MEDICAL GRAND ROUNDS
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INTERSTITIAL PULMONARY FIBROSIS

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In 1933 Hamman and Rich (1) presented a clinical pathologic conference of a 47 year old black man who presented on December 16, 1931, complaining of cough, shortness of breath, and swelling of the ankles of three weeks duration. The patient's symptoms rapidly worsened, and he died on March 22, 1932,with extreme cyanosis, dyspnea, and right ventricular failure. At autopsy the patient showed marked pulmonary fibrosis with cor pulmonale. In 1935 (2) these authors reported 3, and possibly a 4th, patients with a similar syndrome; all of the patients were seen from 1931 to 1933. Confidently expecting to see more such cases, the authors delayed a full report of their findings until 1944 (3) at which time they were able to add a confirmed 4th case. The clinical picture of their patients was that of rapid onset of severe dyspnea progressing to dyspnea at rest associated with cyanosis. In 3 of the 4 cases right ventricular failure was marked. The patients died from 31 days to approximately 6 months after the first onset of symptoms. Hamman and Rich considered the pathological findings in the lungs to be specific and to be unlike any previously reported cases. The authors termed this new syndrome acute diffuse interstitial fibrosis of the lungs, but subsequently it has been referred to as the Hamman-Rich Syndrome. Although the original case reports were all of patients with a rather rapidly progressive disease, the syndrome was soon described in patients with a much more chronic course.

The physician faced with a patient complaining of unexplained dyspnea usually obtains a chest x-ray early in the course of evaluation. The finding of a diffuse reticular, nodular or honeycomb infiltrate enters one on a differential diagnostic path which may ultimately result in idiopathic interstitial pulmonary fibrosis. A reticular infiltrate consists of a network of linear shadows which may be conceived as a series of rings surrounding spaces of air density giving a fine, hair net appearance. Some of the linear densities run at right angles to the normal vascular pattern of the lung which radiates in a branching,but not crossing, manner from the hilar areas. The purely nodular interstitial diseases of the lung consist of discreet, punctate shadows which range from tiny nodules 1 mm in diameter which are barely visible roentgenographically to 5 mm shadows. Frequently there is some admixture of the reticulation and the nodularity, and this is termed a reticulonodular pattern. This may be produced by actual nodular deposits on the background of diffuse linear thickening throughout the interstitial spaces, or the orientation of some of the linear densities parallel to the x-ray beam may suggest a nodular component. A honeycomb pattern refers to a very coarse reticulation in which the air spaces in the mesh of the net measure not less than 5 to 6 mm in diameter. The differentiation between reticular and honey comb in many x-rays is clearly a matter of subjective interpretation. In

addition to a reticulonodular pattern, many diseases also cause discreet or confluent "fluffy" densities, termed alveolar infiltrates, mixed in with a background of a reticular infiltrate. Although some radiologists, such as Fraser and Pare (8), feel that the coexistence of alveolar infiltrates alters the differential diagnostic possibilities, most of us are not able to make such a fine differentiation, and the occurrence of a moderate amount of alveolar infiltrate does not alter the differential diagnostic possibilities.

Having determined that the patient has an interstitial pulmonary disease process, the differential diagnosis is extremely broad. Table I, compiled from several references (4-11) which are extensively documented, indicates the diagnostic possibilities.

TABLE I

Differential Diagnosis of Interstitial Pulmonary Diseases

I. Infectious

A. Bacterial
1. Miliary tuberculosis sputum ⊕ < 50%
2. Staphylococcus aureus
3. Salmonella species
4. Streptococci
5. Klebsiella pneumoniae
6. Burcellosis
7. Tularemia
8. Shigella
9. Pertusis

B. Fungal

1. Histoplasmosis
2. Coccidiomycosis
3. Blastomycosis
4. Actinomycosis
5. Cryptococcosis
6. Nocardiosis
7. Aspergillosis
8. Candidiasis
9. Geotrichosis
10. Sporotrichosis
11. Mucor

C. Viral

1. Chickenpox
2. Influenza
3. Measles
4. Psittacosis
5. Cytomegalovirus
6. Adenoviruses
7. Parainfluenza
8. Coxsackie
9. ECHO viruses

D. Mycoplasma pneumoniae

E. Rickettsial

1. Q fever
2. Rocky Mountain spotted fever

F. Spirochetal

1. Syphilus

G. Parasitic

1. Pneumocystis carinii
2. Schistosomiasis
3. Filariasis
4. Toxoplas mosis

II. Inhalational Diseases

A. Diseases of alveolar hypersensitivity

(Extrensic allergic alveolitis)

1. Farmers lung
2. Bagassosis
3. Pigeon breeders lung
4. Mushroom worker's lung
5. Suberosis
6. Maple bark disease
7. Pituitary snuff disease
8. Smallpox handler's lung
9. Sisal worker's disease
10. Malt workers lung
11. Sequiosis
12. Hen-litter sensitivity
13. Lycoperdonosis

B. Inorganic dust pneumoconiosis

1. Silicosis
2. Coal workers pneumoconiosis
3. Asbestosis
4. Talcosis
5. Siderosis (arc welders disease)
6. Kaolin pneumoconiosis
7. Berylliosis
8. Aluminum pneumoconiosis (Shaver's disease)
9. Radiopaque dust pneumoconiosis
    a. Stannosis (tin oxide)
    b. Barium sulfate
    c. Rare earth (cerium, etc.)

