MYELOFIBROSIS ASSOCIATED WITH TUBERCULOSIS
A REPORT OF FOUR CASES

By Howard W. Crail, M.D., Howard L. Alt, M.D.,
and Walter H. Nadler, M.D.

INTRODUCTION AND REVIEW OF THE LITERATURE

MYELOFIBROSIS is a disease in which the normal blood-forming elements of the bone marrow are replaced by fibrous tissue with compensatory extramedullary hemopoiesis arising in other organs of the reticulo-endothelial system. Clinically, it is characterized by pains in the long bones, back or abdomen, progressive weakness, pallor and subsequent loss of weight. The spleen, liver and sometimes the lymph nodes become enlarged and a refractory anemia of the myelophthisic type develops. Immature leukocytes with or without an increase in total count and frequently the platelet count is either decreased or increased. Bone marrow studies show hypoplasia, usually an increase in the megakaryocytes and eventually, fibrosis. The onset of the disease is insidious and it may last from a few months to years, depending upon the degree of compensation, but the eventual outcome is fatal.

Myelofibrosis was first described by Heuck in 1879, and since that time approximately 100 cases have been reported in the literature under a great variety of titles; the most common of these are "leuco-erythroblastic anemia," "chronic non-leukemic myelosis," and "myelofibrosis associated with a leukemoid blood picture." The name "myelofibrosis" was first applied to this disease in 1937 by Mettier and Rusk. In 1944, Erf and Herbut contributed materially to this subject by their extensive review of the literature and classification of myelofibrosis as either a primary disease or a disease secondary to such conditions as benzene or fluorine poisoning, irradiation and malignant extension. No mention is made of the possible etiologic role of tuberculosis, although such a relationship had been previously suggested. Among 91 cases of myelofibrosis reported in the literature, there were 7 cases with definite evidence of active tuberculosis. A summary of the findings in the 7 cases is recorded in table 1. The first American to report a case of myelofibrosis was Donhauser (case A) in 1908. His case was found to have an active tuberculosis involving the mesenteric lymph nodes and he proposed a toxic etiology for the primary marrow disease. One of the 5 cases reported by Dyke (case B) in 1924 had miliary tuberculosis; the remaining 4 had other bacterial diseases with bone marrow involvement, and he suggested a disseminated bacteremia as an etiologic factor in this disease. Krasso and Nothnagel (case C) in 1925 found atypical tuberculous lesions in their case which they believed were caused by avian tubercu-

From the Department of Medicine, Northwestern University Medical School, Chicago, Ill.
Aided by a grant from Armour and Company.
H. W. CRAIL, H. L. ALT, AND W. H. NADLER

losis. Emile-Weil, Chevallier and See⁹ (case D) in 1933 proposed the possibility of a tuberculous etiology for this disease, and in 1935 Hugonot and Sohier¹⁰ reported a case (case E) of myelofibrosis associated with tuberculosis and agreed with this etiologic relationship. Stone and Woodman¹¹ (case F) in 1938 reported a case of myelofibrosis with tuberculosis. They point out the frequency in which tuberculous lesions are found in diseases of the reticulo-endothelial system. Carpenter and Flory¹² in 1941 concluded that the tuberculosis in their case (case G) was a coincidental terminal disease.

The purpose of this paper is to review in detail the clinical picture and autopsy findings of 4 cases of myelofibrosis associated with generalized tuberculosis and to discuss the pathogenesis, diagnosis and treatment of this syndrome. We have observed 5 cases with idiopathic myelofibrosis which will not be reviewed in detail in this communication but serve for general comparison with the tuberculous group.

**Table 1.—Summary of Cases from the Literature of Myelofibrosis Associated with Tuberculosis**

| Case | Age, Sex | Weight loss | Fever | Splenomegaly | Hepatomegaly | Lymphadenopathy | Anemia | Leukemia reaction | Thrombocytopenia | Duration of illness | Tuber- | Fibrosis of other organs |
|------|----------|-------------|-------|--------------|--------------|----------------|--------|-------------------|-----------------|-------------------|culosis | organs |
| A    | M, 38    | +++        | +++   | ++           | -            | +              | +      | ?                 | ?               | 4                 | -     | +     |
| C    | M, 43    | +++        | +++   | ++           | +            | +              | +      | ?                 | ?               | 24                | -     | +     |
| E    | M, 64    | +++        | +++   | ++           | ++           | +              | +      | ?                 | 26              | -                 | +     | +     |
| G    | M, 33    | +++        | +     | +            | +            | +              | +      | +++               | 40              | -                 | +     | +     |

? = not recorded.

**Report of Cases of Myelofibrosis Associated with Tuberculosis**

**Case I**

C. B., a 39 year old housewife, was admitted to the hospital June 7, 1941, complaining of pallor, weakness, dizziness, a skin rash and fever.

*Family history:* Irrelevant.

*Past history:* Amenorrhea had been present for nine years. She had pneumonia at 36 years of age and again at 38. She was occasionally mildly jaundiced and bruised very easily during the last few years.

*Present illness:* The pallor, weakness, and dizziness had been present for the previous thirteen years accompanying episodes of unexplained anemia. These episodes recurred with increasing frequency and persisted during the previous eighteen months. There was no bleeding from any of the orifices. She failed

*Only contributory clinical and pathologic findings are described.*
1428

MYELOFIBROSIS ASSOCIATED WITH TUBERCULOSIS

to respond to either liver or iron and received whole blood several times. Following a splenectomy and subsequent phlebitis, she had a daily afternoon temperature elevation, occasionally reaching 101 F. The skin rash started on the left leg three weeks before hospital entry; it then extended to the right leg and both arms. The rash was maculopapular at first, later indurated and finally tender.

Physical examination: The pulse was 110 per minute; blood pressure, 116/76; respirations, 24 per minute; temperature, 101.6 F.; and weight, 99 pounds. She appeared somewhat emaciated and chronically ill. Over the hands, elbows, and knees the skin had a dusky appearance. An eruption over the legs and arms varied from small, red maculopapules to reddish purple, eczematoid, tender, indurated, nodular lesions distributed mainly over the extensor surfaces. The sclerae were white and the mucous membranes pale. There were a few small cervical, axillary and inguinal lymph nodes palpable. Occasional coarse rale were heard over the base of the left lung posteriorly, with slight dullness in this same region upon per-

