimulated perhaps by chronic hypoxemia or perhaps by excessive reflexes from the lung or other sites. The principal abnormality, hypoxemia, was attributed for years to a decrease of the diffusing capacity from thickening of the alveolar-capillary membrane.[3, 9, 25] More recently this theory has fallen into disrepute for the following four reasons: (1) The diffusing capacity of the lung membrane is so large that

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normally complete equilibration of oxygen partial pressure between alveolar gas and capillary blood occurs in only one-fourth the time available for gas exchange. Therefore, a marked reduction of diffusing capacity, say to one-half of normal, would not result in an alveolar-end capillary P_{O_2} "gradient"; yet such patients commonly have an elevated $P(A\text{-}a)O_2$. From this it has been reasoned that the $P(A\text{-}a)O_2$ must be due to postcapillary venous admixture rather than to impaired diffusing capacity.[32] (2) It has been shown that at least one-half of the total resistance to diffusion is caused by the slowness of the reaction rate of oxygen with hemoglobin,[31] and this is not altered by lung disease. (3) If impaired diffusion were the sole cause of an elevated $P(A\text{-}a)O_2$, then this $P(A\text{-}a)O_2$ would always increase with exercise, which causes an accelerated flow rate of blood through capillaries.[3, 28] Actually, in about one-third of our patients $P(A\text{-}a)O_2$ decreased with exercise.[6] Finally, (4) the histologic picture evoked by the term "alveolar-capillary block"—a uniform thickening of the blood-gas barrier—is rarely seen. Occasionally, alveolar walls are uniformly lined by epithelial cells, and sometimes there are selected fields where the walls are diffusely thickened by cellular infiltration or amyloid. Except for such uncommon examples, microscopic examination rarely reveals lesions suggesting alveolar-capillary block. Most often there are focal solid lesions and much normal intervening lung tissue, as in sarcoidosis (Fig. 21) and silicosis; or sometimes the alveoli appear to be completely filled by granular debris or macrophages, as in proteinosis. Even in interstitial pneumonia, cellular thickening and fibrosis generally are quite uneven (Figs. 4, 7, 8, and 15). Sometimes the alveolar walls are thick, but the capillaries are seen to spiral around the periphery of the fibrous tissue, which then does not contribute to an increased diffusion distance. Thus, edema and cellular infiltration may not alter the thickness of the blood-air barrier, a possibility confirmed by electron microscopic studies discussed elsewhere in this monograph.[26] For all of these reasons, it is now assumed that hypoxemia in this group of disorders is largely the result of ventilation/perfusion discrepancies.[12, 35] Such mismatching of gas and blood is easily explained on histologic grounds considering the very uneven involvement in most cases and the predilection of some lesions for the broncho-vascular rays.[7] These ventilation-perfusion discrepancies undoubtedly fully explain hypoxemia at rest. During exercise, however, the contact time between alveolar gas and capillary blood is greatly reduced, especially in patients with a compromised pulmonary capillary bed. Then impaired diffusing capacity may well contribute to hypoxemia in some cases.

Financially or physically traumatic procedures: Many more elaborate diagnostic procedures have been performed almost routinely in the past. Indeed, until 1965 our consulting physicians generally would not permit lung biopsy until virtually all other "special procedures" had been exhausted and until several extrapulmonary sites had been biopsied. Thus, virtually all patients had gastrointestinal series, barium enemas, intravenous pyelograms, skeletal surveys and a variety of scans, ostensibly in search of a primary tumor that might be the source of diffuse pulmonary metastases. Conjunctivae, muscle, bronchial walls, and liver were biopsied routinely in search for sarcoidosis, and renal biopsy was not uncommon to rule out Wegener's granulomatosis, Goodpasture's syndrome, or neoplasm. Finally, supraclavicular triangle exploration and, more recently, me-

diastinoscopy[3] were used routinely until we demonstrated that these procedures had a yield of less than 1% in diffuse infiltrative disease without hilar adenopathy.[14] With this approach, the average interval between the discovery of infiltrative disease and diagnosis was 1.53 years,[15] often with multiple admissions and repetitive examinations; frequently patients were unemployable during this entire time. We found that extensive radiographic studies and extrapulmonary biopsies not only were not justifiable on the basis of cost-benefit analysis but also that the combined morbidity and mortality of all of these studies far exceeded that of open lung biopsy.[14, 15] Also, it should be noted that about one-third of the disorders listed in Table 1 do not have extrapulmonary manifestations nor do they lead to characteristic secretions.

these considerations have persuaded us that lung biopsy should be ed forthwith when: (1) chronicity has been demonstrated, generally by persisting for more than one month; (2) there are no specific leads; and the simple studies, including blood tests, sputum examination and skin ctivity, have been unrevealing. In the past, 39.7% of our 1,234 patients with iffuse infiltrative disease eventually came to open lung biopsy (Table 1).

PATHOLOGIC EVALUATION OF THE BIOPSY

Diagnosis from Histology and Accessory Data

The histologic features of the many diseases listed in Table 1 have been described previously and will not be repeated here. However, in approaching the differential diagnosis of such lesions, there are several broad categories and specific questions which should be considered, and the features listed in Table 3 merit assessment. In many cases, one can quickly decide whether a lesion is acute or chronic, interstitial or alveolar or both, granulomatous or not, exudative or organizing. Thus, a lesion dominated by hyaline membranes and proteinaceous debris is more likely to be an acute reaction. The presence of tumor, dust, or infectious agents is also easily decided in most cases, although a few simple aids such as special stains may be needed and cultures should *always* be done. We have made it a rule to scan all sections under polarized light; it may be mentioned in passing that birefringent crystals are readily missed without high intensity illumination. Special studies that may aid in analyzing dusts are discussed elsewhere in this monograph.[1]

The distribution of parenchymal lesions is sometimes a useful clue. For example, pneumoconioses, sarcoidosis, and malignant lymphoma are the only diseases in which the lesions commonly tend to concentrate along the lymphatic pathways. Similarly, noting whether a lesion is diffuse or focal and whether it is uniform throughout or highly variegated helps in making some diagnoses. Finally, it is important to note lesions of blood vessels and of conducting airways (in most biopsies this means bronchioles). It must then be decided whether these are the dominant lesions or simply components of a more diffuse reaction. Bronchiolitis obliterans, for example, may result from infection, toxic injury, or allergy; and the resolution of this differential depends more on the associated parenchymal changes than on the morphology of the bronchioles themselves.

It is worth noting that the significance of some of the features in Table 3 may

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TABLE 3 HISTOLOGIC FEATURES ASSESSED IN DIFFUSE INFILTRATIVE LUNG DISEASE

A. Alveoli, small air spaces
- hyaline membranes
- proteinaceous exudates
- stasis of secretions
- epithelial regeneration
- hemorrhage
- hemosiderosis (macrophages)
- alveolar cell population (kind and number)
- organisms, inclusion bodies
- dust

B. Interstitium
- edema
- diffuse cell population
- localized lymphoid follicles
- dust
- granulomas, with or without necrosis
- destruction
- organization, fibrosis, honeycombing

C. Conducting Airways
- narrowing by mural or external lesions
- obstruction or obliteration by scar or mucus
- cellular infiltrates
- granulomas
- loss

D. Vessels
- diffuse hypertrophy, intimal proliferation
- thrombi, emboli
- fibrous obliteration
- angiitis

E. Tumor

be difficult to assess from the biopsy alone. The presence of widespread alveolar hemorrhage may be the only apparent lesion in an early stage of pulmonary hemosiderosis, but more often it is an irrelevant result of the trauma of the biopsy. Radiographic and hematologic data clarify this situation. Acute alveolar injury occasionally closely simulates pulmonary alveolar proteinosis. This observation has interesting implications in regard to the pathogenesis of such lesions. However, the practical problem of deciding the likely course and prognosis in such a patient is best resolved by evaluating the history and chest radiograph, since in these respects the usual form of proteinosis and acute alveolar injury are quite different. The need for epidemiologic data in interpreting the significance of a few dust particles has already been noted.