C. Inorganic chemicals

1. Nitrogen dioxide (Silo-filler's disease)
2. Nitrogen oxide (electric welding)
3. Chlorine
4. Smoke inhalation
5. Phosgene
6. Mustard gas
7. Lewisite
8. Carbon tetrachloride
9. Acetylene
10. Picric acid
11. Ammonia
12. Sulfur dioxide
13. Bromine
14. Hydrogen flouride
15. Nitric acid
16. Hydrochloric acid

III. Neoplastic

A. Bronchioloalveolar carcinoma

B. Lymphangitic carcinomatosis

exceedingly dyspneic

1. Bronchogenic
2. Breast
3. Stomach
4. Thyroid
5. Pancreas
6. Larynx

C. Micronodular hematogenous

not dyspneic entibater

1. Renal cell
2. Thyroid
3. Sarcoma of bone
4. Choriocarcinoma

D. Hodgkins' disease

E. Lymphosarcoma

F. Leukemia

IV. Therapeutic agents

A. Oxygen toxicity

B. Radiation therapy

C. Drugs

1. Nitrofurantoin (Furadantin)
2. Hexamethonium
3. Mecamylamine (Inversine)
4. Hydrochlorthiazide (Diuril)
5. Pteroylglutamic acid (Methotrexate)
6. Busulfan (Myleran)
7. Methysergide (Sansert)
8. Bleomycin

V. Connective Tissue Diseases

- A. Scleroderma
- B. Rheumatoid arthritis
- C. Lupus erythematosis
- D. Periarteritis nodosa
- E. Dermatomyositis
- F. Sjogren's syndrome
- G. Wegener's granulomatosis

VI. Cardiovascular

- A. Pulmonary edema
- B. Hemosiderosis
- C. Rheumatic pneumonia
- D. Embolism from oily contrast media

VII. Aspirational

- A. Gastric juice
- B. Lipoid pneumonia
- C. Hemoptysis
- D. Post drowning

VIII. Airways Disease

- A. Cystic fibrosis
- B. Bronchiectasis
- C. "Small airways" disease
- D. Acute bronchiolitis
- E. Riley-Day Syndrome

IX. Trauma

- A. Blast injury
- B. Lightning stroke pulmonary edema

X. Miscellaneous or Idiopathic

A. Sarcoidosis
B. Goodpasture's syndrome
C. Pulmonary alveolar proteinosis
D. Eosinophilic granuloma
E. Sickle cell anemia
F. Letterer Sieve
G. Niemann Pick
H. Hand-Schuller-Christian
I. Pulmonary alveolar microlithiasis
J. Amyloidosis
K. Waldenstrom's macroglobulinemia
L. Tuberous sclerosis
M. Pulmonary myomatosis
N. Wilson-Mikity syndrome
O. Infectious mononucleosis
P. Mycosis fungoides
Q. Spider angiomas in cirrhosis
R. Ideopathic interstitial pulmonary fibrosis

1. Usual or classical (UIP)
2. Bronchiolitis obliterans and diffuse alveolar damage (BIP)
3. Desquamative interstitial pneumonitis (DIP)
4. Lymphoid interstitial pneumonia (LIP)
5. Giant cell interstitial pneumonitis (GIP)

Thus, the physician faced with a patient with dyspnea, a diffuse interstitial process, and the physiological and clinical accompaniments of a diffuse interstitial process may be dealing with approximately 150 specific or semi-specific diseases. It is clear that a systematic approach to making a diagnosis is indicated, but this approach will vary depending on the severity and acuteness of the patient's process. It is not my purpose to discuss these categories in detail, but I would like to indicate a few general guide lines that may be helpful.

Several chest infections may present with findings that can be confused with the Hamman-Rich Syndrome, which itself is associated with fever on occasions. I do not intend to imply that a reticular infiltrate is the usual method of presentation of each of these entities, but each is reported to present this way on occasions. Since bacterial infections are responsive to therapy but may cause death if untreated, it is especially important to consider these possibilities.

Miliary tuberculosis must always be suspected, since its subacute onset, clinical physiological, and radiological presentation may mimic many of the other interstitial diseases. Although sputum should always be obtained for smear and culture for acid fast bacilli, in miliary tuberculosis it can be expected to be positive in 50% of the cases at best. Skin tests are frequently negative. Not infrequently it is found that this possibility can be neither ruled in nor out without an appropriate biopsy. If the patient is extremely ill, it is sometimes necessary to begin treatment for tuberculosis without a definitive diagnosis. Such treatment should include three antituberculosis drugs such as INH, Ethambutol, and streptomycin or INH, PAS, and streptomycin.

In an extremely ill, febrile patient with an acute interstitial process, it is reasonable to obtain sputum and blood cultures and then treat with antibiotics, even though one cannot be assured of the bacterial etiology of the process. Since the most likely bacterial etiology of this syndrome is staphyloccocus, the antibiotic coverage should include an agent such as Keflin. However, since this would not be adequate treatment for klebsiella, Kanamycin usually is added also.

Several fungi may also produce an interstitial pneumonia. It is the typical picture of acute histoplasmosis and coccidiomycosis, but it also may be caused by other fungi. These infections are not usually rapidly fatal,and their treatment is not without risk; a definitive diagnosis is necessary before treatment. Sputum culture is frequently rewarding, and the complement fixation tests may be helpful in histo and cocci. Skin tests are not to be relied on in any of these diseases in the acute phase.