<table>
<thead>
<tr>
<th>Case</th>
<th>Date</th>
<th>Erythrocytes, million per cu. mm.</th>
<th>Hemoglobin (Gm./100 c.c.)</th>
<th>Leukocytes, (per cu. mm.)</th>
<th>Thrombocytes (per cu. mm.)</th>
<th>Myelocytes</th>
<th>Promyelocytes</th>
<th>Myelocytes</th>
<th>Bands</th>
<th>Spermatozoa</th>
<th>Eosinophils</th>
<th>Basophils</th>
<th>Metamyelocytes</th>
<th>Monocytes</th>
<th>Broken cells</th>
<th>Normal/100 WBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. B.</td>
<td>1/31/40</td>
<td>5.38</td>
<td>6.0</td>
<td>3,400</td>
<td></td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4/23/40</td>
<td>5.39</td>
<td>6.0</td>
<td>9,000</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6/7/41</td>
<td>2.14</td>
<td>7.0</td>
<td>6,050</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W. M.</td>
<td>11/10/43</td>
<td>5.40</td>
<td>8.5</td>
<td>8,400</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12/10/43</td>
<td>5.00</td>
<td>5.8</td>
<td>11,800</td>
<td>254,320</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/13/44</td>
<td>2.76</td>
<td>7.5</td>
<td>3,500</td>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W. D.</td>
<td>1/1/46</td>
<td>4.42</td>
<td>13.1</td>
<td>2,850</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/1/46</td>
<td>4.70</td>
<td>14.0</td>
<td>4,700</td>
<td>147,000</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5/16/46</td>
<td>3.93</td>
<td>10.5</td>
<td>1,700</td>
<td>133,350</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6/1/46</td>
<td>3.50</td>
<td>9.5</td>
<td>2,100</td>
<td>208,320</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. B.</td>
<td>1/19/44</td>
<td>3.60</td>
<td>8.1</td>
<td>17,600</td>
<td></td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6/30/45</td>
<td>1.90</td>
<td>4.33</td>
<td>60,000</td>
<td>3,000,000</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8/13/45</td>
<td>3.50</td>
<td>8.7</td>
<td>11,150</td>
<td>700,000</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion. There was a tachycardia and a coarse systolic murmur audible over the entire precordial region. The abdomen was soft and not tender; the liver was not palpable.

Laboratory examination: The urinalysis showed no sugar and a trace of albumin. The sediment contained 3-5 erythrocytes per high power field and on one occasion hyaline and granular casts. The Wassermann and Kahn tests were negative. A fractional gastric analysis showed 48 units of free HCl and 70 units of total acid. The BMR was plus 6 per cent. The Van den Berg test was 0.8 mg. per cent and the icterus index was 8 units. Other blood chemistry studies were normal. A total of ten stool examinations for blood were found negative. Agglutination tests for typhoid, paratyphoid, dysentery and brucella were negative. Sputum cultures revealed no acid-fast bacilli but many gram-positive diplococci. Blood cultures and fecal cultures were negative. X-ray examination of the chest was normal on 6/7/41, but one week later there was evidence of fluid at the base of the left lung. Hematologic studies (table 2) showed a pronounced normocytic, normochromic anemia with numerous nucleated erythrocytes and a few immature granulocytes in the peripheral blood. There was a moderate variation in the size and shape of the erythrocytes. The reticulocyte count was 1.3 per cent and the platelets were reduced to the lower limit of normal. The bone marrow (table 3) was hypoplastic and revealed a maturation arrest of the erythrocytic series and an increase in the number of megakaryocytes. The red cell fragility test
was normal on two occasions. The spleen, surgically removed on 8/28/40, was reported essentially normal. A skin biopsy of a nodule from the left arm on 6/10/41 was diagnosed as possible erythema nodosa. Acid-fast organisms were found in sections made from paraffin blocks containing sediment from pleural fluid. A guinea pig inoculated with pleural fluid was found to have epitheloid tubercles of the lungs, liver and spleen.

Clinical course: The patient had a very stormy course throughout her hospital stay with spiking daily afternoon temperature elevations, sometimes to 106 F., preceded by chills. She became dyspeptic, irrational and very restless and expired on 7/3/41.

Necropsy:
Thoracic cavity: The left pleural cavity contained 1000 cc. of bright red fluid. Both lung bases were adherent to the diaphragm and mediastinum by firm fibrous adhesions. The pleural surfaces were studded with pin-head sized grey, raised tubercles. Microscopically, the alveoli in the left lung base were filled with a fibrinous exudate. The tiny tubercles showed a central necrosis with almost no surrounding cellular reaction.

<table>
<thead>
<tr>
<th>Case</th>
<th>Date</th>
<th>Total count</th>
<th>Myeloblasts</th>
<th>Promyelocytes</th>
<th>Normoblasts</th>
<th>Metamyelocytes</th>
<th>Blasts</th>
<th>Segmented</th>
<th>Eosinophils</th>
<th>Basophils</th>
<th>Lymphocytes</th>
<th>Malignant</th>
<th>Red cells</th>
<th>Normal</th>
<th>Megakaryocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. B.</td>
<td>3/5/40</td>
<td>11,500</td>
<td>8</td>
<td>2</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>55</td>
<td>Inc.</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td>W. M.</td>
<td>12/10/43</td>
<td>12,500</td>
<td>31</td>
<td>2</td>
<td>12</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>14</td>
<td>Inc.</td>
<td>4/1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/13/44</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11/1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W. D.</td>
<td>2/1/46</td>
<td>176,000</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>28</td>
<td>33</td>
<td>Inc.</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5/16/46</td>
<td>45,000</td>
<td>7</td>
<td>8</td>
<td>13</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>18</td>
<td>Inc.</td>
<td>2.4/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. B.</td>
<td>7/9/45</td>
<td>6,100</td>
<td>16</td>
<td>15</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>9</td>
<td>4</td>
<td>10</td>
<td>3</td>
<td>33</td>
<td>Inc.</td>
<td>2/1</td>
<td></td>
</tr>
</tbody>
</table>

Heart: The greater vessels and epicardium were covered with the same tiny tubercles seen on the lungs. Histologic study showed an occasional necrotic focus in the myocardium.

Liver: The liver was enlarged and an occasional tubercle was seen on the capsule and cut surface. The sections showed thickening of the capsule with increased intercellular connective tissue. Numerous tiny areas of necrosis were seen in the parenchyma and each was surrounded by a zone of immature blood cells. A few small foci of extramedullary hemopoiesis containing occasional megakaryocytes were seen.

Pancreas: Grossly, the pancreas appeared normal but microscopic studies revealed pronounced interacinar fibrosis and numerous small necrotic tubercles, a few of which were surrounded by immature blood cells.

Lymph nodes: The hilar, retroperitoneal and abdominal lymph nodes were all grossly enlarged. Many showed discrete pin-head sized, grey tubercles on their cut surfaces. Microscopically the normal architecture of the glands was completely destroyed and replaced by proliferating granulomatous, fibrous tissue occasionally surrounding small foci of extramedullary hemopoiesis. A few hyperchromatic, multi-nucleated cells resembling megakaryocytes were seen. Many of the sections showed small foci of tuberculous necrosis and a rare Langhan giant cell.