The relationship of honeycombing to diffuse infiltrative lung disease merits special comment. Honeycombing is a nonspecific end stage of a wide variety of pulmonary lesions which cause loss and revision of architecture with scarring.[19,20,27] When seen more or less diffusely, it is usually the result of some interstitial process. The honeycombing itself is not useful in identifying the original process, however, but merely indicates that it was destructive and scar-forming. The characteristic features and patterns of the active disease are increasingly obscured as the lesion progresses and the scars accumulate. The closer a lesion approaches the final common pathway of honeycombing, the more

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difficult it becomes to distinguish it from the other interstitial diseases which similarly organize (Fig. 6). Such progression to honeycombing is illustrated by a patient whose original biopsy had typical lesions of eosinophilic granuloma (Fig. 7). When the patient died of respiratory failure two years later, the autopsy revealed only nonspecific honeycombing (Fig. 8).

Confidence of Diagnosis and Differential Diagnosis. In a classic case, the pathologist may be certain of the diagnosis, but often this certainty is diluted (1) by the lack of some components, that is, either when the lesion is mild and early or when it is severe but burned out and late; (2) by the presence of atypical features; (3) because the lesion is a rather nonspecific one such as noncaseating granuloma; or (4) because similar histologic findings have different significance when they are localized rather than diffuse. A DIP-like or UIP-like reaction is sometimes encountered adjacent to other focal lesions such as neoplasms or abscesses or even near the granulomas of histiocytosis X, and an early stage of UIP also may be mimicked by a resolving viral pneumonia. Sometimes one encounters relatively focal lesions which resemble UIP but which never progress to affect other parts of the lung. Even more commonly, end-stage honeycombing is encountered as the focal residue from a variety of processes such as healed necrotizing pneumonia. When such impostors of a diffuse interstitial process are met, it is invaluable to have available the physiologic and radiographic data to determine whether or not one is dealing with a widespread process. The pathologist can gain some help from reports by the radiologist, but actual inspection of films is preferable. This will give him a much better concept of the lung as a whole and of the extent, distribution, and character of the radiographic abnormalities which must be correlated and explained. The patient whose roentgenogram is shown in Figure 9 illustrates this problem. The biopsy from the solid nodular lesion (Fig. 10) suggests there is little normal lung, whereas the other biopsy (Fig. 11) implies there is only normal lung. This disparity is readily explained by examination of the roentgenogram.

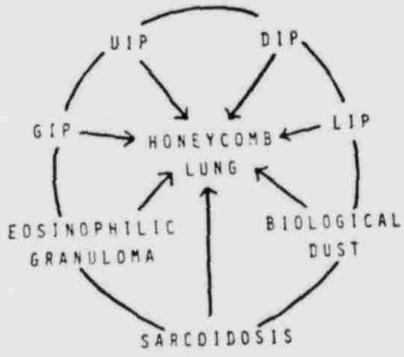


FIG. 6. Schematic representation of some of the pulmonary lesions which, in some patients, may progress to a nonspecific end-stage scarring or "honeycomb lung." The more closely the lesion approaches this final stage, the more difficult is recognition of the original pattern of reaction. *GIP, UIP, DIP,* and *LIP* = giant cell, usual, desquamative, and lymphocytic interstitial pneumonias. (Reproduced from *Chest* 69: 324, 1976.)

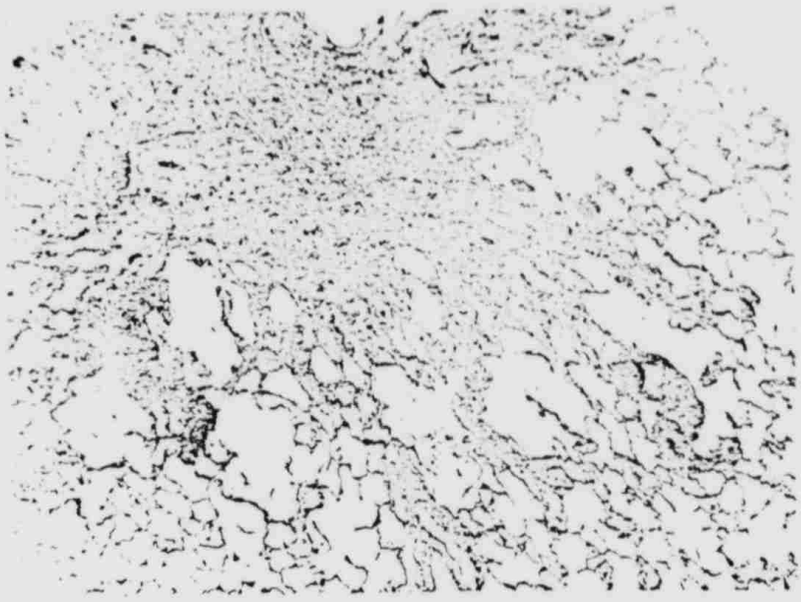


FIG. 7. Open lung biopsy from a 38-year-old dairy farmer who had a wedge resection because of progressive dyspnea. This has a classical focal interstitial lesion of eosinophilic granuloma, and under greater magnification the characteristic Langerhans histiocytes were easily identified. These same cells and a scattering of eosinophils infiltrate irregularly into adjacent alveolar walls.

Irreversible Change and Activity. In addition to rendering a diagnosis, it is important to estimate histologically the extent of destruction, fibrosis, and other irreversible damage and also the activity of the lesion. Both the diagnosis and the amount of irreversible damage affect the prognosis and the likely response to therapy. For example, a patient with UIP is not likely to do well with corticosteroid therapy irrespective of the extent of fibrosis, but a patient with DIP and mild fibrosis may well have arrest of his disease and even considerable improvement with such treatment.[6] In contrast, a patient with DIP at a stage of extensive fibrosis and honeycombing is unlikely to recover with steroids even though he has a disease which is usually responsive to such treatment. This is illustrated by the following case.

Case 3. A 56-year-old physician with tuberculosis first noted cough and exertional dyspnea in the fall of 1969. A chest roentgenogram had shown fine triangular densities and irregular markings in both cardiophrenic angles since 1966, in the spring of 1970 there was marked progression with reduction of lung volume and the irregular markings had become coarser and were now visible everywhere (Fig. 12). Functional impairment was also severe with marked restriction and a diffusing capacity of only 39% of predicted (Table 2). His tuberculin skin test had been positive for many years and now, treated with isoniazid, he failed to improve and therefore eventually consented to lung biopsy. The biopsy (Fig. 13) had many features characteristic of DIP but this process had progressed to a stage in which there was considerable interstitial fibrosis. This implied at best a limited potential for recovery on drug treatment and more likely only a possibility of arrest of the progression. He then received prednisone for about 1 year with some initial improvement, but this was not sustained (Table

2). In 1974 his physiologic studies were comparable to those 4 years earlier, dyspnea was unchanged, and the chest roentgenogram showed further increase of coarse irregular markings and some patchy ground glass densities.