Inhalational diseases are of three types: Diseases of alveolar hypersensitivity of which the prototype is farmer's lung; inorganic dust pneumoconiosis such as silocosis; and inhalation of inorganic chemicals exemplified by silo-filler's disease. In the hypersensitivity diseases not all persons exposed to the inhalational antigen will become ill. The first episode of illness may occur several hours after exposure, and hence the patient may not make an association without direct questioning. The illness may be clinically indistinguishable from a viral pneumonia which is self limiting. On repeated exposure, the syndrome recurs, and with sufficient exposure diffuse pulmonary fibrosis ultimately results. The inorganic dust pneumoconioses develop only after considerable exposure to the offending agent and cause an insidious onset of diffuse pulmonary fibrosis. The fibrosis may become manifest months to years after the patient has discontinued work in the dust environment, so a history of previous occupational exposure in addition to the current occupation is necessary. The inorganic chemicals tend to cause an acute syndrome of pulmonary edema, but the onset of pulmonary edema may be delayed for a few hours after the exposure. The severity of the pulmonary edema is not necessarily related to the time of onset of the syndrome. In some types of chemical exposure, if the patient recovers from the acute pulmonary edema, lung function is evidently normal. With other chemicals the patient may survive the acute pulmonary edema, but a progressive bronchiolitis obliterans develops over the following weeks. It is apparent that the key to diagnosis in the inhalational diseases is a meticulous history of inhalational exposure.

Patients with diffuse pulmonary carcinomatosis due to lymphangitic spread are usually extremely short of breath, but patients with hematogenous spread may be relatively asymptomatic until the disease is far advanced. There are no distinguishing characteristics that indicate malignancy as far as pulmonary involvement is concerned, although there is a tendency for patients with neoplastic interstitial disease to have enlarged hilar and mediastinal lymph nodes. These patients are also more likely to have Kerley B. lines and pleural effusions than other types of interstitial disease. However, the diagnosis depends on extrathoracic findings or biopsy of appropriate tissue.

Patients with interstitial diseases due to therapeutic intervention, aspiration of liquid, or trauma should have the diagnosis strongly suspected from history alone.

Connective tissue diseases all may produce an interstitial infiltrate. Pulmonary fibrosis is the rule in scleroderma and not unusual in rheumatoid arthritis, but it is only occasionally seen in the other connective tissue diseases. Considerable confusion may exist in differentiating a connective tissue disease with

pulmonary fibrosis from idiopathic pulmonary fibrosis, since serological tests used in the diagnosis of the connective tissue diseases are frequently also positive in the latter. The differentiation of the two is made on the finding of involvement of extra thoracic organs in the case of connective tissue diseases. This will be discussed more extensively in the section concerned with the etiology of idiopathic pulmonary fibrosis.

Pulmonary edema due to left ventricular failure is probably the most common cause of a reticular or reticulonodular pulmonary infiltrate. The diagnosis of interstitial pulmonary edema or hemasiderosis caused by cardiac disease is made on the basis of the cardiac findings. In a particular patient the diagnosis may be difficult at a single point in time, but the diagnosis may become apparent on following the patient serially, since pulmonary edema due to heart failure tends to change radiographically more rapidly than most other causes of reticular infiltrates.

The common airways diseases to produce this radiographic picture are cystic fibrosis and bronchiectasis. Here the diagnosis is frequently more easily made than in other categories. These patients tend to produce large amounts of vicid or purulent mucous, and this is an unusual accompaniment of most interstitial diseases. In addition, the patient's spirographic findings usually include severe airways obstruction, which is not common in other interstitial problems.

Diseases in the miscellaneous or idiopathic category are so diverse that no generalizations are justified. In some the lung is acting as a mirror of systemic disease, and the diagnosis is based on the extra thoracic findings. However, in those diseases which effect the lung primarily, such as sarcoidosis, Goodpasture's syndrome in some stages, pulmonary alveolar proteinosis, eosinophilic granuloma, and idiopathic interstitial pulmonary fibrosis the diagnosis may not be reached short of lung biopsy.

Perhaps the best data on the diagnostic yield of various procedures are found in Gaensler's series of 381 patients with interstitial lung disease collected over a 15 year period (10). One should note however, the types of patients with which Gaensler was dealing.

TABLE 2

Gaensler's Series of 381 Patients with Interstitial Lung Disease (10)

		No. Cases
I.	Infections	22
II.	Inhalational	114
III.	Neoplastic	19
IV.	Therapeutic agents	3
V.	Connective tissue diseases	11
VI.	Cardiovascular	35
VII.	Aspirational	0
VIII.	Airways disease	0
IX.	Trauma	0
X.	Miscellaneous or Idiopathic	150
	No diagnosis	27
	Total	381

Working at the Boston City Hospital, Gaensler is in an area of high industrial exposure, and it is quite likely that his incidence of inhalational diseases is higher than would be seen in the Dallas area. For example, he had 22 cases of silicosis, 22 of asbestosis, and 54 cases of chronic berylliosis. Conversely, the incidence of inhalational diseases from industrial exposure may be much higher than one's clinical impression, since it is unusual to find an adequate occupational or exposure history in our charts.

Gaensler was also dealing with a referral practice. He included in this series no cases of acute infection excepting two atypical pneumonias, and he had no aspirational, airways, or traumatic diseases. The distribution of these cases does not indicate their relative prevalence, but indicates the preselection of patients sent to a thoracic surgeon for study. Nevertheless, when interpreted in this light, his data on the frequency of diagnostic yield by various procedures is valid.