Bone marrow: The marrow from the sternum and vertebrae appeared dark red and dry. Histologically, the sections showed a fibrous tissue replacement of the marrow cavity, leaving small islands of hemopoietic tissue and no fat. The megakaryocytes were increased in number.
MYELOFIBROSIS ASSOCIATED WITH TUBERCULOSIS

Bacteriologic examination: All the sections were stained by the Ziehl-Neelson technic and the necrotic foci found filled with acid-fast organisms.

Pathologic diagnosis: Generalized miliary tuberculosis; extramedullary hemopoiesis in the liver and lymph nodes; fibrosis of the liver, pancreas and bone marrow.

CASE 2

W. M., a 50 year old lawyer, was first admitted to the hospital November 10, 1943, complaining of anginal pain, intermittent claudication and pallor.

Family history and past history: Irrelevant.

Present illness: For two years the patient had noted viselike pain in his chest upon exertion. During the last thirteen months, shortness of breath came with the chest pain; both were relieved by rest. Simultaneously, he developed cramplike pains in the calf of his left leg, brought on by walking. An electrocardiogram in February 1943 showed no significant change. These symptoms became progressively worse and he subsequently noticed that he was becoming fatigued and pale.

Physical examination: The temperature was 99.6 F.; blood pressure, 120/60; pulse, 96 per minute; respiration, 18 per minute; and weight, 178 pounds. The lymph glands were normal. There was no cardiac abnormality. The lungs were clear except for inspiratory wheezes over both apices. The abdomen was soft, and the liver, spleen and kidneys were not felt.

Laboratory examination: The urine was repeatedly negative. The Wassermann and Kahn tests were negative. The total serum proteins, albumin/globulin ratio and icterus index were all normal. X-ray examination of the heart showed the lung fields to be clear and the heart shadow less than 10 per cent enlarged. Roentgenologic examination of the gall bladder and digestive tract revealed no pathology. The electrocardiogram showed only a left axis deviation. The BMR was minus 7.5 per cent. Repeated blood cultures, stool cultures for enteric pathogens, agglutination tests for typhoid, paratyphoid, and a brucellergen skin test were all negative. The blood studies (table 2) revealed a moderate normochromic, normocytic anemia with immature leukocytes and normoblasts in the peripheral blood. The reticulocyte count was normal and the platelets were slightly decreased in number. The sternal marrow (table 3) showed an initial hyperplasia with increased erythropoietic activity followed by a marked hypoplasia with an increase in megakaryocytes.

Clinical course: Seven days after entry into the hospital the patient was seized with excruciating precordial and epigastric pain with tenderness over the gall bladder, all of which disappeared two days later. During this stay, he had a slight fever for the first two days, again on the seventh day and again on the tenth, eleventh, and twelfth days. He was discharged November 27. He was next seen December 14 as an outpatient complaining of increased weakness and had a decline in the erythrocyte count. He was readmitted to the hospital December 19 for two days and given 400 cc. of whole blood. He continued under ambulatory care without response and was readmitted to the hospital on February 2, 1944. There was no fever at this time. A slight systolic murmur was heard over the apex of the heart. The lungs were normal. The liver was normal in size and the spleen was felt for the first time, extending two fingerbreadths below the left costal margin. There was a slight generalized lymphadenopathy. He was given two transfusions of 500 cc. of whole blood each and discharged after twenty-four hours. On February 17, while the patient was ambulatory, the spleen was found to be the same size. The liver was now found three fingerbreadths below the right costal margin and the anemia continued to progress.

His last hospital entry was February 23. In addition to previous complaints, he had painful defecation and gross blood in the stools for ten days. His temperature on admission was 100.6 F.; pulse, 68 per minute; respirations, 10 per minute; and weight, 164 pounds (a loss of 14 pounds since his first admission). The liver and spleen were palpable as previously noted. A proctoscopic examination was done under caudal anesthesia and a diagnosis of ulcerative proctitis was made. Four days later, an indurated region just outside the sphincter ruptured and spontaneously drained mucopurulent material. He was under caudal anesthesia and a diagnosis of ulcerative proctitis was made. Four days later, an indurated region just outside the sphincter ruptured and spontaneously drained mucopurulent material. He was readmitted to the hospital December 29, 1943, complaining of increased weakness and pallor.

Physical examination: The temperature was 100.6 F.; blood pressure, 120/60; pulse, 96 per minute; respirations, 18 per minute; and weight, 178 pounds. The lymph glands were normal. There was no cardiac abnormality. The lungs were clear except for inspiratory wheezes over both apices. The abdomen was soft, and the liver, spleen and kidneys were not felt.

Laboratory examination: The urine was repeatedly negative. The Wassermann and Kahn tests were negative. The total serum proteins, albumin/globulin ratio and icterus index were all normal. X-ray examination of the heart showed the lung fields to be clear and the heart shadow less than 10 per cent enlarged. Roentgenologic examination of the gall bladder and digestive tract revealed no pathology. The electrocardiogram showed only a left axis deviation. The BMR was minus 7.5 per cent. Repeated blood cultures, stool cultures for enteric pathogens, agglutination tests for typhoid, paratyphoid, and a brucellergen skin test were all negative. The blood studies (table 2) revealed a moderate normochromic, normocytic anemia with immature leukocytes and normoblasts in the peripheral blood. The reticulocyte count was normal and the platelets were slightly decreased in number. The sternal marrow (table 3) showed an initial hyperplasia with increased erythropoietic activity followed by a marked hypoplasia with an increase in megakaryocytes.

Clinical course: Seven days after entry into the hospital the patient was seized with excruciating precordial and epigastric pain with tenderness over the gall bladder, all of which disappeared two days later. During this stay, he had a slight fever for the first two days, again on the seventh day and again on the tenth, eleventh, and twelfth days. He was discharged November 27. He was next seen December 14 as an outpatient complaining of increased weakness and had a decline in the erythrocyte count. He was readmitted to the hospital December 19 for two days and given 400 cc. of whole blood. He continued under ambulatory care without response and was readmitted to the hospital on February 2, 1944. There was no fever at this time. A slight systolic murmur was heard over the apex of the heart. The lungs were normal. The liver was normal in size and the spleen was felt for the first time, extending two fingerbreadths below the left costal margin. There was a slight generalized lymphadenopathy. He was given two transfusions of 500 cc. of whole blood each and discharged after twenty-four hours. On February 17, while the patient was ambulatory, the spleen was found to be the same size. The liver was now found three fingerbreadths below the right costal margin and the anemia continued to progress.