Grading the activity of a lesion is also helpful in estimating prognosis. Thus, although UIP is a progressive disease in most patients, the rate of progression varies from barely perceptible to very rapid. The activity of the lesion, as indicated by cellular infiltrates, proteinaceous debris, epithelial regeneration, and fibroblasts, helps in predicting this course. The following case illustrates this correlation.

Case 4. This 68-year old retired secretary was referred on 9/73 because of an abnormal chest roentgenogram obtained during an annual checkup. She had always been entirely well and had no c[illegible]. When questioned about shortness of breath, she reported that she could climb two flights carrying all of her groceries without difficulty. She had never smoked, and no occupational e was reported. The chest roentgenogram showed striking coarse irregular linear opacities, marked in the right mid and basal zones, and honeycombing was suspected (Fig. 14). The left diaphragm was elevated but not paralyzed, and the mediastinum was shifted to the right. The mass in the right hilar area was the ascending aorta. *Interestingly, two and one years earlier, her chest* films had exactly the same appearance.

Examination revealed bilateral dry rales. Usual skin tests, sputum examination, routine blood and urine tests, electro- and immunoelectrophoresis, LE preparations, and latex fixation were all negative or normal. Lung function studies revealed normal lung volumes and no obstruction. However, her single breath diffusing capacity was only 64% of predicted and there was severe hypoxemia with an exercise $P(A-a)O_2$ of 61 torr (Table 2).

A lung biopsy revealed a usual interstitial pneumonia (Fig. 15). There was a sparse interstitial cellular infiltrate in some regions and minimal proteinaceous exudate in the air spaces. In some foci

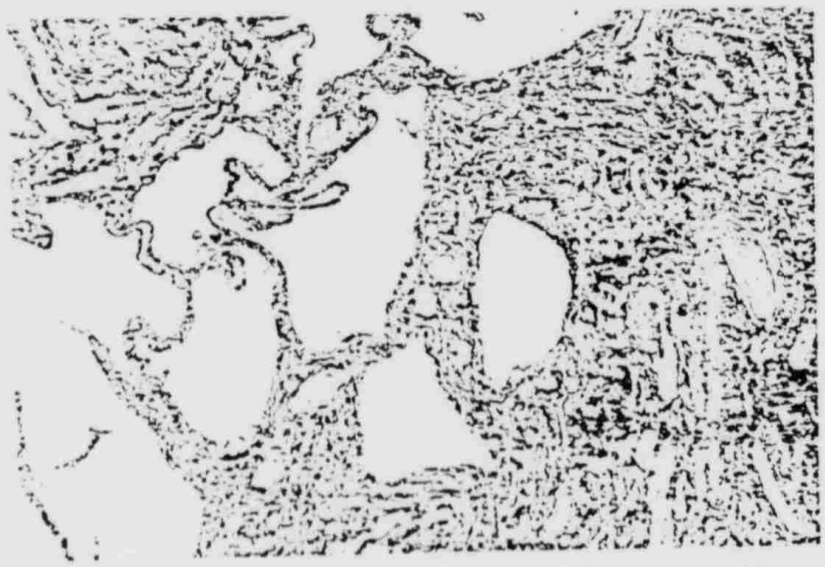


FIG. 8. Lung from autopsy of same patient as in Figure 7 who died from respiratory failure two years after biopsy. The lungs now have extensive honeycombing, and there is no longer any clue to the diagnosis of eosinophilic granuloma.

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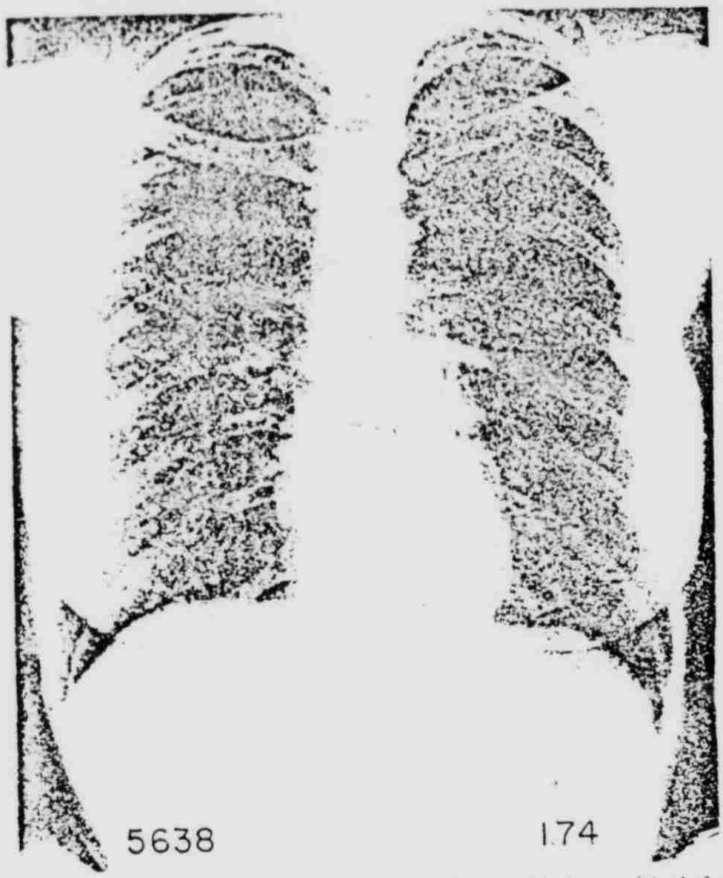


FIG. 9 Chest roentgenogram of a 28-year-old photographer's model who complained of marked weight loss. The film shows fine nodular infiltration apparently limited to both anterior segments of the upper lobes, more noticeable on the right. Lung function was entirely normal. A small anterior thoracotomy was performed with a preoperative diagnosis of talcosis because, for some years, she had sniffed cocaine cut with talc. Two biopsies were obtained, one from a hard nodulated mass in the anterior segment of the right upper lobe, and one from a normal-appearing middle lobe.

there was end stage fibrosis and fine honeycombing. Although the cellular components were sufficient to permit a diagnosis of UIP, the low degree of activity suggested that a relatively slow progression could be anticipated. Because of the histologic diagnosis, a favorable response to steroid therapy was thought to be unlikely.

During the next two years there was minimal deterioration of lung function (Table 2) but she developed slight dyspnea and a productive cough. Therefore prednisone was prescribed by her physician but three months and one year later lung function (Table 2) and the appearance of her roentgenogram had worsened considerably. Therapy was discontinued.

