Familial Hamman-Rich Syndrome*

Report of Eight Cases

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A family group of eight members is described of which seven members have or had histologically proved Hamman-Rich syndrome. From the onset of symptoms, the age range is from four months to 39 years. The case data of a mother, daughter, and granddaughter with proved disease are presented. The latter two members are alive and well at the present time, being maintained on low doses of steroids. One of these patients was 3.5 years old when the diagnosis was confirmed by lung biopsy. She probably represents one of the youngest living patients with Hamman-Rich syndrome. Two brothers of this group had coexistent pulmonary fibrosis and bronchogenic cancer; an association in the familial disease not previously recorded, though isolated cases have been reported. It is now firmly established that Hamman-Rich syndrome can occur as a distinct familial entity that is transmitted as an autosomal dominant trait.

Since Hamman and Rich¹ described four cases of acute diffuse interstitial fibrosis of the lung in 1944, numerous studies of this entity have been published. The eponym of Hamman-Rich syndrome should probably designate only those cases of short duration. However, many physicians consider the more protracted cases to be just a variant of the originally described syndrome. We use the term fibrosing interstitial pneumonitis to refer to the pathologic picture seen in the chronic cases.

The familial occurrence of this entity was noted by Peabody and associates,² in 1950, when they described twin sisters who had similar clinical and roentgenographic changes suggestive of idiopathic pulmonary fibrosis, with the pathologist’s confirmation in regard to one sister. Since that time there has been increasing awareness of the occurrence of the disease in families. Because of genetic transmission of this entity, Donahue and associates³ suggested that the term “familial fibrocytic pulmonary dysplasia” should be used to distinguish this syndrome from the nonfamilial idiopathic diffuse interstitial fibrosis. They concluded that a significant proportion of patients who have the Hamman-Rich syndrome, possibly as high as 25 percent, must possess a heritable congenital defect. They believed that the disease was transmitted as an autosomal dominant trait. This concept has been partially verified by subsequent familial studies. Up until the present time we have found published reports of 51 cases of Hamman-Rich syndrome in 14 family groups. Some of the reports include those by Hughes,⁴ Adelman, Chertkow, and Hayton,⁵ Koch,⁶ Bonanni, Frymoyer, and Jacox.⁷

Our report concerns seven members in three generations of one white family group with histopathologically studied disease (Fig 1). Of particular interest is the finding of the disease in a woman, in her daughter, and in her granddaughter, with the latter two members living and relatively asymptomatic some nine, and four years, respectively, after histologic diagnosis and initiation of therapy.

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Figure 1. Family pedigree for four generations. Male members are designated with squares, females with circles.
Coexistent carcinoma of the lung was found in two brothers of this family group; an occurrence not previously reported as a possible complication of the familial type of the Hamman-Rich syndrome.

**REPORT OF CASES**

**CASE 1**

The propositus was a man who was 40 years old when respiratory symptoms began to develop in 1941. After an illness diagnosed as primary atypical pneumonia, he noted the onset of gradually progressive dyspnea. This continued until his first hospitalization in 1952, when the dyspnea was present even at rest. A cough, productive of thick, gray sputum, was present during the previous three years. Examination revealed a well-developed white man who did not appear acutely ill. The only positive findings at that time were many bilateral, coarse, crackling rales over the lower halves of both lung fields.

A chest roentgenogram showed finely diffuse infiltration both of a linear as well as of a patchy nature as shown in Figure 2. The blood count, urinalysis, urea nitrogen content, and serum protein electrophoretic pattern were within normal limits. The erythrocyte sedimentation rate was 34 mm in one hour. A first-strength purified protein derivative (PPD) skin test was negative. Sputum and gastric bacteriologic studies were negative for acid-fast bacilli. Bronchoscopy showed no specific abnormality, and an axillary lymph node biopsy showed only reticular hyperplasia. The patient was discharged from the hospital to receive symptomatic treatment at home.

The symptoms gradually worsened and necessitated the patient's readmission to the hospital in January 1954. At that time he was febrile, tachypneic, and appeared clinically ill. Cyanosis of the lips and the fingernails, and was tachypneic. Many crepitant rales were heard throughout both lung fields. The blood pressure was 130/92 mm Hg. No murmurs were present. There was no organomegaly or peripheral edema. A chest roentgenogram showed a diffuse symmetric fine reticular infiltration throughout both lungs (Fig 3). The vital capacity was 63 percent of normal. An electrocardiogram showed prominent right axis deviation. The blood hemoglobin content was 17 gm/100 ml; a midstrength PPD skin test was positive; sputa were negative for acid-fast bacilli. His condition gradually deteriorated and the patient died in August 1952. Autopsy was performed.