His last hospital entry was February 23. In addition to previous complaints, he had painful defecation and gross blood in the stools for ten days. His temperature on admission was 100.6 F.; pulse, 68 per minute; respirations, 10 per minute; and weight, 164 pounds (a loss of 14 pounds since his first admission). The liver and spleen were palpable as previously noted. A proctoscopic examination was done under caudal anesthesia and a diagnosis of ulcerative proctitis was made. Four days later, an indurated region just outside the sphincter ruptured and spontaneously drained mucopurulent material. He was given numerous transfusions of whole blood for profound anemia but failed to maintain a satisfactory hemoglobin and red cell count level. The sternal puncture (table 3) on February 18 showed a pronounced hypoplasia of the marrow with a marked increase in the number of megakaryocytes. The temperature rose daily to over 100 F., and after the seventeenth hospital day to over 104.5 F. The highest temperature rise (105.2 F.) was recorded on the thirty-eighth hospital day, and the patient expired two days later, April 1, 1944.

From www.bloodjournal.org by guest on October 23, 2017. For personal use only.
Necropsy:

Lungs: Neither gross nor microscopic miliary nodules were described. The sections showed emphysema and focal hemorrhages surrounded by a few hyperchromatic multi-nucleated cells. Pleural thickening was also seen.

Mediastinum: A firm nodular mass measuring 6 by 3 by 1 cm. was found in the right mediastinum lying just behind the superior vena cava, superior to the root of the right lung and lateral to the arch of the aorta. This mass cut with ease, revealing a bulging, pinkish surface. Several grey-green areas 1-2 cm. in diameter were seen on the cut surface and several small cystic structures contained puslike material. Microscopic studies of this mass revealed confluent lymph nodes almost completely replaced by granulomatous tissue. There were central zones of caseation and necrosis surrounded with varying numbers of epitheloid cells and lymphocytes, all of which were encased in a fibrous tissue structure. A few multinucleated cells similar to those described in the lung were seen. No Langhan giant cells were present. Several large nerve bundles coursed through the dense fibrous tissue.

Abdominal cavity: Firm fibrous adhesions were found about the gall bladder and the recto-sigmoid portion of the colon.

Liver: The liver was enlarged (1500 Gm.) and small yellowish nodules were seen beneath the capsule and on the cut surface. Histologic examination showed the sinusoids distended and filled with blood. A fibrous tissue and lymphocytic infiltration was noted about the portal triad. Small caseding foci were seen surrounded by a few epitheloid cells, lymphocytes, and plasma cells. An occasional megakaryocyte was seen. Pronounced fibrous tissue infiltration and hyalinization in the regions adjacent to these atypical tubercles were constant findings.

Spleen: The spleen weighed 550 Gm. and several small nodules were palpated beneath the capsule. Microscopically, small foci of caseous necrosis were surrounded by a few round cells. In one of these, a single Langhan-type giant cell was seen. The sinuses were distended and filled with blood and pigment. Small lymph follicles remained. Throughout the pulp, numerous large cells with large oval or indented, hyperchromatic nuclei were found. Many resembled megakaryocytes. Hemopoiesis was not pronounced but the number of immature myeloid cells indicated the presence of this function. The capsule was thickened.

Adrenals: The gross features of this organ were not unusual but microscopically both the medullary and cortical layers showed focal necrosis and rather extensive dense fibrous tissue replacement and hyalinization.

Gastro-intestinal tract: The only finding of significance in the gastro-intestinal tract was a nodular mass 1 cm. above the pectinate line in the rectum. The mass was produced by a thickening of the wall of the gut but the mucosa appeared intact over the area. Microscopically, the wall was found to be almost completely destroyed by a necrotic process which had begun to include the mucosa as well. Numerous inflammatory cells were seen at the border of this lesion. Many bacteria were seen but no acid-fast organisms were demonstrated.

Lymph nodes: The lymph glands throughout the body were enlarged and firm. The histologic study revealed a complete destruction of the normal architecture. The capsule was thickened and the stroma increased. The sinuses were distended and contained cells. Extramedullary hemopoiesis was seen and a few megakaryocytes were present. Lymphocytes in various stages of development were noted.

Bone marrow: Specimens were taken from the sternum, ribs, and vertebrae and all had a dry appearance. The histologic changes included complete alteration of the normal architecture. The marrow was hyperemic and there was a great increase in the number of megakaryocytes. Eosinophilic debris and young fibrous tissue were replacing the normal marrow elements and isolated islands or pockets of myeloid activity were seen. One of the rib sections showed an area of necrosis and increase in the number of small lymphocytes.

Bacteriologic examination: All the sections were stained by the Ziehl-Neelson technic and the caseous foci found filled with acid-fast organisms.

Pathologic diagnosis: Caseous tuberculoma of the mediastinum, miliary tuberculosis involving the liver, spleen and bone marrow; extramedullary hemopoiesis in the spleen and lymph nodes; fibrosis of the bone marrow, pleura, liver, spleen and lymph nodes; phleghmonous proctitis.
MYELOFIBROSIS ASSOCIATED WITH TUBERCULOSIS

CASE 3

W. D., a 29 year old male, entered the hospital on January 2, 1946, complaining of weakness, backache, intermittent chills and fever with associated nausea and vomiting.

Family history: Irrelevant.

Past history: Between 1936 and 1937 the patient was employed by General Electric X-ray Corporation and was exposed to considerable x-ray radiation and phenol. His leukocyte count at that time was 6,750. In December, 1943, he had a soft mass 6 cm. in diameter in the lower left side of the neck with two lymph nodes palpable below this. Aspiration of the mass was unsuccessful but it disappeared after five x-ray treatments with a total of 750 r. He served a tour of military duty in the United States without illness and was discharged in March, 1945.

Present illness: His weakness, backache, and a temperature of 99 F. were first noticed in April, nine months before admission. In July, the patient had chills and fever rising to 103 F. which lasted for about an hour and recurred every four to eight hours for eight days. He remained symptom-free for three weeks when he had a similar attack also lasting eight days. In early October, he had a third bout. For three months he remained free from chills and fever but was weak. On December 31, he had still another attack. On each occasion, nausea and vomiting appeared at the height of the febrile episodes. During this entire period, the patient had a weight loss of 25 pounds.

Physical examination: The temperature was 100.4 F.; pulse, 90 per minute; blood pressure, 110/70; and weight, 128 pounds. The heart and lungs were normal. The lymph glands and spleen were not palpable. The liver was felt one fingerbreadth below the right costal margin.