In summary, when evaluating a lung biopsy it is useful for the pathologist to know the history, radiographic appearance, and results of the pulmonary function tests. And it is important for the clinician to know the confidence with which the

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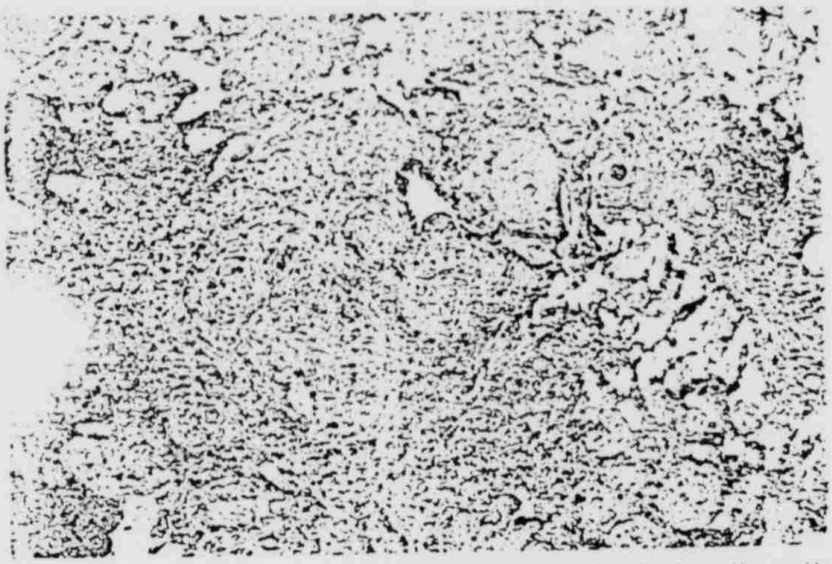


FIG. 10. The upper lobe biopsy from the patient in Figure 9. Most of the alveoli are obliterated by partly fibrotic, coalescent noncaseating granulomas typical of sarcoidosis. A bronchiole near the center is invaded and compressed by the granulomas. No extrinsic dust is seen, and none was identified by examination under bright polarized light. Compare with Figure 11.

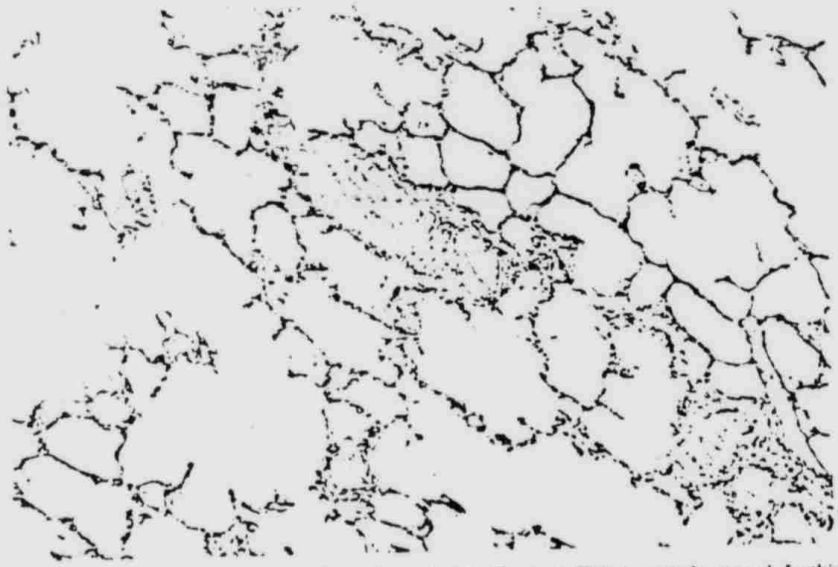


FIG. 11. The middle lobe biopsy from the patient in Figure 9. This is entirely normal. In this entire section there was but a single miliary granuloma, adjacent to a small venule in the pleura. Compare with Figure 10.

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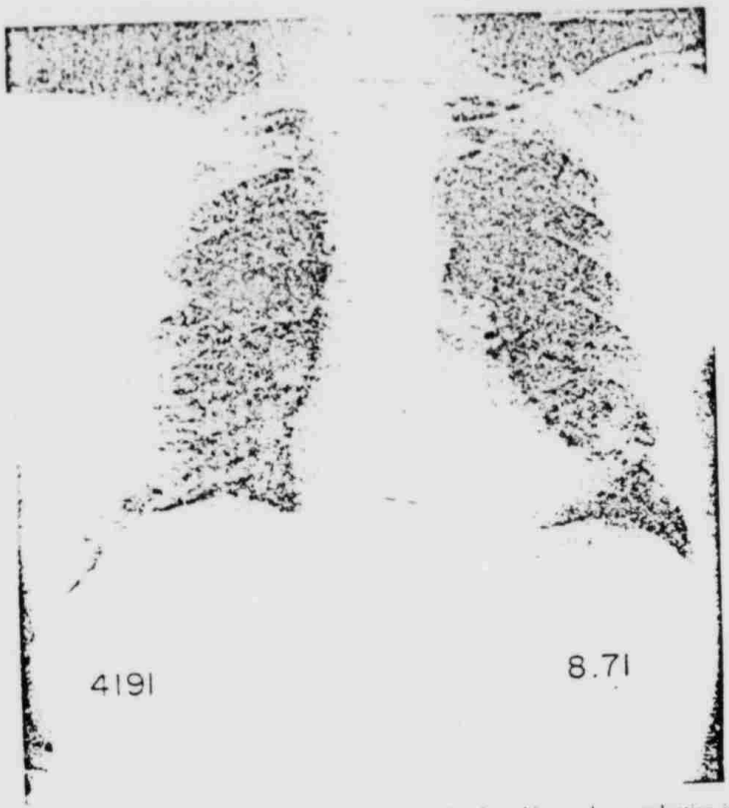


FIG. 12. Chest roentgenogram of patient #3 shortly after lung biopsy shows reduction in lung volume and moderately coarse, irregular lines distributed evenly throughout both lung fields. There are also a few patchy, "ground glass" opacities.

pathologist offers the diagnosis, the differential which was considered, the activity of the process, and the extent of tissue destruction and fibrosis.

Histologic Severity and Biopsy Quality: For assessing the severity of pulmonary disease in terms of diminished respiratory function, there are obviously better means than examination of a biopsy. Nevertheless, an estimate of this severity histologically serves a practical purpose. Conclusions regarding diagnosis, activity, permanent damage, and prognosis obviously will be sound only when the biopsy is representative. The degree to which this is true can be estimated by matching the histology to the pulmonary function and to the chest radiographs. In regard to abnormalities in function, both the type and the severity of the lesion should fit. Thus oxygen exchange at the parenchymal level is sensitive to interstitial infiltrates, alveolar destruction and usually to a small extent, by alveolar filling. A composite assessment of all of these should correlate closely with laboratory measurements of gas exchange (Fig. 16).[7, 17, 18] Air flow, on the

contrary, is most sensitive to those lesions of emphysema, bronchitis, and bronchiectasis which cannot be assessed reliably from a lung biopsy. As described above, certain radiographic patterns are common in interstitial lung disease. The histologic findings should match the radiograph within certain limits, although it is true that some interstitial lesions may be found in patients with relatively normal radiographs. A mild interstitial infiltrate or irregular alveolar filling will not explain "cannon-ball" shadows on the radiograph, however, nor will the presence of a fibrocalcific granuloma or similar discrete nodule explain a diffuse haziness or reticular pattern. A marked disparity between the histology and the function or the radiograph should raise doubt that the biopsy is tive and, accordingly, doubt that its interpretation is meaningful. the quality and validity of the biopsy are affected by the choice of e, the selection of biopsy site, and the subsequent handling of the tissue i.