TABLE 3

Gaensler's Method of Diagnosis of 381 Patients with Interstitial Lung Disease (10)

	No. Patients	Per Cent
History	121	32
Physical exam	35	9
Routine laboratory exam	4	1
Skin tests	3	1
Sputum culture and cytology	11	3
Special x-rays	9	2
Bronchoscopy	?	0
Prescalene biopsy	25	6
Other non pulmonary biopsy	21	6
Lung biopsy	116	30
Autopsy	13	3

The clinical history was found to be the most important diagnostic device at the physician's disposal. The chief complaint was usually quite non-specific. It was dyspnea, alone or with cough and other symptoms, in one half of all patients no matter what the ultimate diagnosis. The part of the history dealing with occupation, recreational activities, and travel was the most significant. In 73 patients (20%) this led to the presumed diagnosis. Gaensler may have weighed the history somewhat too heavily, however; in 37 patients he was willing to make the diagnosis of non-specific fibrosis from historical data together with serial chest x-rays and did not go on to prove the diagnosis.

The physical examination of the chest is virtually never diagnostic nor are the findings of clubbing of the fingers or cyanosis, which are found in a high percentage of all patients. The physical examination was helpful in regard to the heart and in some patients with lymphadenopathy or skin lesions. Routine laboratory examination led to a presumptive diagnosis in only four patients, two with sarcoidosis and one each with leukemia and Loeffler's Syndrome. Skin testing was helpful only in 3 patients with chronic histoplasmosis. More specifically, 4 of 11 patients with miliary tuberculosis had a negative second strength PPD skin test. Only 3 of 11 patients with miliary tuberculosis

had acid fast bacilli in the sputum. Special x-ray procedures such as metastatic bone surveys, barium swallows in scleraderma, etc., also yielded few diagnoses.

It is apparent that invasive techniques are frequently necessary to make a diagnosis. However, bronchoscopy, which is so important in other types of lung diseases, is of virtually no benefit. The interstitial processes do not cause characteristic changes in the bronchial mucosa. Gaensler did not perform cervico-mediastinal explorations, but he did perform prescalene biopsy in 197 patients. The procedure yielded 25 (13%) diagnoses. However, in the 54 patients with diffuse lung disease who had obvious hilar adenopathy prescalene biopsy was diagnostic in 43%, whereas in 143 without this x-ray finding lymph nodes were positive in only 2%. It seems warranted to state that prescalene lymph node biopsy, and probably CME, is not indicated for diagnosis of miliary lung disease unless there is hilar adenopathy. Other non pulmonary biopsies were helpful if there was lymph node or skin involvement by the primary disease process. Liver biopsy is of questionable benefit. In this series a diagnosis of sarcoidosis was made on 5 occasions from liver biopsy; however, one of the patients ultimately proved to have miliary tuberculosis, one bronchiolar cell carcinoma, and one silicosis.

It is apparent that the correct diagnosis will be made only by lung biopsy in many patients with interstitial pulmonary disease. I have not documented in the bibliography a controversy regarding the relative merits of needle biopsy and open lung biopsy. The major argument against needle biopsy is the small specimen that is obtained which may not be representative of the primary disease process. Nevertheless, needle biopsy is probably safer than open lung biopsy, although the latter is said to have a mortality of only approximately 1%. It seems reasonable to believe that many patients can be diagnosed by needle biopsy when specific findings are obtained. However, the physician should be prepared to proceed with an open lung biopsy if a specific diagnosis is not made. Pulmonary fibrosis is not considered a specific diagnosis.

Having outlined the general approach to patients with reticular or reticulonodular pulmonary infiltrates, let us turn to the typical clinical presentation of the patient with the idiopathic variety. Mr. Tucker was a 69 year old home design consultant who was apparently entirely well until 12 years prior to his admission at Parkland Memorial Hospital, when he had an episode of severe cough productive of a moderate amount of mucopurulent sputum. This induced him to quite smoking the two or three packages of cigarettes

per day to which he had been accustomed all of his adult life. His cough cleared completely over a period of several days. He remained well until 8 years prior to admission, when he experienced another episode of cough, sputum production, and subjective fever of several weeks duration. When this finally cleared he remained well until 4 years prior to admission. At that time he developed episodic cough and dyspnea on exertion. During the ensuing three years the exertional dyspnea gradually progressed. Intermittent cough continued, but there was little mucous production. One year prior to admission, his dyspnea became incapacitating and it was noted that the patient was cyanotic after exercise. He was hospitalized elsewhere, and it was observed that he was cyanotic and had harsh breath sounds and crepitant rales in the lung bases. A chest x-ray showed a reticular infiltrate. Bronchoscopy revealed a normal tracheobronchial tree, and skin tests were negative. The hematocrit was 48%; white blood count 6,200; and urine was normal except for a trace of albumin. The serum proteins, albumin-globulin ratio, calcium,and phosphorus were normal. Sputum examination for acid fast bacilli, cytology, and special stains for pulmonary alveolar proteinosis were negative. Pulmonary functional evaluation carried out at Parkland revealed a restrictive ventilatory defect, a marked decrease in pulmonary capillary volume, and a very reduced diffusion capacity. Blood gas studies showed a low arterial P02 at rest which was markedly decreased with exercise. An open lung biopsy obtained a piece of right middle lobe which on gross examination looked like "hobnailed liver". Microscopic examination revealed diffuse, chronic, interstitial fibrosis and inflammation with no indication of specific etiology. The patient was started on steroids, and the dyspnea dramatically improved allowing him to return to work. Three months before his final admission steroids were gradually decreased over a period of several weeks and then discontinued altogether. Near the time of cessation of steroids, the patient noted gradually increasing dyspnea and developed ankle edema. Digitalization and mercurial diuretics were of no benefit, and steroid therapy was re-instituted. He again noted marked improvement and returned to work one month prior to admission. However, two weeks later, peripheral edema recurred and his dyspnea was worse. Copious diuresis and large fluid intake persisted in the absence of diuretics. A blood sample revealed lactescent serum; the blood sugar was 850 mg/ml, and he was re-admitted. He appeared chronically ill and poorly nourished, and there was evidence of marked muscle wasting. He was tachypneic and cyanotic whenever oxygen therapy was discontinued. He had marked bilateral crepitant rales in both lung bases and a persistent tachycardia. The second pulmonic sound was accentuated and split throughout the cardiac cycle. The liver was palpable 5 cm below the right costal margin and was moderately tender. He had mild pitting