**CASE 2**

A 41-year-old man (brother of the propositus) was first seen in September 1950, because of shortness of breath on exertion, a symptom he first noted in 1947. At that time a roentgenogram of the chest revealed "pulmonary fibrosis of undetermined etiology." Since 1947 he had frequent colds with mildly productive cough, fatigability, and a 10-lb loss in weight.

On examination the patient had cyanosis of the lips and the fingernails, and was tachypneic. Many crepitant rales were heard throughout both lung fields. The blood pressure was 130/92 mm Hg. No murmurs were present. There was no organomegaly or peripheral edema. A chest roentgenogram showed a diffuse symmetric fine reticular infiltration throughout both lungs (Fig 3). The vital capacity was 63 percent of normal. An electrocardiogram showed prominent right axis deviation. The blood hemoglobin content was 17 gm/100 ml; a midstrength PPD skin test was positive; sputa were negative for acid-fast bacilli. His condition gradually deteriorated and the patient died in August 1952. Autopsy was performed.

**CASE 3**

A 21-year-old woman (niece of the propositus) was apparently quite well until one year before admission to the hospital.
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hospital in 1957. At that time a persistent cough had begun, with gradually increasing dyspnea. A roentgenogram of the chest was reported as highly suggestive of pulmonary fibrosis. The patient's father, uncle, and an aunt had been disabled by similar pulmonary conditions (according to the history obtained). Her condition rapidly deteriorated and death ensued. Autopsy was performed.

CASE 4

A 43-year-old woman (sister of the propositus) had noted increasing shortness of breath during the four years before she was hospitalized in November 1956. At that time she was experiencing dyspnea at rest, with orthopnea. There had been generalized weakness with a 10-lb loss in weight during the previous several months. As a teenager, she had experienced mild asthma, and at the age of 18 years, an episode of "pleurisy with fluid." Two of her brothers had recently died from an "unusual lung disease."

On examination the patient was in moderate respiratory distress. Her blood pressure was 120/80 mm Hg, pulse rate 116, and respiratory rate 32. Coarse, crackling, inspiratory rales were noted over both lower lung fields. No jugular venous distension, gallop rhythm or hepatomegaly were present. The roentgenogram of the chest showed diffuse bilateral changes both of the linear and of the small nodular types of densities. The cardiac silhouette was slightly enlarged. Results of laboratory tests including blood count, serum protein electrophoresis, and sputum examinations for acid-fast bacilli were within normal limits. Skin tests with midey muscle PPD, coccidiodin, and histoplasmin were negative. Pulmonary function tests revealed a maximum breathing capacity of 49 liters per minute (82%); total lung volume of 1.72 liters (1.53); a vital capacity of 1.04 liters, and residual volume of 0.68 liter (1.18). The oxygen content of the arterial blood was 19.5 vol percent; the Po2 was 58 mm Hg and Paco2, 33 mm Hg.

The patient was discharged from the hospital after 28 days. One month later, because of a worsening condition she was readmitted to the hospital in respiratory failure and died 24 hours later. Autopsy was performed.

CASE 5

A four-month-old girl (niece of the propositus) was admitted to the hospital in March 1938 because of vomiting and failure to thrive. Little other information is available from her records in regard to initial findings or the subsequent clinical course except for the development of pneumonia soon after admission to the hospital. She died ten days later. Autopsy was performed.

CASE 6

A 5½-month-old girl (niece of the propositus) was admitted to the hospital in January 1951 because of a feeding problem present since birth; her weight was 12 pounds 4 ounces. Results of examination, including a roentgenogram of the chest, were negative.

During the next year at home she failed to thrive, and a persistent cough developed with frequent choking spells. On readmission to the hospital in April 1952, she looked chronically ill with severe tachypnea. A roentgenogram of the chest showed a diffuse, fine infiltrate throughout both lungs. A family history of pulmonary disease was elicited at that time. A blood hemoglobin determination was 14.2 gm/100 ml; white blood cell count was 12,500/mm³ with 52 per-

*Value in parentheses represents predicted volume.

cent neutrophils and 47 percent lymphocytes; serum protein electrophoresis was normal. An old tuberculin (OT) test (1/1000 strength) was negative.