TECHNICAL CONSIDERATIONS OF LUNG BIOPSY

EN LUNG BIOPSY

This procedure was rarely performed before 1945 and then only by formal postero-lateral thoracotomy.[15] In 1949 Klassen[25] suggested a small thoracotomy. This simpler and briefer operation greatly increased the scope and usefulness of open biopsy, made it available to much sicker patients, and reduced the morbidity and possibly also the mortality.[15] It called for local anesthesia and resection of a

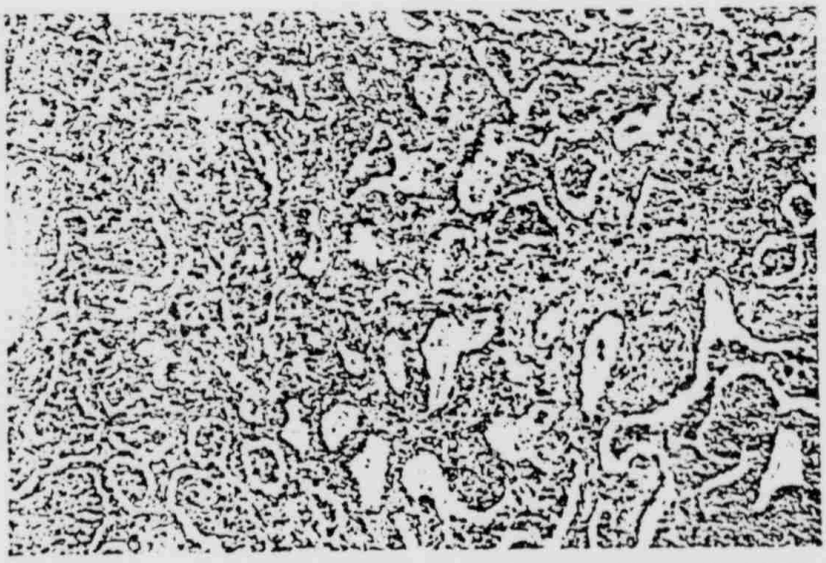


FIG. 13. Open lung biopsy from patient #3. The typical features of desquamative interstitial pneumonia are clearly seen. Note, however, that there is considerable scarring of some alveolar walls, and in some foci the normal architecture is obscured.

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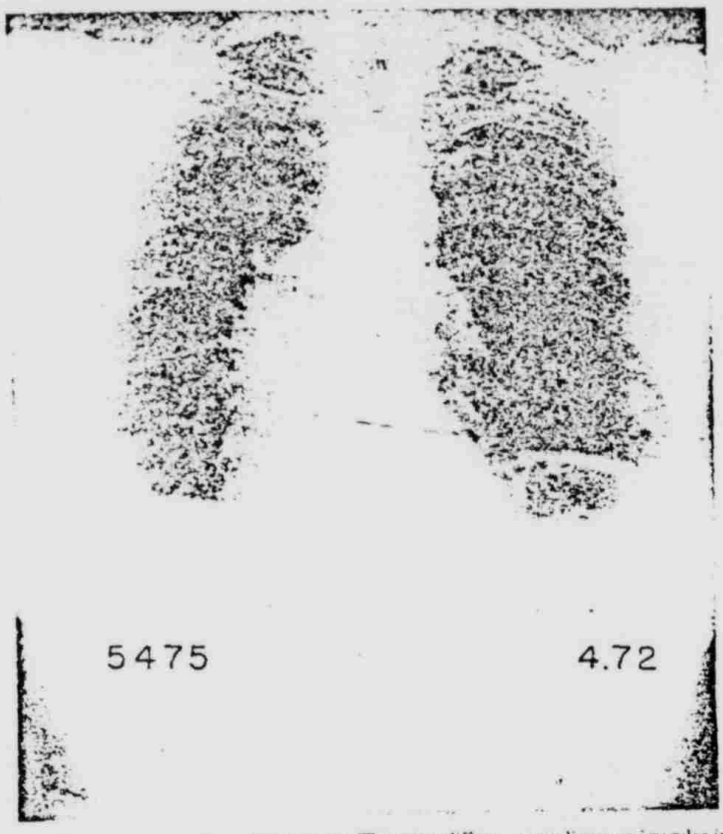


FIG. 14. Chest roentgenogram of patient #4. There is a diffuse, coarse linear or irregular infiltration, most marked in the right midlung region. Honeycombing is suspected. The left diaphragm is elevated but not paralyzed and the mediastinum is shifted to the right. The bulge at the right hilus is the ascending aorta.

small segment of rib; a portion of the lung was forced through the incision by positive pressure to avoid pneumothorax after excision.

Our own technique, used since 1952, is quite different and was designed for minimal trauma while permitting exploration and optimal choice and preservation of lung tissue. General endotracheal anesthesia is mandatory for control of inflation; local anesthesia has been associated with a much higher mortality and morbidity.[34] The anesthetic of choice is one that permits rapid intubation, is short-acting so that the patient is fully conscious at the end of the procedure, is not a respiratory depressant and permits administration of increased inspired oxygen concentration. Muscle relaxation is not required.

The incision is 4–7 cm long depending upon the thickness of the chest wall, and its location is dictated by the distribution of the disease. With diffuse involvement,

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we prefer an approach originally suggested by Chamberlain* for mediastinal exploration in the second interspace anteriorly, beginning medially just lateral to the sternum and internal mammary artery. This approach permits inspection and possible biopsy of the anterior aspect of the upper lobe, the entire middle lobe, and the superior and anterior segments of the lower lobe. The anterior mediastinum and hilus from the midportion of the superior cava to the superior pulmonary vein are easily exposed for inspection and possible node biopsy. Parenthetically, we also prefer this incision for mediastinal exploration, because, unlike the neck incision of mediastinoscopy,[5] it is not visible in clothing and ...er exposure and hemostasis. In patients with infiltration apparently ...he lower lung regions and in young women, the incision is made in the ...breast such that it is not visible with a brassiere or a bikini. The breast ... retracted upwards for a thoracic incision in the 4th interspace. This ...space may be too low in patients with very small fibrotic lungs.

The lung is allowed to collapse, and the thoracic cavity is explored. Enlarged lymph nodes or pleural lesions are biopsied. An infant-size Tuffier retractor is then placed between the ribs and the reinflated lung is inspected and palpated as far as is possible.