Laboratory examination: Previous to entry, studies included tuberculin and brucellergen skin tests, agglutination studies for the enteric pathogens and brucella, the Davidsohn heterophile agglutination test, x-ray of the lumbosacral spine, retrograde and intravenous urograms, and fluoroscopic examination of the chest and gastro-intestinal tract. All of these were negative with the exception of a small gastric ulcer demonstrated by fluoroscopy. Proctoscopic and cystoscopic examinations were negative. During hospitalization, the urine had a specific gravity of 1.010, albumin one plus, sugar negative, 10-40 erythrocytes and occasional leukocytes per high power field. Direct and bacterial examinations of the stools were negative. A guinea pig inoculated with urine did not reveal any evidence of tuberculosis. The Wassermann and Kahn tests were negative. The cephalin flocculation test was two plus in twenty-four hours and four plus in forty-eight hours. The chest x-rays repeatedly showed a few clean-cut calcified deposits on the left side radiating from the lung root outward. The last film was made about two months before death. The tuberculin skin test was again negative and the electrocardiogram was normal. The prothrombin time was 56.4 per cent of normal, the bromsulfalein showed 12 per cent retention of dye, total protein 6.18 to 3.88 Gm., albumin 3.94 to 2.15 Gm., globulin 2.34 to 1.73 Gm., icterus index 5 units and blood urea nitrogen 12.7 mg. The peripheral blood studies (table 2) showed a slowly progressive normocytic, normochromic anemia, and leukopenia. A few normoblasts and immature leukocytes were seen. The reticulocyte count was 1.8 per cent and the platelets were normal. Aspirated sternal marrow (table 3) showed hyperplasia at first, followed later by a distinct hypoplasia with an increase in megakaryocytes. No malarial parasites were found. Biopsy studies of the sternal bone marrow (fig. 2) in July revealed complete alteration of the normal architecture. The myeloid and erythroid elements were greatly reduced and widely scattered. No fatty tissue remained. These normal cellular elements were separated by a moderate amount of fibrous tissue and eosinophilic debris. Biopsy material from a retroperitoneal mass at the same time was composed of large epitheloid cells with pale vesicular cytoplasm. Scattered throughout these cells was a fine network of fibrous connective tissue with new-growing fibroblasts and diffuse, small, round-cell infiltrations more dense in some areas than others. A few polymorphonuclear cells and an occasional large multi-nucleated cell with characteristics of a Dorothy Reed cell were seen. The diagnosis was an inflammatory process with many characteristics of Hodgkin's disease. Sections of the liver were essentially normal.

Clinical course: The patient was discharged January 13 on his fourth afebrile day, only to be readmitted to the hospital January 23 with a recurrence of the backache and weakness followed by chills, fever, nausea and vomiting. Fine, moist, inspiratory rales were heard throughout the chest and a soft systolic murmur was audible over the tricuspid area. The liver was four fingerbreadths below the right costal margin and the spleen could be palpated subcostally. There was no adenopathy. His fever subsided March 7 and he was discharged ten days later. On March 26 the patient was readmitted with another attack
but this time with a severe cough and pain and tenderness in the right flank. The liver and spleen were palpable as before and there was some question of a palpable mass in the region of the right kidney. The fever reached 103 F. on the second day but subsided rapidly and the patient was discharged April 2. Twenty days later the patient made his last entry into the hospital. He weighed 123 pounds. The liver was palpable four fingerbreadths below the right costal margin and was tender. The spleen was again palpable. During this admission, biopsies were taken from the sternal marrow (see Laboratory Examinations). On July 3 a laparatomy was done and enlarged retroperitoneal tumor masses grossly resembling Hodgkin's disease or lymphosarcoma were seen. Biopsies were taken of these and also of the liver (see Laboratory Examinations). Eight x-ray treatments were given over the abdominal mass with no improvement. His temperature ran a very septic course, going to 104 F., and showed daily and almost hourly fluctuations. He continued to lose weight and became progressively worse and on August 19, eight days before death, his peripheral blood picture revealed marked pancytopenia. His spleen and liver increased in size and edema became pronounced. Treatment throughout his illness included sulfonamides, penicillin, oral streptomycin (for seven days), atabrine, quinine, plasmoquin, emetine, salicylates, the x-ray treatment mentioned above, and four blood transfusions. None of these had any effect on the course of the disease.

Necropsy:

Thoracic cavity: Both thoracic cavities contained about 1100 cc. of a clear yellow fluid.

Lungs: The lungs were adherent to the parietal pleura by a few firm fibrous adhesions and their surfaces were covered with greyish-white raised nodules ranging from pin-head size to 0.2 cm. in diameter. The cut surfaces were wet and the same nodules were seen. The microscopic appearance of the lung was that of a multitude of tiny anemic infarcts in all the sections. The centers of these foci were caseous but there was almost a complete absence of the peripheral cellular reaction so common in tuberculosis. No Langhan giant cells were observed. Many of the surrounding alveoli contained cellular debris and fibrin resembling the consolidation of pneumonia. The pleura was thickened.

Abdominal cavity: The abdominal cavity was filled with clear yellowish fluid. There was a large, nodular, perivertebral, retroperitoneal mass in the epigastric region.

Liver: The liver was enlarged (1650 Gm.). The surface was speckled with pin-head sized, subcapsular, greyish-white nodules, a few larger yellowish nodules and firm white irregular patches (fig.
The cut surface was similar except that the firm white areas were very tough and extended deeply into the parenchyma mainly about the larger vessels. Histologic examination revealed a thickened capsule and distention of the sinuses with blood. Scattered throughout the parenchyma were a multitude of tiny tubercles. Many of these contained one or two typical Langhan giant cells. A few were surrounded by the typical cellular reaction seen in tuberculosis. The large white plaques described at autopsy were composed of organized fibrous and hyalinized connective tissue and at the borders the connective tissue extended into the parenchyma, leaving islands of liver cells behind. Foci of lymphocytes were scattered throughout this fibrous tissue. An occasional megakaryocyte and a few small foci of extramedullary hemopoiesis were seen.

Spleen: The spleen was enlarged (700 Gm.) and a small accessory spleen was found. Numerous small greyish-white nodules were seen beneath the capsule and on the cut surface. Firm, white, irregular plaques on the cut surface were similar to those seen in the liver. The sections showed a thickened fibrous capsule. The sinusoids were distended with blood. The lymph follicles were completely dispersed and only an occasional small aggregate of lymphocytes could be found about a vessel. Large areas of fibrosis were seen but the most unusual finding was the widespread seeding of small tubercles as seen in the liver. There was little surrounding cellular reaction though occasional Langhan giant cells were found in the tubercles. Immature myeloid and erythroid cells and a moderate number of large cells with large, irregular, dense nuclei resembling megakaryocytes could be seen diffusely scattered throughout the sections.

Pancreas (fig. 3): Microscopic examination revealed an increased amount of connective tissue and several atypical tubercles similar to those previously described.

Adrenals: The microscopic section showed an increase in fibrous tissue and numerous small atypical tubercles.

Retroperitoneal lymph nodes: The retroperitoneal mass was an irregular, enlarged, adherent group of lymph nodes which when sectioned showed occasional small yellowish foci. Histologic study showed a complete obliteration of the normal architecture with a greatly increased stroma. Much chronic granulomatous tissue was present with a few scattered lymphocytes, an occasional multinuclear Sternberg-Reed type of cell and atypical tubercles. Nerve bundles were seen encased in the fibrous tissue.

