Familial Pulmonary Fibrosis

JOHN M. MacMILLAN, M.D., F.C.C.P.*
Rochester, New York

Over a period of many years there has gradually accumulated, from Iola Sanatorium and Dispensary cases, a large teaching file of interesting and instructive chest x-ray films. This file, as far as present day classification of pulmonary diseases goes, is practically complete. However, it contains a relatively similar group of cases showing bilateral symmetrical involvement where the exact etiological factor is unknown.

These teaching cases, in some instances, have had their diagnoses changed as many as three times. The great frequency with which tuberculosis was given as the initial diagnosis was probably due to its high incidence and ability to simulate any other chest disease and to too little dependence on negative tuberculin and sputum examinations. Next in frequency were broad inclusive terms like pulmonary fibrosis, chronic interstitial fibrosis, and post-infectious fibrosis. Terms such as chronic pulmonary granuloma, or chronic non-infectious granuloma were also freely used. The remaining diagnoses in this relatively homogeneous group were Boeck's Sarcoid, fungus disease, and chronic pulmonary lymphangitis. The primary etiological factor, however, was still lacking, and this fact alone did more to stimulate our investigation than any other.

Even in some of the cases where biopsy or autopsy has been done, the causative factor still remains a mystery. The pathological terms fibrosis or granuloma are inclusive ones, and when one finds them at the end of the road, unless past clinical or laboratory data is available, the primary etiological factor, or factors, remains unexplained.

Tissue repair varying as it does from complete resolution to keloid formation, the idea is entertained that perhaps such an entity as a pulmonary keloid type of response to trauma or infection is possible. Then too, there is the possibility that the lungs are the "Achilles Heel" in certain individuals or families.

With the presentation of the following familial groups, it is felt that sufficient clinical and pathological data is offered to warrant the establishing of a new disease entity, the basic etiological factor being a familial response to pulmonary trauma, of an infectious organic or inorganic nature.

Familial Group I:

This group includes Case I (Figures 1, 2, and 3), and Case II (Figures 4 and 5), supplemented by additional family investigation.

Case I: The first and original case study began in our Out-patient Department in 1918. At this time an apparently precursory examination was negative. On the next examination a chest x-ray film—no longer available—was interpreted as follows: August 28, 1918, Right: Moderate infiltration throughout. Left: Moderate infiltration throughout. There was little change in her clinical condition on subsequent examinations, which were approximately at yearly intervals. On one examination she gave a history of "Recently having raised large mouthfuls of blood; streaked twice later; cough, slight, non-productive of sputum." November 18, 1923, a diagnosis of moderately advanced pulmonary tuberculosis was made. Several sputa were negative for tubercle bacilli. No chest x-ray film was made. A physical examination of the chest was negative June 22, 1927, but one on February 2, 1928, showed scattered rales throughout, anteriorly, and upper thirds of both lungs, posteriorly. A chest x-ray film at this examination revealed: "There is questionable slight haziness at the right apex, and thickening of apical pleura on the left. There is nothing definite enough to make a diagnosis of pulmonary tuberculosis." The next examination occurred November 27, 1935. This followed a cold for the past three weeks. X-ray film interpretation was: Right: Abnormality throughout, more marked at the apex. Left: Abnormality from the first to third ribs, posteriorly; slight, scattered, rather diffuse infiltration from the third to eighth ribs, posteriorly. The findings were considered suspicious of pulmonary tuberculosis. Sanatorium was advised. She didn't follow this advice, and returned for a recheck February 24, 1936. Her chest x-ray findings were unchanged. A laryngeal smear revealed a few acid-fast bacilli on this examination and she entered Iola Sanatorium for the first time on March 9, 1936.

This 49 year old white, housewife, on admission gave a family history of her father dying of pulmonary tuberculosis shortly after her birth. Two sisters died of pulmonary tuberculosis, one in 1918 and the other in 1919. Occupational history was negative. The only past history of significance was the average number of chest colds. There was unexplained hoarseness since childhood. Blood pressure was 146/100. Pulse 84. Temperature 37. Diagnosis was moderately advanced pulmonary tuberculosis. Seven sputum examinations were negative. She was discharged March 20, 1936.