For biopsy, a region of lung is selected with apparently average involvement. If various parts of the lung appear or feel quite differently, then two biopsies of the more and of the less involved areas can be obtained. Generally, the most severely involved areas are avoided, because they may show nothing but nonspe-

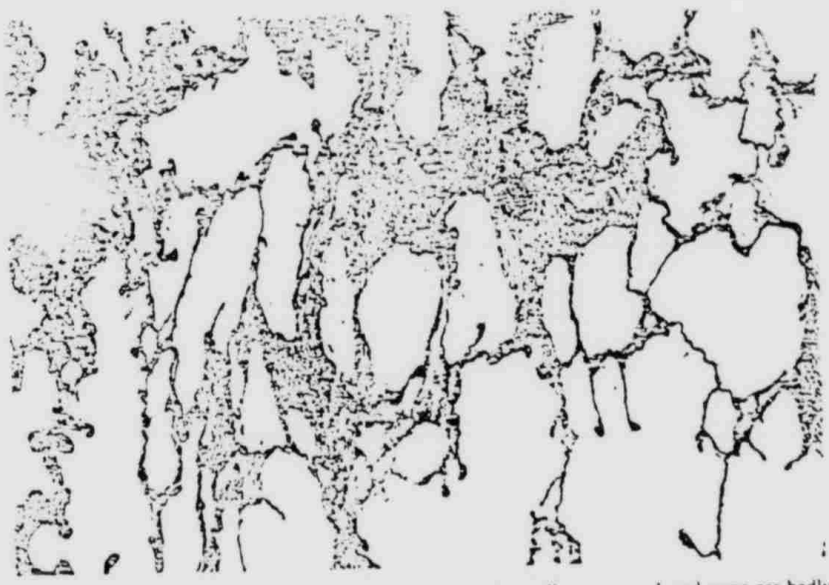


FIG. 15. Open lung biopsy from patient #4. A few alveolar walls are normal, and some are badly scarred. In others there is a definite but sparse infiltrate of monocytes, lymphocytes, and plasma cells. Proteinaceous exudates are virtually absent. This was interpreted as relatively inactive UIP.

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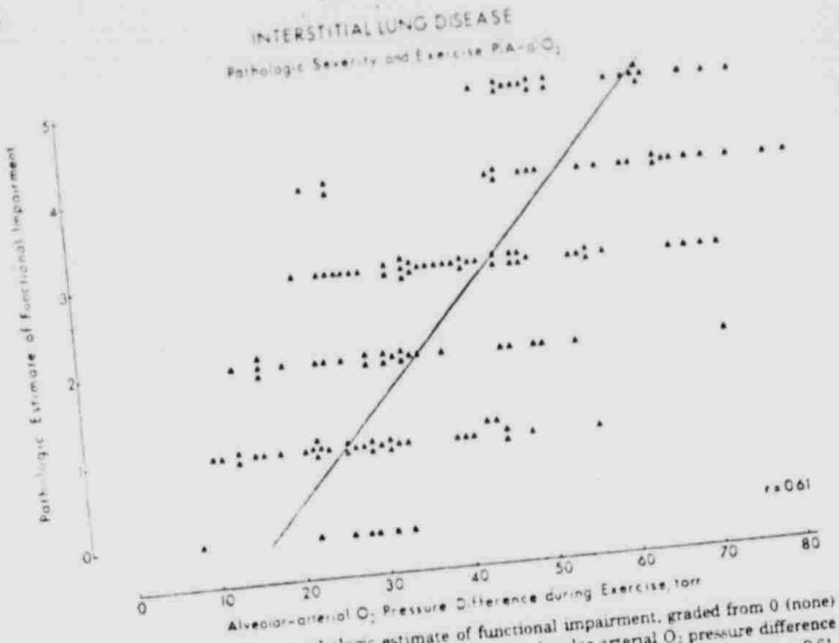


FIG. 16. Relationship of the pathologic estimate of functional impairment, graded from 0 (none) to 5 (worst), with functional impairment as measured by the alveolar-arterial O_2 pressure difference during exercise just before lung biopsy in 137 patients with diffuse infiltrative lung disease ($r = 0.61$, $P < 0.01$)

cific honeycombing. If one is to err it is better to do so in the direction of lesser rather than greater involvement. Unusual solitary nodules are avoided, because usually they show a healed fibrous focus or a healed granuloma that is irrelevant to the diffuse disease. Most surgeons prefer for biopsy the tip of the middle lobe or of the lingular segment, because these are easily delivered into the wound and but a single clamp is needed to delineate the tissue to be resected. This is poor economy of time, because these narrow dependent portions of the lung often show lesions that are not representative and hence should be avoided.

The selected lung margin is delineated for a distance of 4–5 cm, two stay sutures are placed, the lung is inflated until it just fills the thoracic cavity and a triangular segment is delineated by two narrow clamps. Two-thirds of the specimen is excised and immediately dropped into 10% buffered formalin within a few seconds. This procedure traps a maximum amount of air in the lung, and therefore atelectasis is minimal. Preservation of lung tissue in this fashion is most helpful to the pathologist as illustrated by Figures 17 and 18. In this patient with bronchiectasis the lung was fully inflated, and the tip of the middle lobe was clamped across. One-half of the wedge was fixed in formalin immediately as described above (Fig. 17). The other one-half was handed to the nurse "for pathology." It was duly wrapped in a moist sponge and eventually made its way to the refrigerator, from whence it was collected in the afternoon and processed

in routine fashion (Fig. 18). The promptly fixed portion was sufficiently expanded that the individual alveolar walls—all normal—could easily be seen. In the other sample there was so much irregular atelectasis that it was difficult to determine if the alveolar walls were normal or not.

The remaining third of the specimen is then excised. About one-third of this is submitted routinely for aerobic and anaerobic cultures for bacteria, mycobacteria, and fungi. Disposition of the remaining tissue depends upon indications and special interests. Chemical analysis for toxic substances generally requires at least 3–5 gm. Tissue also may be stored for biochemical studies or frozen for immunologic studies. Generally, we immediately place a small portion under glutaraldehyde, cut it into several 1-mm^3 blocks and store it for electron microscopy.

The tissue underneath the clamps is closed with a continuous interlocking "cobbler's" suture, the clamps are removed and the wound is oversewn with an interlocking over and over stitch. The suture line is then tested under warm saline with an endotracheal pressure from 20–30 cm H_2O.

A small No. 18–22 French catheter is placed laterally in the incision and attached to an underwater seal, and the wound is closed in layers while the patient is recovering. The importance of drainage cannot be overemphasized. It is virtually impossible to close lung absolutely airtight. A resulting small pneumothorax is of no consequence to a person with nearly normal lungs. However, if the vital capacity and the pulmonary capillary bed are already severely reduced,

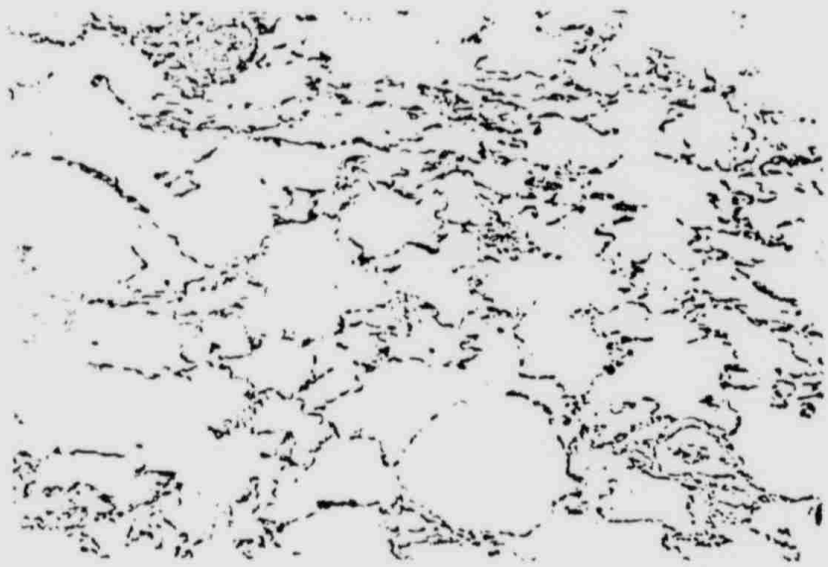


FIG. 17. Wedge from the normal part of lung from patient who underwent a lobectomy because of bronchiectasis. This sample, resected with the lung fully inflated, was immersed in formalin within seconds as described in the text. The individual alveolar walls and other architectual features are easily distinguished, and are all normal. Compare with Figure 18.