Bone marrow (fig. 4): Bone marrow taken from the sternum, ribs and vertebrae showed almost complete obliteration of the marrow cavities by dense fibrous tissue. Only a very few normal myeloid and erythroid foci could be seen. Megakaryocytes were prominent and an occasional atypical tubercle containing acid-fast organisms was found.

Bacteriologic examination: All the sections were stained by the Ziehl-Neelson technic; the caseous foci everywhere and the connective tissue of the liver, spleen and lymph nodes were filled with acid-fast organisms. These acid-fast organisms were cultured on glycerin-egg media, inoculated into a series of laboratory animals and tested as to streptomycin sensitivity. The organism was proven to be a human type of M. tuberculosis, possibly of low virulence and sensitive to streptomycin.

Pathologic diagnosis: Diffuse fibrosis of the liver, spleen, lymph nodes, adrenals and bone marrow, with interacinar fibrosis of the pancreas; extramedullary hemopoiesis in the spleen and liver; generalized miliary tuberculosis.

CASE 4

M. B., a 36 year old housewife entered the hospital June 23, 1945, complaining of weakness, night sweats, headache, chest pain and a nonproductive cough.

Family history: A sister died from tuberculosis.

Past history: Irrelevant.

Present illness: The patient was apparently well and healthy until after the normal delivery of a baby October 11, 1944. Two days postpartum an enlarged spleen was found and subsequently a diagnosis of Banti's disease was made. A splenectomy was done November 14, 1944. The pathologic report on the spleen suggested Hodgkin's disease. Following operation the patient gained 35 pounds and resumed her normal duties. In May 1945, her menstrual period lasted twelve days and she passed numerous large clots. At this time she caught cold and her temperature rose to 103 F. for a few days. She continued
Fig. 2 (upper). Photomicrograph of a sternal marrow biopsy from W. D. showing infiltrating fibroblastic tissue cells with dispersion of the blood-forming element.

Fig. 3 (center). Photomicrograph of the pancreas from W. D. showing interacinar fibrosis.

Fig. 4 (lower). Photomicrograph of the bone marrow from W. D. at autopsy showing extensive fibrosis with little remaining hemopoietic tissue.

1435
to feel ill and began to lose weight. Weakness then became her major complaint and was soon followed by night sweats, a persistent headache, pain in the chest and back and an irritating, nonproductive cough.

**Physical examination:** Her temperature was 100.2°F; pulse, 100 per minute; blood pressure, 130/71; and respirations, 24 per minute. A soft systolic murmur was audible over the base of the heart. The lungs were normal. The liver was enlarged, extending approximately five fingerbreadths below the right costal margin. A moderate generalized lymphadenopathy was noted.

**Laboratory examination:** The urine contained a trace of albumin and 7-10 leukocytes per high power field. The Kahn test was negative and blood chemistry studies, including the icterus index, were all normal. The BMR was plus 10 per cent and the electrocardiogram was normal. X-ray examinations of the chest were repeatedly normal until a few days before death, when a diffuse flocculant increase in density was seen involving both lung fields. This was most pronounced at the bases and suggested an acute pulmonary edema. The peripheral blood studies (table 1) showed a predominance of young myeloid cells with a great increase in the number of megakaryocytes. The pathologic sections from the spleen were re-examined and reported suggestive of myelogenous leukemia.

**Clinical course:** The treatment consisted of repeated blood transfusions. The patient grew progressively weaker and continued to lose weight. Her temperature was high, the peaks ranging between 104°F and 105°F and there was delirium. In the last week of her life, ascites and jaundice were present. She died September 21, 1945.

**Necropsy:**

**Thoracic cavity:** Both pleural cavities were obliterated by firm adhesions between the visceral and parietal pleurae.

**Lungs:** The pleural and cut surfaces of the lungs were studded with numerous small greyish-white, firm nodules varying in size from 0.1 to 0.5 cm. On microscopic study, tiny areas of focal necrosis were surrounded by a zone of immature blood cells and phagocytes. Foci of extramedullary hemopoiesis and numerous megakaryocytes were seen.

**Abdominal cavity:** Five hundred centimeters of dark, straw-colored fluid were found in the abdominal cavity. The visceral and parietal peritoneum was studded with small greyish-white nodules.

**Liver:** The liver was enlarged (1670 Gm.). The capsule and cut surfaces were covered with small tubercles. Histologic study (fig. 5) showed areas of focal necrosis and infarction surrounded by zones of hemopoiesis. The liver cords were small and surrounded by hyalinized connective tissue which obliterated many of the sinuses. Foci of extramedullary hemopoiesis and megakaryocytes were seen.

**Pancreas:** Microscopically, there was a pronounced periductile, perivascular and periglandular fibrosis.

**Adrenals:** The sections showed fibrous tissue replacement with separation of the cortical and medullary cells and microscopic areas of caseation and foci of extramedullary hemopoiesis. The cortices of the ribs, sternum, and vertebrae were thickened and the trabeculae prominent. The medullary spaces were filled with a dry, fibrous-like tissue. Microscopically, the normal marrow was completely distorted (fig. 6). Relatively few hemopoietic cells remained and these were widely dispersed through the connective tissue filling the marrow spaces. The megakaryocytes appeared increased in number. Necrotic foci were also found.

**Lymph nodes:** The mediastinal, retroperitoneal and perivertebral lymph nodes were enlarged and matted together. Microscopic study of these lymph nodes showed proliferating connective tissue infiltrated with immature blood cells and a few megakaryocytes. Many of the nodes contained focal areas of necrosis.

**Bacteriologic examination:** All of the sections were stained by the Ziehl-Neelson technic and huge numbers of acid-fast organisms were found in the areas of necrosis in all the organs.

**Pathologic diagnosis:** Extramedullary hemopoiesis in the liver, lung, spleen and lymph nodes; extensive fibrosis of the liver, spleen, pancreas, adrenals, lymph nodes and bone marrow; generalized acute, diffuse, miliary tuberculosis.

**Analysis of Cases**

A summary of the clinical, hematologic and pathologic data of the four cases of myelofibrosis with tuberculosis are recorded in tables 2, 3 and 4. We studied W. M., W. D. and M. B. during life and the records of C. B. several years after death. M.
FIG. 5 (upper). Photomicrograph of the liver from M. B. showing miliary tubercle with associated fibrosis and hyalinization.

FIG. 6 (lower). Photomicrograph of the vertebral bone marrow from M. B. at autopsy showing extensive myelofibrosis.

B. has been reported previously but is included to make the present study more complete. The diagnosis of tuberculosis was made antemortem in C. B. and was considered but not established in W. D.