pre-sacral and ankle edema. Clubbing was not present.

After correction of the hyperglycemia with 200 units of regular insulin, his steroid induced diabetes was subsequently controlled on 30 units of NPH insulin daily. Subsequent therapy included 40 mgms Prednisolone daily, digitalis, and intermittent positive pressure breathing. He regained strength to the degree that he could walk approximately 20 yards when aided by oxygen from a portable source. Because the peripheral neuropathy was felt to be induced by steroids, Prednisolone dosage was reduced to 20 mgms daily on the 41st hospital day. However, the patient's dyspnea gradually progressed in severity over an 8 day period, and by the 50th hospital day he was moderately dyspneic at rest on 40% oxygen. Steroids were increased to 80 mgms per day but the downhill course was relentless and the patient died on the 51st hospital day.

TABLE 2.—*Pulmonary Function Studies (6 Months Prior to Last Hospital Admission).*

	Rest		Exercise	
I. BLOOD GASES—9/1/61	room air	100% O_2	room air	100% O_2
pH	7.42	7.40	7.47	7.36
CO_2 content (mm./L.)	18		17	
$PaCO_2$ (mm. Hg)	36	36	32	43
Hematocrit	54		56	
O_2 capacity (ml./100 ml.)	20.71		21.77	
O_2 content (ml./100 ml.)	19.85		14.9	
O_2 saturation (%)	96		68	
PaO_2 (mm. Hg)	71	596	35	518
PAO_2 (mm. Hg)	113	668	119	661
PAO_2-PaO_2 (mm. Hg)	42	72	84	143
Minute volume (L./min.)	16.7	17.0	50.4	26.4
Respiratory rate		26	38	26
O_2 consumption (cc./min.)	196		609	
Respiratory quotient	1.10		1.17	

II. MECHANICAL FUNCTIONS	Predicted	Found
Total lung capacity (TLC)	5,580	3,255
Residual volume (RV)	1,730	690
Functional residual capacity (FRC)	2,790	1,780
RV/TLC ratio	0.31	0.21
Forced vital capacity (FVC)	3,850	2,620
Forced expiratory volume (FEV) 0.5 sec.	2,620	1,720
Forced expiratory volume (FEV) 1.0 sec.	3,240	1,880
Forced expiratory flow (FEF)	6,550	8,300
Forced mid flow (FMF)	3,580	2,180
III. DISTRIBUTION OF VENTILATION		
7 min. N_2 washout	<2.5%	0.5%
IV. PULMONARY CAPILLARY BED		
Capillary blood flow (L./min.)		3.93
Pulmonary tissue volume (ml.)	807	430
Membrane diffusion capacity	72	14
Capillary blood volume	93	26

Interpretation.—These measurements indicate a restrictive ventilatory defect associated with a severe diffusion defect. It would appear that the diffusion defect is for the most part a consequence of a severe restriction of the pulmonary capillary bed. Both pulmonary capillary blood volume and membrane diffusing capacity are reduced.

At necropsy the lungs weighed 1800 grams and were firm and nodular. The alveolar septa were visibly thickened and fibrous, and this change was diffuse and relatively uniform throughout both lungs. The histologic changes were similar to those seen in the lung biopsy and showed diffuse interstitial pulmonary fibrosis with foci of squamous metaplasia, cylindrical bronchiectasis, emphysema, bulla, and organizing pneumonia with intra alveolar fibrosis.

Mr. Tucker's case is typical of patients with idiopathic interstitial pulmonary fibrosis as recorded in the literature (12-54). The regularity of the clinical features has led some to believe that the diagnosis can be made in the absence of histologic examination (43). There is no racial or sexual predilections. Although the disease is occasionally reported in childhood, most patients are over 40 years old when first seen. Patients not infrequently date the onset of their symptoms to a respiratory infection, but whether this is important in the course of the disease or merely brings the patient's attention to his respiratory tract is not clear. The presenting problem is usually dyspnea, and there is frequently a bothersome, hacking cough which is usually not productive of sputum. Although the original cases reported by Hamman and Rich were rapidly progressive, in terms of days or weeks, most cases reported in the current literature are more likely to have a gradual progression of dyspnea and cough over the course of months to years. Although most aurhors use the term Hamman-Rich Syndrome synonymously with idiopathic interstitial pulmonary fibrosis, some suggest that this diagnosis should be reserved for the more fulminate cases (43, 46, 53). The patients are not likely to have hemoptysis or pleuritic chest pain. Weight loss and easy fatiguability, however, are extremely common and probably should be considered as typical symptoms of the syndrome.