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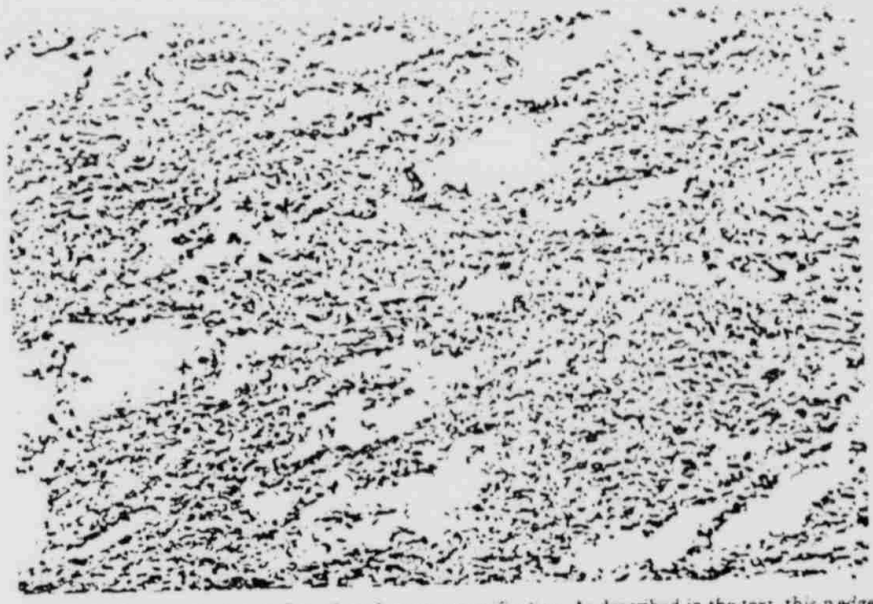


FIG. 18. Same patient as in Fig. 17, and *same magnification*. As described in the text, this wedge was taken immediately adjacent to the biopsy in Figure 17, but this sample was wrapped in a saline-moistened sponge and refrigerated before fixation. Many alveoli are collapsed, and it is much more difficult to determine whether or not the alveolar walls are normal. The only real difference between the two samples, however, was the way in which they were handled after resection.

then even a small pneumothorax is poorly tolerated. In series where this precautionary drainage was omitted, mortality and morbidity have been excessive.[21]

Postoperatively, oxygen may be given to hypoxic patients with appropriate monitoring, and mobilization is begun immediately. If the roentgenographic appearance is satisfactory, the tube is removed after 24 hours; and, generally, discharge is possible on the 3rd or 4th postoperative day.

Following this procedure for 25 years we have lost only one patient following 490 open biopsies. This single death occurred more than 20 years ago on the 13th postoperative day in a patient with advanced carcinomatosis and multiple pulmonary emboli.

CLOSED LUNG BIOPSY

Review of the diagnostic criteria for many diffuse infiltrative lung diseases reveals a strong reliance on histologic patterns, especially for the chronic lesions for which there is no histologically demonstrable causative agent. Hence the preference of many lung pathologists for open lung biopsies, the size of which facilitates pattern recognition. Nevertheless, there are some situations in which other biopsy techniques are sufficient; and then, because of the speed with which they are arranged, minimal hospitalization and cost, and perhaps lower morbidity, they are even preferable. Thus, in an attempt to identify an infectious agent such as pneumocystis carinii in the appropriate clinical setting, a closed biopsy may

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obviate the need for a thoracotomy. Similarly, the finding by a closed lung biopsy of lymphangitic carcinomatosis or numerous noncaseating granulomata typical in all aspects of sarcoidosis is quite adequate for diagnosis. The following case illustrates the value of transbronchial lung biopsy.

Case 5. A 27-year-old white electronics repair manager had infectious hepatitis in 1969. He recovered uneventfully and since then had had annual examinations including a chest roentgenogram. The films were normal until 1977 when a very fine diffuse infiltration was noted. This consisted of tiny rounded opacities of less than 1 mm in diameter which could be seen only on close inspection (Fig. 19). Although entirely asymptomatic, he was referred to us for evaluation. Upon arrival three w[illegible]s film was normal both with high and low kilovoltage techniques and with several [illegible]posures (Fig. 20). The history, including a detailed account of environment, physical [illegible] and routine laboratory studies were all unremarkable. Skin tests for histoplasmosis,

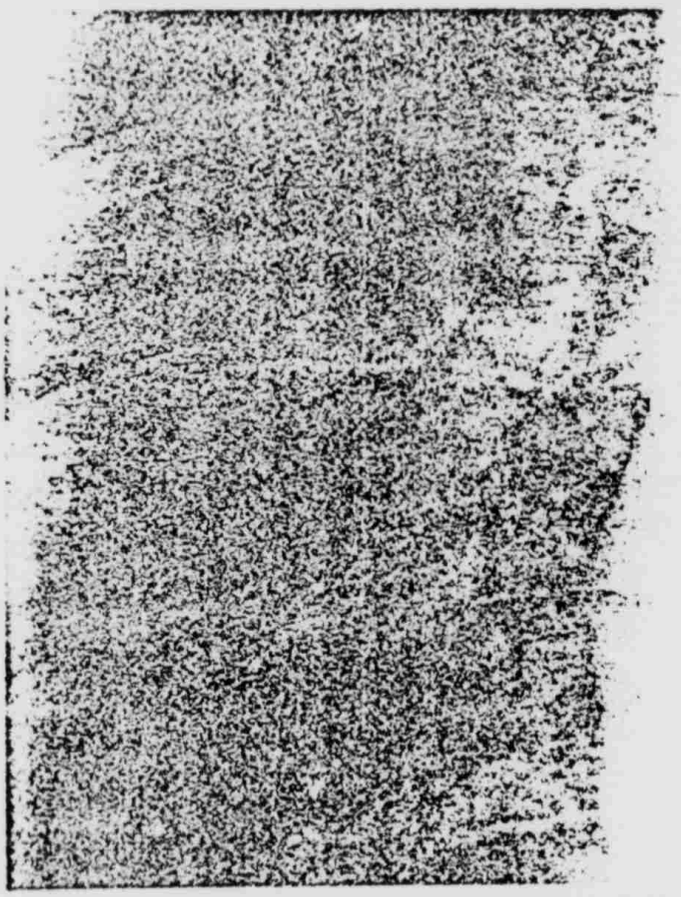


FIG. 19. Detail of chest roentgenogram of patient #5 obtained during routine health examination shows a delicate diffuse infiltration which, on close inspection, consists of tiny rounded opacities each apparently less than 1 mm in diameter.