History. The primary complaints of these cases were pain in the long bones, back
or abdomen, fatigue, progressive weakness, pallor and loss of weight. Their ages ranged between 29 and 50, averaging 33 years. The sex distribution was equal. A definite history of a tuberculous contact was obtained in M. B. W. D. gave a history of cervical adenopathy which was suggestive of tuberculosis.

Physical findings: All of the patients showed a daily afternoon fever with occasional spikes to 104 F. During the last few months, the daily elevations frequently went above this mark. W. D. had repeated recurrences of chills and fever, sometimes two or three a day with afebrile remissions lasting eight to twenty days. The spleen in each case was moderately enlarged. Splenectomies were done on C. B. and M. B. early in their illnesses with probable adverse effects. The livers were markedly enlarged, smooth and nontender in three cases. In C. B., the liver was palpable only on deep inspiration. Generalized lymphadenopathy was moderate in all cases. The retroperitoneal lymph nodes were greatly enlarged in W. D. and were palpable through the abdominal wall as a firm, epigastric mass.

Laboratory findings: A refractory anemia was present in all cases. The anemia was profound throughout the illness of W. M. and he required frequent transfusions. In the remaining cases, the anemia was slowly progressive but became terminally pronounced. A leukemoid reaction characterized by the presence of immature leukocytes and normoblasts occurred in each case. Three cases (C. B., W. M. and W. D.) had a progressive leukopenia. On the other hand, M. B. had a leukocyte count above 100,000 and the differential closely resembled an acute myelocytic leukemia. The platelet count paralleled the leukocyte count; it was reduced to the lower limits of normal in three cases and was well above 500,000 in M. B. Giant platelets and megakaryocytes were seen in peripheral blood smears of the latter case. In each case, the reticulocyte count was normal. The sternal marrow aspirations in W. M. and W. D. early revealed a hyperplastic marrow. Later the marrow became hypoplastic and sternal aspirations then resembled the peripheral blood both in total and differential cell counts. The number of megakaryocytes was increased in each case. Single marrow aspirations on the two remaining cases showed hypoplasia with an increase in the megakaryocytes. A bone marrow biopsy was done on only one patient (W. D.). The sections revealed a depletion of the normal hemopoietic tissue and fat with beginning fibroblastic replacement and a marked increase in the megakaryocytes. One patient (W. D.) consistently had a low grade hematuria. Stool examinations for blood were repeatedly negative in all instances. Uniform blood chemistry studies were not carried out on these patients; however, W. D. and M. B. showed evidence of a slightly decreased liver function. The icterus index was normal in each case. Bacteriologic and serologic studies were repeatedly negative in all but C. B., where acid-fast organisms were recovered from fluid aspirated from the chest late in the illness. Unfortunately, tuberculin skin tests were made in only one case (W. D.) and were reported negative. Roentgenologic examinations of the chest revealed evidence of old, healed tuberculosis in each case. Terminally, pleural effusion was found in C. B. and mottling suggestive of edema in M. B. Since miliary tubercles were found in the lungs at autopsy, serial roentgenograms might have been of diagnostic aid late in the disease.

Clinical course: All patients ran a continued down hill course with progressive
weakness, loss of weight and fever ending in death. C. B. and M. B. developed
terminal jaundice. The duration of illness ranged from twelve to eighteen months
with an average of 16.2 months.

Necropsy findings: Generalized, caseating, miliary tuberculosis was found in all of
the organs in these cases. These lesions were small but were found filled with large
numbers of acid-fast organisms. Extramedullary hemopoiesis and an increase in mega-
karyocytes were evident in every instance, most commonly in the spleen, lymph
nodes and liver. The lymph nodes in each case were enlarged and the normal cellular
elements were replaced by proliferating granulomatous tissue. Bone marrow from
the sternum, rib and vertebra in each case was replaced by varying amounts of
connective tissue which was confirmed by special staining.* The most massive
fibrosis was present in W. D. where it had progressed extensively since the time of
biopsy three months before death (figs. 2 and 4). Fibrosis and hyalination of organs
other than the bone marrow, particularly of the liver, (figs. 1 and 5) spleen, pleura,
pancreas (fig. 3) and adrenals were prominent in all of our cases.

Comparison of the Four Tuberculous Cases with Five Cases of Idiopathic Myelofibrosis

We have observed and analyzed 5 cases of idiopathic myelofibrosis (table 4)
which will be reported elsewhere. Three are still living and 2 have died. These pa-
tients have many features in common with the tuberculous group; namely the
splenomegaly, anemia, leukemoid blood picture, fibrosis in the bone marrow with
an increase in megakaryocytes and extramedullary hemopoiesis. On the other hand,
there were certain differences in the two groups. The idiopathic cases were in an
older age group (53 to 77 years), there was no fever except terminally in one case,
the spleens were larger and lymphadenopathy was less prominent. The average
duration of illness in this group at the time of writing was thirty-two and one-half
months as compared to sixteen months in the tuberculous patients. There was no
evidence of active tuberculosis in the idiopathic group. In general, the idiopathic
cases resembled the tuberculous cases hematologically, but the latter group ran a
septic course and terminated fatally within a shorter time.

DISCUSSION

Pathogenesis: The possible role of tuberculosis in the production of myelofibrosis
has been considered by previous writers (see Review of the Literature). However,
there is no clean-cut evidence in favor of this relationship. In a preliminary study
of this subject, one of us (H. W. C.) suggested that the acid-fast organisms found
in the atypical tubercles of M. B. and in other cases reported in the literature may
be responsible for the myelofibrosis. Furthermore, since the atypical tubercles in
these cases resembled the lesions produced experimentally with avian tuberculosis,
it was suggested that the organisms be identified in subsequent investigations.
This was done in W. D. where the acid-fast bacilli were obtained at autopsy and
identified according to the method described by Feldman. The organism in this
case was found to be a human tubercle bacillus, possibly of low virulence and
definitely sensitive to streptomycin.