The physical findings, although not specific, are likely to be impressive. The patient is usually tachypneic and apparently dyspneic. Cyanosis is frequently present at rest and more frequently present on exercise. The chest tends to show limited expansion, and there are diffuse bronchovesicular breath sounds. Late inspiratory crepitant rales are almost invariably present at least in the bases and may be heard scattered throughout the chest. Many authors describe the rales as being peculiar in that they sound so close to the ear, and this is used by some as a differential diagnostic point. The heart quite frequently shows the findings of cor pulmonale; specifically, the point of maximal impulse is right ventricular along the left border of the sternum, and the pulmonic component of the second heart sound is louder than the aortic component. Clubbing occurs in greater than 50% of the cases. Peripheral edema depends on the cardiac status.

The pathophysiological mechanisms of this syndrome have been studied extensively. Baldwin, Cournand, and Richards (Medicine 28:1, 1949) and Austrian, et al., (55) were the first to characterize the abnormalities fairly completely, and the latter group coined the term "alveolar capillary block syndrome". The basic defect is a stiffening of the lung parenchyma. In physiological terms this is a decreased compliance; that is, a smaller volume than normal is caused by a given pressure change across the lung. The stiffened lung does not expand to the extent that would be expected of a normal lung based on the patient's age, height, and sex, and therefore the total lung capacity is reduced. The other static subdivision of the lung are also decreased, excepting that the residual volume is usually not as decreased as the other subdivisions. Indeed, in many patients the residual volume is not decreased at all, and with a markedly abnormal lung architecture the residual volume may be increased above its predicted value. Since the residual volume is not as decreased as the total lung capacity, the vital capacity is decreased. Since the lung is stiffened, more pressure is required to maintain it fully inflated. The clinical measurement used to demonstrate this phenomonon is the maximal transpulmonary pressure at total lung capacity, P_{max}. In normal subjects P_{max} is in the range of 20-30 cm H_2O, while in patients with pulmonary fibrosis P_{max} exceeds 30 cm H_2O.

Despite the decrease in static lung volume, measurements of air flow (maximum breathing capacity, forced expiratory volume in 1/2 or 1 second, and forced expiratory flow during 25 to 75% of the vital capacity) are not markedly impaired in most patients. These measurements are determined primarily by the patency of the airways, and involvement of airways is not characteristic of interstitial pulmonary fibrosis. In some patients with severe disease an obstructive component may be manifest by decreases in these measurements. This has been estimated to occur in up to 25% of the patients, and is thought to represent marked distortion of airways due to the pulmonary fibrosis or to concomitant bronchitis.

Part of each tidal volume in a normal person is expended in filling the conducting airways where no gas exchange takes place with pulmonary capillary blood. This amounts to approximately 30% of each tidal volume at rest, and is referred to as the dead space to tidal volume (V_D/V_T) ratio. As the normal person takes larger and larger tidal volumes, the airways do not distend commensurate to the alveoli, and the dead space to tidal volume ratio decreases proportionately. Interstitial pulmonary fibrosis destroys pulmonary capillaries in some areas of lung where ventilation continues. These areas constitute additional dead space, since no gas exchange takes place in them. Therefore, patients with interstitial pulmonary fibrosis have an enlarged physiological dead space, and the V_D/V_T ratio is increased, averaging approximately

.48 at rest (59, 62, 66). However, unlike normal persons, increases in tidal volume may not cause a decrease in the V_D/V_T ratio. (59). Thus, at rest or exercise the patient performs more external ventilation per unit of alveolar ventilation than is true in normal subjects. Since the work of breathing is high in these patients due to their stiff lungs, this excess ventilation is particularly deleterious.

Patients with interstitial pulmonary fibrosis tend to be mildly to moderately hypoxemic at rest, and the hypoxemia is worsened with exercise. Austrian, et al, (55) suggested the term alveolar-capillary block to indicate that such hypoxemia is caused by a defect in diffusion of oxygen from the alveolus into capillary blood. Although these workers noted that the physiological consequences of a thickened alveolar capillary membrane could not be differentiated from a decrease in the total alveolar capillary diffusion surface available for gas transfer, considerable controversy has ensued concerning the role of diffusion defects in causing hypoxemia in these patients (56-58, 60, 65, 68). There are, in fact, two separate arguments. The first is the relative contribution to impaired diffusion of a thickened alveolar capillary membrane versus a loss in membrane surface. The second argument revolves around the importance of any diffusion defect compared to mismatching of ventilation and blood flow in causing hypoxemia. To the best of my knowledge, the data to resolve the former argument are not at hand. Insofar as the cause of hypoxemia is concerned, it appears that there is some truth on all sides; that is, the hypoxemia at rest may be contributed to by right to left shunting, mismatching of ventilation and perfusion, and diffusion defects. In an extremely sophistocated analysis Briscoe's group (68) determined in 10 patients with the clinical syndrome of alveolar capillary block that the major factors interfering with oxygen transfer at rest were shunts in two patients, inequalities in ventilation: perfusion ratios in four patients, and in four patients the only disturbance of oxygen transfer was in the total diffusing capacity or in its distribution between the different parts of the lung. Most investigators agree that during exercise the total diffusing capacity is an important factor causing hypoxemia.