During the next few months the symptoms worsened with increasing dyspnea, intermittent cyanosis, and coughing spells. She was again hospitalized in severe respiratory distress, and this time had clubbing of the fingers. A roentgenogram of the chest showed an increase in the diffuse infiltrate with increased cardiomegaly. Treatment was instituted with adrenocorticotropic hormone and digitalis; there was some initial improvement and she was discharged from the hospital to receive further treatment at home. Five months later, the clinical state having worsened, she was readmitted to the hospital; the infant died 24 hours later. Autopsy was not performed.

CASE 7

An 18-year-old girl (niece of the propositus) was first examined at the Cleveland Clinic in February 1958 because of an acute respiratory infection. A roentgenogram of the chest showed a generalized increase in linear markings suggestive of diffuse interstitial disease. She stated that she had had no chronic respiratory symptom, but was aware of the fact that her mother and two uncles had died recently from unusual lung conditions.

In view of the family history, and changes evident on the chest roentgenogram, further studies were carried out.

A surgical lung biopsy was performed in October 1958; the pathologic findings were consistent with chronic fibrosing interstitial pneumonitis of the Hamman-Rich syndrome. Steroid therapy was instituted and maintained, with resultant stabilization of the clinical picture. During the next four years the patient delivered three full-term infants, without complications. However, in one of her children (patient 8), the same pulmonary involvement developed. The patient at the present time is completely asymptomatic, the previous abnormalities seen on chest roentgenograms having regressed.

CASE 8

A 3½-year-old girl (grandniece of the propositus) was first examined in April 1964 because of a nonproductive cough that had persisted for eight months. At that time, scattered rales were noted throughout both lung fields. The remainder of the findings were within normal limits. The roentgenogram of the chest showed fine nodular and linear infiltrations throughout both lung fields. The family history indicated that both the patient's mother and grandmother (patients 7 and 4, respectively) were known to be affected by "pulmonary fibrosis," and this was fatal in the latter in 1957.

Laboratory tests, which included blood counts, a test for lupus erythematosus, and serum protein determinations, gave normal values. The arterial oxygen saturation was 94 percent.

A surgical lung biopsy was performed in May 1964 and revealed chronic fibrosing interstitial pneumonitis of the Hamman-Rich syndrome. Therapy was begun with steroids in low dosages. Since then the patient has improved and is at the present time asymptomatic; the roentgenograms demonstrate the improvement. The most recent one on May 22, 1968, is essentially normal.

PATHOLOGIC FEATURES

At autopsy, four of the deceased patients (cases 1, 2, 3, 4) showed similar microscopic changes that
have been described as “honeycomb lung.” Small cystic spaces were separated from each other by bands of collagen of various thicknesses (Fig 4). The spaces were occasionally lined by a bronchiolar type of epithelium and contained hemorrhagic or granular coagulum, or aggregates of histiocytes and other inflammatory cells (Fig 5). An acute type of intracystic pneumatic process was occasionally seen. Some of the bordering fibrotic zones were large and contained a variety of enmeshed structures. Aggregates of smooth muscle were often prominent (whether hyperplastic or not is a matter of opinion); collapsed bronchi were often present. The pulmonary vasculature was greatly altered, with arteriosclerosis and occlusion of the small arteries, and atherosclerosis of the major arteries being the prominent changes. A superimposed inflammatory infiltrate within the collagenous tissue was usually slight and consisted predominantly of aggregates of lymphocytes, although plasma cells were also present. Normal pulmonary architecture was sparse.

In one of the men (case 1) there was also found a prominent bronchiolar epithelial dysplasia that blended into a well-differentiated scirrhous adenocarcinoma (Fig 6). Although one of the other patients (case 2) (a brother of the one with carcinoma) was also found to have carcinoma, the slides available to us did not show it.