Out-patient Department x-ray films on May 20, August 26, and December 23, 1936, and February 19, 1937, revealed no increase in pulmonary disease. Outside of several colds, her clinical condition remained unchanged until December, 1936, when she began to complain of dyspnoea. Out-patient Department examination June 16, 1927, showed increased dyspnoea, otherwise she felt "fine." The chest x-ray film, compared with that of February 16, 1937, showed: Right: Slight but definite progression, evidenced by increased infiltration throughout. Left: Shows definite progression evidenced by increased infiltration throughout.

She was admitted to Iola Sanatorium July 6, 1937. There was no appreciable change over her previous admission physical examination. She was 11 pounds overweight. Dyspnoea was now supplemented by orthopnea. Blood pressure was 150/100. Cough was non-productive. Cyanosis in-
Figure 1: Familial Group I. Case 1. Film taken February 2, 1928.

Figure 2: Familial Group I. Case 1. Film taken November 27.

Figure 3: Familial Group I. Case 1. Film taken June 16, 1937.
creased. She expired suddenly during the night of July 24, 1937, and the necropsy revealed the following:

Gross: Left: 370 gms. Right: 600 gms. The lungs appear quite small. The pleura of the left lung is smooth. Scattered all over the surface there are slightly raised, pale areas, which apparently are due to emphysematous changes. The lungs feel very firm and rather rubbery in consistency. The bronchi are injected and much tenacious exudate is found within them. The pulmonary arteries show slight thickening, and there are areas of fatty degeneration. On section, throughout both lobes there are many areas which are grayish due to fine scar tissue, apparently involving the alveolar wall. These are firm. The bronchioles contain thick yellowish exudate. The lung tissue is congested. No definite areas of pneumonia are found, and no tubercles seen. The right lung is similar in appearance. There is an apparently chronic pneumonitis with fibrosis.

Microscopic: Numerous sections show the same picture. Only occasionally small areas show normal appearing air sacs, and often these are full of fresh blood and the capillaries are congested. Alveolar walls elsewhere show fibrosis with loss of capillaries. There are scattered areas of well developed granulation tissue rich in vessels that are dilated and full of red cells. The pleura contains many dilated vessels also. There are mononuclear wandering cells and some alveoli contain polys. There are scattered collections of mononuclear and foreign body giant cells. There is nothing to indicate tuberculosis. Bronchi show some desquamated epithelium, some polys, and some are dilated. There are scattered areas where alveoli are dilated and the epithelium lining them looks like bronchial type. This could go on to malignancy, but as yet there is no indication of such degeneration. There is evidence of organization of exudate within alveoli. Arteries show some intimal thickening. Occasional thrombi are present in small vessels.

Heart: Weight, 320 gms. The epicardium is smooth, with moderate amount of fat. The right ventricular wall measures .7 cm. in thickness in some areas; the left 1.4 cms. There is very marked hypertrophy of the right ventricle and the chamber is dilated. The myocardium is firm in consistency, and free from scars. The coronary arteries are patent.

Microscopic: The right ventricle wall shows hypertrophy of muscle fibers, which are enlarged as compared with those of the left ventricle. There is some increase in interstitial tissue, particularly about large vessels.


Pathologist Note: Lung sections show fibrosis with more recent organization occurring, indicating that process is active and continuous. There is nothing specific about the reaction, so etiology cannot be stated. It would appear that there must be a low grade infection which from time to time has acute exacerbations.

Case II: Daughter of Case I (Figures 4 and 5).
Family History: At the time of its taking the story was unchanged. Mother died of pulmonary tuberculosis, as well as two aunts. Two sisters and one brother were alive and well.
Occupational and Allergic History: Negative.
Past History: A chest x-ray film taken in 1938 was negative. There was some indefinite history of sinus trouble.

Present Illness: This patient enjoyed good health until August 1945, when she developed a sore throat, followed by fatigue. November 1945 she developed pleurisy on the left side for several days. In the several months that followed she lost 20 pounds. A chest x-ray film at Iola Dispensary January 18, 1946, revealed pulmonary disease, which was felt to be of tuberculous etiology. She was on home treatment in the months that followed, with a resulting gain in weight and disappearance of pulmonary symptoms—notably cough. In January 1946 she resumed light household duties. December 1946 cough returned. January 1947 there developed increasing dyspnoea for which she was admitted to a general hospital June 14, 1947. There a diagnosis of pulmonary tuberculosis was again made, and she was subsequently transferred to Iola Sanatorium July 11, 1947.