Patients with interstitial pulmonary fibrosis may have such a high minute ventilation at rest that they not only overcome their high physiological dead space but in addition maintain chronic alveolar hyperventilation resulting in a low arterial P_{CO2}. This has been most extensively investigated by Lourenco, et al (64, 66). These investigators confirmed abnormally high minute ventila-

tions, and they observed that this was accomplished by increases in respiratory frequency rather than in tidal volume; the mean respiratory frequency of the patients was 34.6. Lourenco reasons that the heightened minute ventilation in the patients could arise from an excessive amount of work performed by the respiratory muscles in response to a normal number of stimuli from the respiratory center or from an abnormally large number of nervous stimuli to the respiratory muscles from the respiratory center. The former seemed unlikely in that there is no unusual stretch of the respiratory muscles to cause them to function more efficiently. Two mechanisms could cause an abnormally large output of nervous stimuli from the respiratory center to the respiratory muscles: an increased rate of discharge from the respiratory center in response to normal afferent stimulation, and an abnormally large afferent stimulation to the respiratory center. The first mechanism might have two origins: an abnormal "setting" of the respiratory controlling system, or a decrease in intracellular buffering capacity of the cells of the respiratory center. The former is not the primary mechanism, at least in all patients, since many patients with diffuse fibrosis have a normal carbon dioxide tension. The latter possibility is unlikely since (1) many of the patients have normal blood buffering capacities, (2) an infusion of THAM caused less of a fall in minute ventilation in the patients than in normal subjects rather than a greater fall, and (3) the slopes of the ventilatory response curves to carbon dioxide breathing of the patients did not differ significantly from those of normal subjects. That hypoxemia does not account for an increased number of nervous stimuli to the respiratory center is indicated by the failure of breathing an enriched oxygen mixture to decrease the minute ventilation in any of the patients. The evidence cited favors a predominent role of peripheral nervous stimuli inducing the high minute ventilations in these patients. The origin of such nervous stimuli was not elucidated by the study, but was felt most likely to arise from the abnormal lungs.

The pathological findings in patients with the typical Hamman-Rich Syndrome, which Liebow (71) refers to as "usual interstitial pneumonia" (UIP), may have virtually all stages of the process from the acute inflammatory phase to completed fibrosis within a single case. The earliest lesion consists of a marked dilatation of the capillaries in the alveolar walls and an exudation of fluid into the walls of alveoli. Shreds of fibrin are found within alveolar walls and fibrin clots the exudate that escapes into the alveoli. There is a tendency to the formation of a thick, hyaline membrane which lines the alveoli. Cellular exudation is sparse, and is limited to a few polymorphonuclear and mononuclear cells in the alveoli and in their walls. Hemorrhage into the alveoli

from the dilated capillaries is common. The epithelial cells that line the alveoli are markedly swollen, and some are necrotic. Some of the bronchioles have lost their epithelium and are lined by a hyaline membrane or re-lined by flat, regenerated epithelium.

The next stage of the process is marked by the appearance of large fibroblasts within the edematous alveolar walls, and the fibroblasts proliferate until the walls become very much thickened. Mononuclear inflammatory cells also increase in number in the walls; there is a scattering of eosinophiles; and there is a new formation of capillaries. Where the hyaline membrane rests against the wall at sites at which the lining epithelium has been lost, it often becomes invaded by fibroblasts from the wall and becomes incorporated into the wall adding to the latter's thickness.

There is very little organization of the exudate within the alveoli. Here and there intra-alveolar hemorrhage or fibrin undergoes organization, but this is less conspicuous than the organization process within the alveolar walls.

In the later stages of the process the newly formed interstitial connective tissue becomes mature, and the alveolar walls appear as thick septa rich in connective tissue. In foci the architecture of the lung may become altogether obliterated and replaced by scars. In the areas of more advanced involvement, numerous small branches of the pulmonary artery show an intimal proliferation that narrows the lumen considerably. In numerous places bronchial epithelium has spread from terminal bronchioles to line adjacent alveoli, sometimes assuming a squamous character. Some of the terminal bronchioles are stenosed by surrounding connective tissue, leading to emphysematous dilatation of associated alveoli. There is an inconspicuous scattering of mononuclear cells in the walls of some of the bronchioles, but this nowhere approaches the degree of infiltration familiar in interstitial bronchopneumonia.

In 1965 Liebow, et al, (75) described 18 patients considered to have a distinctive type of interstitial pneumonia and named the syndrome desquamative interstitial pneumonia (DIP). The syndrome was characterized by (1) extensive desquamation of masses of large alveolar cells which proliferate actively on the walls and within the lumens of the alveoli, and which contain PAS positive granules often of brown color but devoid of iron; (2) the accumulation of minute lymphoid follicles in the periphery of the lung; (3) the absence of necrosis, hyaline membranes and exudation of fibrin; (4) the relative slight thickening of alveoli; (5) the monotonous uniformity of the lesion; (6) a typical but not specific radiographic appearance of basilar

opacification of ground-glass quality concentrated at the periphery of the lung; (7) an apparently good response to steroid therapy, usually with stabilization, and sometimes by remission of clinical symptoms and radiographic changes. In an addendum to their paper, the authors note that they had encountered 14 more patients after the conclusion of their paper. Since that time at least 28 additional patients have been reported (76-85) and the general characteristics originally outlined by Liebow have been substantiated. By electron microscopy it has been demonstrated that membranous (Type 1) pneumonocytes which normally line the alveoli are replaced by granular (Type 2) pneumocytes. The desquamated intra-alveolar cells were granular pneumocytes, similar to those lining the alveoli, and smaller numbers of macrophages.