The necropsy in case 5 had findings of a more acute nature than those in cases 1 through 4. The honeycomb lung was not present. The sections instead showed a severe chronic fibrosing interstitial pneumonitis without evidence of intra-alveolar organization; hyaline membranes were quite prominent, as well as an interbronchial and interalveolar exudate that mainly was composed of polymorphonuclear leukocytes, but occasionally the alveoli contained moderate numbers of plasma cells and large numbers of alveolar macrophages. The morphologic pattern was similar to that we have seen many times in adults of various ages who underwent biopsy during the initial phases of fibrosing interstitial pneumonitis.

The two patients (cases 7 and 8) who underwent biopsy of the lung showed a distinctly different type of change, caused in the main by the sparsity of pathologic lesions. In case 6 was found what we have diagnosed as fibrosing interstitial pneumonitis in miniature. There were large areas of normal-appearing lung, but patchily throughout were minute zones of alteration (Fig 7) showing a severe interstitial fibrosis enmeshing a severe inflammatory reaction consisting mostly of lymphocytes and plasma cells, although there was a rare minute granuloma. There was no intra-alveolar organization, although there were aggregates of eosinophilic histiocytes and macrophages. The microscopic findings in the patient's daughter (case 8) varied only in quantity. Interstitial fibrosis was

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minimal, but the aggregates of interstitial inflammation were quite prominent and consisted mainly of lymphocytes and occasional plasma cells (Fig 8).

COMMENT

The familial transmission of the Hamman-Rich syndrome as an autosomal mendelian dominant characteristic is now firmly established. The preponderance of affected females with the familial disorder at first seemed to make sex-linkage a real possibility, but since Koch\textsuperscript{6} described a case of father-to-son transmission, complete sex-linkage has been excluded. The occurrence of histologically proved disease in three generations of one family group has not been previously reported. The fact that such was found in a mother, her daughter, and her granddaughter seems of particular interest and suggests that the genetic disturbance giving rise to the familial disease can be manifest at any age. The youngest patient in this family showed involvement clinically at four months of age, the oldest at 39 years of age. The first descriptions of the Hamman-Rich syndrome concerned primarily the older age group; more recently, there have been reports of the occurrence of the disease in children and even in infants.\textsuperscript{8-10} Scadding\textsuperscript{11} suggested that the "acuteness of the disease and the rate at which it progresses tend to vary inversely with age; the older the patient the more likely is it to be only slowly progressive." It is of interest that one of the living members in the present family was 3\frac{1}{2} years of age when the diagnosis of Hamman-Rich syndrome was confirmed by lung biopsy. With treatment comprising low maintenance doses of steroids she is clinically asymptomatic at the present time, some four years after the onset of symptoms. This family member probably represents one of the youngest living patients with pathologically proved Hamman-Rich syndrome. This patient's mother, also with histologically proved Hamman-Rich syndrome, is clinically well at the present time nine years after diagnosis. She, also, is receiving low doses of steroids.

The coexistence of carcinoma of the lung in two brothers with familial Hamman-Rich syndrome has not been previously reported. There have been several reports of isolated cases in both the familial and the nonfamilial forms of the disease and its coexistence with lung carcinoma.\textsuperscript{6,12,13} It is believed by some clinicians that that finding is coincidental, notably because it has been found in an older age group of patients, and especially in long-standing
smokers. Both brothers in our series had smoked moderately for a number of years before the onset of symptoms.

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REFERENCES

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MEDICINE IN ANCIENT INDIA

The creative period (600 B.C. to 200 A.D.) of Indian Medicine, also referred to as the rational period or the samhita period, is the period of medical schools and scientific teaching in India. During these glorious years of medical history, one witnesses the publication of various monographs and texts-books of medicine and surgery, the establishment and growth of famous teaching centers in Taxila and Benares, and a shift of emphasis in medical thinking from the supernatural and magical to the scientific and rational. During the creative period of medicine, medical literature began with the so-called tantras (or texts) and kalpas (or monographs on special subjects). Of the former, the best known are the Salyatantra (a treatise on major surgery) by Susruta, the Rasayanatantra and the Vajikarana-tantra. Several kalpas and monographs on pharmacologic and pharmacopeal subjects were also in existence. It is claimed by one reliable source, that during the days of Gautama Buddha (568–488 B.C.), there flourished in India two great centers of learning, with widely renowned teachers of medicine and surgery. The two centers of seats of learning were Taxila or Taksa-sila in the West with Atreya as the professor of medicine, and Benares or Kasi in the East with Susruta as teacher of surgery and medicine.


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