As a result of our study following admission, the diagnosis of tuberculosis could not be substantiated, and we made a diagnosis of chronic interstitial fibrosis. It should be noted at this time that this diagnosis was made in view of negative findings for tuberculosis and a recollection of the findings in her mother's case. Physical examination of the chest was no different from the findings in the case of her mother. She reacted to tuberculin. Repeated sputa were negative for tuberculosis. White blood count was 9,600, with neutrophils 49 per cent, lymphocytes 39, and monocytes 11. Sedimentation rate was elevated. Histoplasmin skin test was 1 plus. Electrocardiogram was not unusual, other than a tendency to right axis deviation. One week before death axis deviation became marked. With increasing dyspnoea and no evidence of peripheral failure, she died September 3, 1947.

Following the autopsy of Case II, in which the pathological gross and microscopical findings were exactly the same as Case I (her
mother), further investigation brought out the following additional interesting familial details. The sisters of Case I died of pulmonary tuberculosis—one in 1918 and the other in 1919. A remaining sister had been killed accidentally.

Rechecking scanty hospital records of the sister who died in 1918, she was found to have died in our County Hospital. The only available data was that at the age of 36 she became acutely ill of a respiratory disease, and 24 days after admission died of, supposedly, pulmonary tuberculosis.

The second sister of Case I died in 1919, at the age of 30. She too became acutely ill of pulmonary disease and was admitted to the Rochester General Hospital. She died a respiratory death 15 days after admission. The only available data is nurses' notes and records of temperature, pulse, and respirations. On admission her temperature was 99.8 degrees F.; pulse 85; respiration 20. Gradually over the ensuing days her temperature rose to 104 degrees F.; pulse to 140; and respiration to 50. From the nurse's notes—at death—"There was cyanosis, rapid shallow breathing, cough, sputum—but no blood." Chest roentgenogram was reported as follows: "Consolidation, right apex, first and second interspaces; dense infiltration first, second, and third interspaces." Cause of death was given as pneumonia. Her admission diagnosis was influenza. No autopsy was performed on either case.

The possibility of a familial factor cannot be denied, but still in these last two cases that is as far as we can go. They were not typical of the diagnoses given, and they are not typical of pulmonary tuberculosis.

Familial Group IZ: Identical Twins.

This familial group has been admirably described in a recent paper by Drs. Peabody, Peabody, and Hayes.3 To further strengthen their contentions and the author's conclusions, the surviving twin has since died and the pulmonary pathological findings were identical with her twin sister. It is the author's opinion that KI, used late in the course of the surviving twin's illness, may have been a factor in prolonging her life.

Familial Group III: Involving Non-identical Twins.

Case I (See Figure 6). Regarding white, married housewife, born April 3, 1908.

Family History: Father died of pneumonia. A brother died at the age of 36 of pneumonia. Three others are alive and well. One sister alive and well (non-identical twin). Regarding remaining sister, see Case II, which follows.

Past History: Negative. The patient was examined for the first time
at Iola Dispensary because of frequent colds and weight loss. A chest x-ray film of November 25, 1940, was negative.

Present Illness: On June 12, 1947, she was referred to Iola Dispensary because of dyspnoea. A more detailed history revealed that she had frequent chest colds for the past nine years. Orthopnea was now the major symptom. Vital capacity was 1100 cc. Sedimentation rate was normal. Red blood count 4,500,000. Hemoglobin 15 gms. Electrocardiogram showed tendency to right axis deviation, but no characteristic findings of chronic cor pulmonale. Her chest x-ray film (Figure 6) was interpreted as showing increased markings throughout both lungs. A diagnosis of pulmonary emphysema was made.

She was seen next by a physician in October 1948, at which time she demonstrated marked dyspnoea, orthopnea, cyanosis, and edema of both legs and sacrum. These symptoms had been gradually increasing in severity during the previous six months and had finally become so disabling that she sought medical aid. As a result, she was admitted to Strong Memorial Hospital on October 25, 1948.