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coccidioidomycosis, candida, and PPD were negative. Urine, blood counts, protein electrophoresis, and serum calcium, phosphorous, and uric acid were also normal. LDH 5 was elevated to 20% suggesting hepatocellular damage. Serum precipitins for thermophylic bacteria and fungi were negative. Lung function studies showed normal lung volumes and air flow. However, the screening single breath diffusing capacity was only 60% of predicted, and the steady state diffusing capacity failed to rise during exercise (Table 2). A transbronchial biopsy revealed many coalescent miliary, non-necrotizing sarcoid granulomas (Fig. 21). These involved a small bronchus and a bronchiole, but there was no other bronchitis or bronchiolitis in these two small conducting airways. Most of the alveolar walls between granulomas were normal, but a few had a minimal round cell infiltrate. There was a tendency for the granulomas to concentrate near small blood vessels, *i.e.*, along lymphatic routes. Because the biopsy was so typical of sarcoidosis, an open biopsy was not believed to be necessary.

It must again be emphasized, however, that the presence of a few granulomas is not specific, and the diagnosis of sarcoidosis must be made with consideration

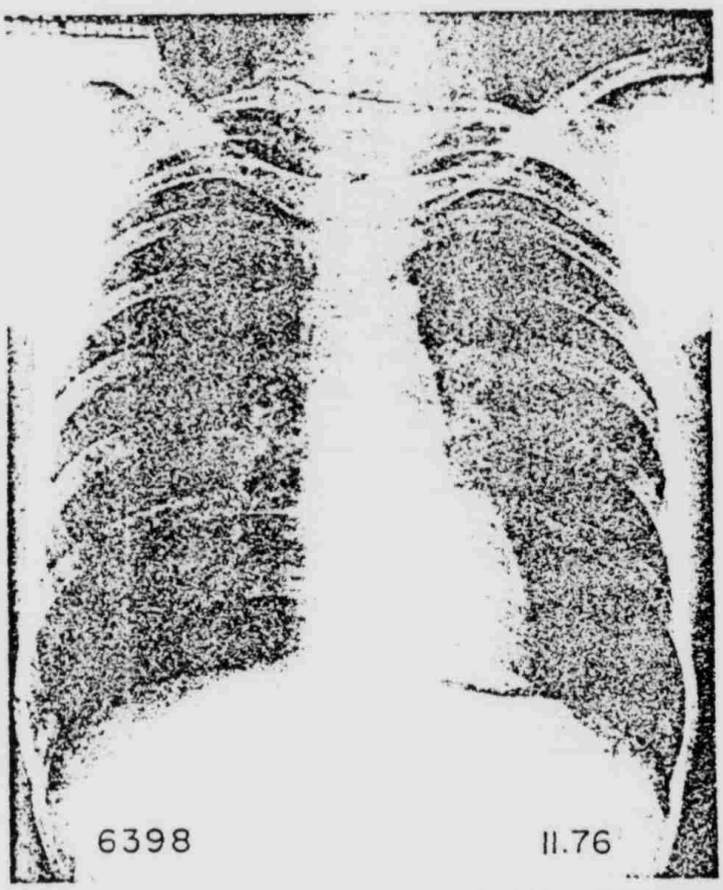


FIG. 20. A film of patient #5 obtained 3 weeks later than that in Figure 19 was within normal limits.

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of the rest of the histologic features and the clinical setting (Case 2). Both the transthoracic and transbronchial approaches have been employed for closed biopsy.

Transthoracic Needle Biopsy. A variety of needles such as those described by Vim Silverman[34] and electric drill driven needles[32] have been used for core biopsy of lung tissue for the diagnosis of diffuse infiltrative lung disease. The literature suggests, and our experiences confirm, that this procedure entails a higher mortality than open lung biopsy because of several complications, including bleeding, tension pneumothorax, massive hemoptysis, and especially air embolism,[36] which are not encountered with open biopsy. The procedure thus entails all the disadvantages of a small specimen selected without thoracic inspection but not the advantages of lower morbidity; and, therefore, it should be avoided.

Transbronchial Biopsy. This procedure was first performed through a rigid bronchoscope[2] but gained popularity only with the advent of the fiberoptic bronchoscope.[21] The design of the larger of these instruments permits introduction of a tiny forceps. This is advanced to the periphery of the lung either by measurement or by fluoroscopic control. The instrument is then withdrawn slightly, the patient is asked to expire while the forceps are opened and several biopsies are obtained in this fashion. The fragments of tissue are tiny, usually 1 mm, and rarely up to 3 mm in diameter; but several specimens can be obtained. Mortality and morbidity in several series have been very low,[33, 37] but have not been finally evaluated. The procedure has the great advantage that it can be performed under topical anesthesia, thus not requiring expensive operating room time; and also hospitalization is shortened. Studies comparing diagnostic yield of

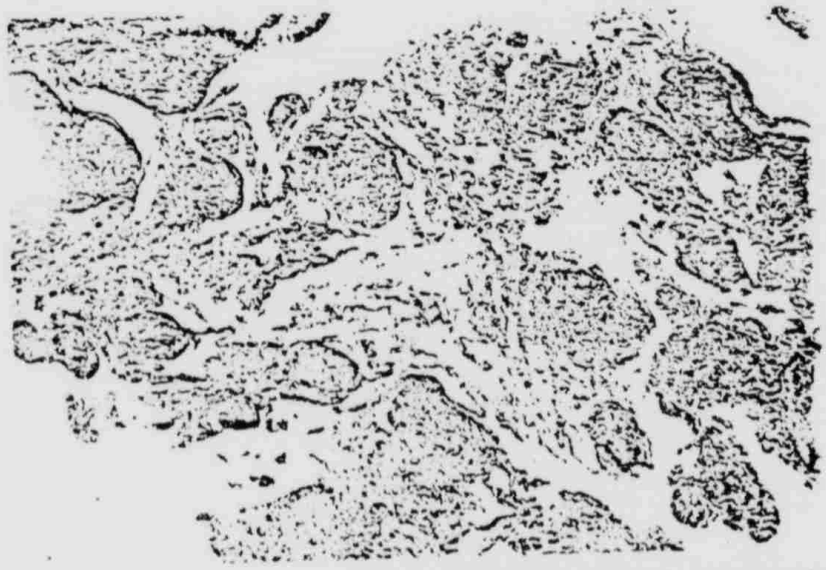


FIG. 21 Transbronchial biopsy from patient #5. There are many small, coalescent noncaseating granulomas, one of which involves the wall of a small bronchus. This is typical of sarcoidosis.

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transbronchial and open biopsy are in progress, and the definitive place for the transbronchial procedure is not established. The diagnosis of UIP or interstitial fibrosis is especially foolhardy with a specimen obtained by transbronchial biopsy. Many patients with old or current bronchitis—which, unfortunately, includes a large part of our population—have changes confined to peribronchial alveoli which simulate UIP when no other alveoli are sampled. We have seen several instances where such a diagnosis from a transbronchial biopsy was invalidated by study of tissue subsequently obtained by open biopsy or at autopsy. We have seen another example where a transbronchial biopsy failed to confirm a clinical diagnosis of chronic eosinophilic pneumonia with an atypical roentgenogram because the bronchial and nearby parenchymal changes were indistinguishable from those which could be expected solely from the patient's underlying asthma. An open biopsy resolved this question and confirmed the original clinical impression. Thus there are still a variety of situations in which open biopsy is necessary. When this technique is chosen, proper site selection, inflation, and immediate fixation greatly enhance the value of that part of the specimen used for routine microscopy.

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