Scadding (74) has disagreed with Liebow and sees no reason for a sharp distinction between patients with the usual form of interstitial fibrosis and DIP. He feels that there is a spectrum of disease from those with pure fibrosis to those with more proliferating cells with no clear line of demarcation. He finds, however, that those with more cells and less fibrosis respond better to steroids.

Liebow (71) has separated out three additional groups of patients with interstitial pneumonia: bronchiolitis obliterans and diffuse alveolar damage (BIP); lymphoid interstitial pneumonia (LIP); and giant cell interstitial pneumonia (GIP). The differentiation is based on histological findings; it is not clear whether these patients follow a different clinical course from those with the usual type of interstitial fibrosis. There are also numerous reports (86-91) of entities given a variety of names which are probably variants of interstitial pulmonary fibrosis. The histological picture of most of these includes an overgrowth of the smooth muscles usually found in the lung.

Treatment of this syndrome must be evaluated on the back-ground of a number of factors: the etiology or etiologies are unknown; the histological picture varies markedly from patient to patient and frequently in any given patient; the clinical course is extremely varied, and spontaneous regression occasionally occurs; there are few reported series of patients managed uniformly. With few exceptions, the only treatment attempted has been with adrenal cortical steroids. Taking interstitial pulmonary fibrosis as a whole, evidently about 15% of patients receive gratifying benefit from such treatment. In some of these patients there is a dramatic improvement in symptoms accompanied by radiographic clearing. Only occasionally, however, has the diffusion capacity been measured to increase. This gratifying response is much more likely to occur in those patients whose biopsy shows little fibrosis and

marked cellular proliferation, whether this be called desquamation interstitial pneumonia or not. In approximately another quarter of the patients there is apparently some response to steroid therapy with stabilization of the process. Since the disease may run a protracted course, it is frequently difficult to differentiate the response to therapy from the natural history of the disease. In approximately 60% of the patients there is no apparent response to steroid therapy.

In 1953 Peabody, Buechner, and Anderson (18), who first coined the term Hamman Rich Syndrome, reported the precipitous deaths of 3 patients following abrupt withdrawal of cortisone or ACTH, despite reinstitution of the drug while the patient deteriorated. There have been several subsequent reports of a similar nature. Such deterioration has occured even in patients who received no beneficial effects from the steroid. Although it is difficult to be sure that the patients reported deteriorated precipitously due to the withdrawal of steroids, the case reports are impressive enough to suggest only gradual withdrawal of steroids once they have been started.

There is obviously no universal treatment regimen. In the more recent literature, large doses of steroids have usually been administered. However, Scadding (74) indicates that all of his patients who responded did so on a daily dose of 30 mgms of Prednisolone or less. The work by Berliner and Ruhmann (Endocrinology 78:373, 1966) with tissue cultures of fibroblasts suggests an inhibition of fibrogenesis with 11 beta-OH corticosteroids (such as cortisol and Prednisolone), whereas the corticosteroids with a keto group in the 11 position (such as cortisone or Prednisone) lacked inhibitory activity. This suggests that Prednisolone is currently the drug of choice.

The etiology of the Hamman Rich Syndrome was originally proposed to be infection, but no evidence has accrued to support this hypothesis. Since many industrial inhalational agents may produce diffuse pulmonary fibrosis that is indistinguishable from idiopathic pulmonary fibrosis, it has been suggested that all pulmonary fibrosis has this origin. However, most reported cases have no history of inhalational exposure to known toxins, even when a careful search is made, and the equal incidence in men and women further argues against this etiological possibility.

It is clear that the incidence of pulmonary fibrosis is greater in some families than could be accounted for by chance alone (88, 93-96). The extensive family studies of Bonanni, et al, (94) and Swaye, et al, (96) suggest that in some families interstitial pulmonary fibrosis is transmitted as a simple autosomal

dominant characteristic. The sporadic nature of most reported cases, however, suggests that this is not the usual event.

The most prevalent current hypothesis is that idiopathic pulmonary fibrosis may be an autoimmune disease. The relationship of rheumatoid arthritis to lung disease has long been recognized (97-107), and this has stimulated a search for autoantibodies in interstitial pulmonary fibrosis. Further stimulus was gained from the work of Read (108) who injected rabbit anti-rat lung serum intratracheally into rats and produced a "pneumonotoxic pneumonia" with lesions resembling those seen in the Hamman Rich Syndrome. Of 80 patients with interstitial pulmonary fibrosis without extrathoracic manifestation of connective tissue disease which have been reported, 34 (42%) have had some test positive for rheumatoid factor in the serum (105, 110-112). Moreover, such patients may show antinuclear factor in the serum (111-113), although they do not demonstrate LE cells. In one instance (113) IgM has been demonstrated by immunofluorescent technique in the alveolar septum of a patient with pulmonary fibrosis and serum IgM antinuclear factor. The IgM was demonstrated only in those areas of lung where mononuclear cells were proliferating and could not be demonstrated in those alveolar septa that exhibited marked fibrosis and little cellular infiltration.

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