Examination showed temperature 37.7 degrees C. Respiration 20. Pulse 120 and regular. Blood pressure 130/80. She was markedly dyspneic, orthopneic, and cyanotic. She had pitting edema of both legs and sacrum. On physical examination of the chest there was found increased resonance throughout; breath sounds were poorly heard. A chest x-ray film showed increased peribronchial markings throughout the entire lung parenchyma. The pulmonary conus was prominent and the right auricle enlarged. Electrocardiogram showed right axis deviation, sinus tachycardia, abnormal T waves. Red blood count was 5,000,000; hemoglobin 18 gms. per cent. CO₂ persistently 85 per cent volume. She gradually improved under medical care, but at the time of discharge still had tachycardia, high CO₂, high red blood count and hemoglobin. She was discharged on November 24, 1948, with a diagnosis of pulmonary emphysema, with fibrosis; cor pulmonale.
The patient got along fairly well at home for a period of about nine to 10 months. However, she gradually became so dyspneic, orthopneic, and cyanotic again that she was admitted of necessity for the second time to Strong Memorial Hospital, principally for oxygen treatment. She rallied from this state and became stabilized so that she could do fairly well without oxygen. She was discharged on August 28, 1949, only to return two months later. She was admitted to Strong Memorial Hospital for the third time on October 17, 1949. On October 21, 1949, she developed Cheyne-Stokes respiration and on October 22, 1949, she became comatose and expired.

Autopsy Findings: Lungs Gross: Left lung weighed 450 gms. and the right 550 gms. The left lung pleural surface is not remarkable with the exception of several adhesions. Dissection of pulmonary blood vessels reveals them to be widely patent throughout with thin walls and no thrombi. Bronchi contain a large quantity of thick blood-tinged mucoid material. Hilar nodes are not enlarged. The left lung is crepitant and air-containing throughout with bullous emphysematous blebs covering the entire surface. In some areas the blebs are seen to consist of numerous small areas of emphysematous tissue producing a coarsely honeycombed appearance. The basilar portion of the lower lobe is moderately wet and congested. The hilar portions of the lung show slight congestion but are air-containing throughout. The right lung is similar to the left in all respects.

Lungs Microscopic: All sections show marked enlargement of alveoli and atria, some symmetrically enlarged, others showing disappearance of interalveolar septa and irregular increase in alveolar diameter. In these areas the septa are very thin, consisting of only capillaries and a few fine fibrous strands. There is a patchy fibrosis, chiefly in perivascular and peribronchial areas, but fibrosis is interstitial in some places. Most sections show capillaries distended by blood. Many alveoli which are not emphysematous and which are in relation to vessels and bronchioles are lined by cuboidal epithelium. A few areas show pigmented macrophages within alveoli; other alveoli contain a small amount of granular acidophilic material in contact with alveolar walls. Bronchioles are lined by ciliated respiratory epithelium, which rests on congested connective tissue comprising the submucosa. Lumina are filled with macrophages, many filled by lipoid material. There is no inflammatory exudate or infiltration in any section. A few arterioles have organizing thrombi.

Heart: Weight 375 gms. The epicardium is smooth, contains a moderate amount of normal appearing fat, and epicardial vessels appear soft and pliable. The heart is considerably dilated in all diameters, but the size of the right heart is predominant. The right auricle is markedly dilated, measuring 6 x 6 x 5 cms. Dissection of the cardiac chambers reveals dilatation of the right ventricle with bulging of the interventricular septum towards the left. All cardiac chambers are filled by recently clotted blood. The foramen ovale is closed, and the ductus arteriosus is obliterated. The endocardium is smooth and thin throughout, and the papillary muscles, chordae tendinae, and trabeculae appear normal. Valves: Tricuspid 13 cms.; pulmonic 9; mitral 10; and aortic 8 cm. Valve leaflets appear anatomically normal and are thin and pliable. The root of the aorta shows normal caliber, a few scattered plaques of atheromatous material in the walls, and intact intima. Coronary vessel ostia are patent. The myocar-
dium of the left ventricular wall measures 1.3 cm. and the right 1 cm. It is dark red throughout, firm, and shows no local lesions. Coronary vessels are all widely patent with thin pliable walls and no occlusions.

Heart Microscopic: Myocardial fibers vary in size, tend to be large. Cross striations are well-preserved. Moderate perivascular fibrosis and edema.


Case II: Housewife, born April 3, 1906. This is the non-identical twin of Case I, who is well, asymptomatic, and presents a normal chest x-ray film.

Case III (See Figure 7). Housewife, born August 7, 1902, sister of non-identical twins, Cases I and II.

Family history is same as Group III, Case I. Occupational and allergic history were negative. Past history showed bronchitis in March and April of 1943. On June 12, 1944, she was referred to Iola Dispensary because of cough. A chest x-ray film was interpreted as negative and she was discharged.

Present Illness: February 6, 1947, this patient was seen in consultation because of progressive cough, sputum, and increasing dyspnoea over the past eight years. At this time she was definitely a pulmonary invalid. Her chest x-ray film of January 28, 1947 (Figure 7), was interpreted as showing increased markings throughout both lungs with bilateral infiltration suggestive of fibrosis in both infraclavicular regions. Pulmonary emphysema was rather marked. Chronic interstitial fibrosis, pulmonary emphysema, and chronic bronchitis was felt to be the most likely diagnosis. Under a closely supervised rest regime the patient's clinical condition has remained unchanged to date.

Discussion

This so called “Pulmonary keloid response” to tissue damage and repair has already been mentioned. This response, which is relatively chronic in nature, carries with it numerous variables of reactions to disease and trauma. Pulmonary emphysema is a running mate to this entity. It too bares the variability of time and is also greatly influenced in its degree and extent by speed of reaction of the primary disease, as well as cough, age of patient, and familial predisposition. It is this reasoning which the author uses to explain the difference between the radiographic pictures of Groups I and II over Group III. Groups I and II were in build of a rather medium stocky type. Group III were slight and thin. Again where dyspnoea was the predominant symptom as compared to cough, it is felt that naturally the contracture of fibrosis will result in the predominate picture. Where cough is a predominate symptom, it naturally tends to produce a higher degree of emphysema, with resulting over-distention of the lungs.

This paper seems to present a disease involving the female side
of the family. This is not felt to be true. Similar disease has been seen in males, but at the present a familial group where males are the major factor has not been satisfactorily uncovered. The father of Group I, Case I, died supposedly of tuberculosis when she was a child. The parents' history of Group II is unknown. The father of Group III was supposed to have died many years ago of pneumonia. Because of time and the sparsity of details, one can only surmise. The fact that they further strengthen the "Achilles Heel" contention cannot be denied.

It is too early to make any positive statement regarding therapy and, of course, too late for those of this group who have died. Reviewing other suspicious cases of possible familial fibrosis, where potassium iodide has been used, it can be said that in every instance it has seemed to exert a beneficial effect. Three previously progressive cases are at present stationary or improved.

The question of cor pulmonale resulting from peripheral pulmonary vascular change is receiving further study. It is late in the course of these patients' illness that electrocardiographic evidence is present to substantiate pulmonary hypertension. At autopsy, however, rather marked right ventricular hypertrophy is very much in evidence. It is the author's impression that chronic cor pulmonale is a terminal change rather than a part of the disease entity.

Where this entity represents a true chronic process it is felt that some of the acute cases of chronic interstitial fibrosis reported in the past are undoubtedly of the same etiology. Cases described by Hamman and Rich and also Eder and others clinically and pathologically are identical with mine. It is interesting to note that of the four cases presented by Hamman and Rich three are females and one a male.

SUMMARY

1) The term Familial Pulmonary Fibrosis is felt to be a definite entity.
2) This disease is a familial response to chronic pulmonary insult in the nature of bilateral pulmonary fibrosis.
3) The disease, once it manifests itself clinically, is usually progressive to death.
4) The age incidence is from 30 to 55 years.
5) The possibility of potassium iodide being an inhibitor to increasing fibrosis warrants further investigation.
6) The importance of a detailed family history and an inquiry of the manner of death, rather than a diagnosis, is invaluable.
RESUMEN

1) Se considera que la designación Fibrosis Pulmonar Familiar corresponde a una entidad definida.
2) Esta enfermedad es una respuesta familiar a una afección crónica pulmonar, respuesta que es en forma de fibrosis pulmonar bilateral.
3) Una vez que la enfermedad se manifiesta clínicamente, generalmente es progresiva hasta la muerte.
4) La incidencia es en edades de 30 a 55 años.

RESUMEN

1) L'expression de tuberculose fibreuse familiale représente une entité définie.
2) Cette affection est la réaction que peuvent opposer certaines personnes de la même famille à la tuberculose pulmonaire chronique en constituant une forme fibreuse bilatérale.
3) Cette affection, quand elle se manifeste cliniquement, évolue en général progressivement jusqu'à la mort.
4) Elle survient de préférence entre 30 et 55 ans.
5) L'action possible de l'iode de potassium, qui paraît arrêter l'accroissement de la fibrose, demande des recherches ultérieures.
6) Les antécédents familiaux détaillés, et l'enquête sur les causes de la mortalité dans cette famille prennent une importance considérable. Ces éléments ont plus de valeur que les éléments donnés par l'examen du malade.

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BIBLIOGRAPHY