* Mallory's connective tissue stain.
### Table 4.—Summary of Cases

<table>
<thead>
<tr>
<th>Number and case</th>
<th>History</th>
<th>Physical Findings</th>
<th>Laboratory Examination</th>
<th>Clinical Course</th>
<th>Autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number and case</td>
<td>Age, sex</td>
<td>Weight loss</td>
<td>Fever</td>
<td>Splenomegaly</td>
</tr>
<tr>
<td>1. C. B.</td>
<td>M, 60</td>
<td>+ + + + + + + + + + + + + Dec.</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>2. W. M.</td>
<td>M, 50</td>
<td>+ + + + + + + + + + + + + Dec.</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>3. W. D.</td>
<td>M, 29</td>
<td>+ + + + + + + + + + + + + Dec.</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>4. M. B.</td>
<td>F, 36</td>
<td>+ + + + + + + + + + + + + Inc.</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
</tr>
</tbody>
</table>

**Cases of myelofibrosis associated with tuberculosis**

<table>
<thead>
<tr>
<th>Number and case</th>
<th>History</th>
<th>Physical Findings</th>
<th>Laboratory Examination</th>
<th>Clinical Course</th>
<th>Autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. W. H.</td>
<td>M, 66</td>
<td>+ + N + + + + + N</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>6. M. S.</td>
<td>F, 57</td>
<td>+ + + + + + + + + N</td>
<td>+ +</td>
<td>Dec.</td>
<td>+ +</td>
</tr>
<tr>
<td>7. J. K.</td>
<td>F, 53</td>
<td>N N + + + + + + N</td>
<td>+ +</td>
<td>Dec.</td>
<td>+ +</td>
</tr>
<tr>
<td>8. W. B.</td>
<td>M, 77</td>
<td>+ + N + + + + + + + + Dec.</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>9. L. K.</td>
<td>F, 70</td>
<td>+ + + N + + + N</td>
<td>+ +</td>
<td>+ N</td>
<td>+ +</td>
</tr>
</tbody>
</table>

*? = not recorded; Dec. = decreased; Inc. = increased; N = normal.

†Splenectomy.
Acute caseating miliary tuberculosis is the name Rich\textsuperscript{11} applied to the atypical disease seen in our cases. He points out this disease may be overlooked at autopsy or, if recognized, may be misinterpreted as avian tuberculosis. Rich\textsuperscript{11} has experimentally produced the lesions of caseating tuberculosis by injection of large numbers of bacilli into the blood stream of a hypersensitive animal. They become widely disseminated and are characterized by tiny caseous foci without epithelioid cells, lymphocytes or giant cells; the organisms multiply rapidly in these lesions and large numbers are found at autopsy. If the animals survive, the organisms are reduced and typical tubercles develop. Complete healing may take place with or without scar formation. Pinner\textsuperscript{15} believes that this type of reaction is due to an atypical response of the host. Clinically and experimentally, this massive dissemination of organisms is characterized by toxemia and spiking temperature elevations.

The proliferative reactions in tuberculosis have led to widespread investigations. According to Rich,\textsuperscript{14} the factors influencing fibrosis are as follows: (1) virulence of the organism, (2) race, (3) presence and degree of immunity or hypersensitivity, and (4) resistance of the host. Sabin\textsuperscript{16} studied the tissue response to various fractions of acid-fast organisms. She found that an unsaponified higher alcohol derived from the waxes produced a remarkable proliferation of fibroblasts both diffusely and in small clumps. Kaufmann\textsuperscript{17} described a relatively benign form of tuberculosis involving the lymph nodes which he called 'attenuated tuberculosis,' it runs a chronic course with massive enlargement of the glands due to a proliferative reaction. There is little or no caseation. The organisms are often difficult to demonstrate. Pinner\textsuperscript{15} describes sarcoidosis as a hematogenous tuberculosis with a productive tissue response and no caseation. He believes this is an expression of a high degree of specific resistance as manifested by the benign course, the absense of tissue destruction and toxemic symptoms and the efficient destruction of tubercle bacilli shortly after focalization has taken place. Such a concept embraces a large field of fibrotic and hyalinized lesions resembling tuberculosis. Ewing\textsuperscript{18} and L’Esperance\textsuperscript{19} have strongly supported the concept of a tuberculous etiology of Hodgkin’s disease.

Arneth,\textsuperscript{20} Muller,\textsuperscript{21} Pinner\textsuperscript{15} and others\textsuperscript{22} occasionally observed hematologic findings in miliary tuberculosis similar to those described in our cases. These authors point out that a shift to the left of the granulocytes is one of the heralding features of active, progressive tuberculosis. This may be accompanied by a leukocytosis or a leukopenia.\textsuperscript{*} Leukemoid reactions often accompanied by a leukocytosis and the presence of myeloblasts do occur and are at times difficult to differentiate from leukemia.\textsuperscript{23} A low grade or moderate anemia is common in pulmonary tuberculosis. However, Pinner\textsuperscript{15} states that marked degrees of anemia (below 75 per cent) are strongly indicative of extrapulmonary involvement or of nontuberculous complications. Marrow studies in miliary tuberculosis have shown early hyperplasia of all the hemopoietic tissue and later hypoplasia or aplasia. Muller,\textsuperscript{21} in some of his cases, describes marrow of generalized tuberculosis, filled with eosinophilic debris

\* Recently, in our clinic, autopsy has been performed on a patient who had miliary tuberculosis associated with a hypoplastic marrow without fibrosis. During life, she had a leuko-erythroblastic anemia.
and sometimes connective tissue fibrils with islands of hyperplastic myelopoietic tissue. Further evidence that tuberculosis depresses the marrow is demonstrated by the suppression of leukemia by an active tuberculous infection (Jaffe, Heinle and Weir and Ulrich and Parks). Undoubtedly the atypical miliary tuberculosis seen at autopsy in the cases reported here and in the literature represent a terminal dissemination of the type described by Rich. However, a review of the clinical course, physical findings hematologic and pathologic examinations coupled with the autopsy findings and bacteriologic studies, strongly suggest a protracted, progressive granulomatous disease of tuberculous origin. The degree and extent of fibrosis of the marrow and other organs may be dependent upon factors previously enumerated and upon the length of life of the patient. The marrow fibrosis in these cases is considered to be part of a generalized disease.

Diagnosis: The possible diagnosis of myelofibrosis must be entertained when a patient complaining of bizarre pain, weakness and weight loss is found to have splenomegaly, hepatomegaly, lymphadenopathy and hematologic findings of refractory anemia with a leukemoid reaction. Tuberculous involvement is to be thought of if there is in addition a recurrent, spiking or persistent unexplained fever.

A sternal aspiration in myelofibrosis reveals a hypocellular marrow with an increase in the megakaryocytes. The tuberculous case frequently shows an initial marrow hyperplasia followed by hypoplasia. This material must be carefully studied for tuberculosis as described by Schleicher. A bone marrow biopsy must be obtained to confirm the diagnosis of myelofibrosis. Lymph node biopsies and splenic punctures may be of assistance. These tissues should be cultured, inoculated into guinea pigs and examined pathologically for acid-fast organisms. X-ray examination of the chest may reveal evidence of miliary tuberculosis but the absence of findings does not rule out this disease. With the proper diagnostic approach it should be possible to make the diagnosis of myelofibrosis with tuberculosis ante-mortem in many cases.

Treatment: Blood transfusions temporarily raise the oxygen carrying power of the blood but have no effect on the course of the disease. As is to be expected, there is no response of the anemia to liver and iron, and sulfonamides and penicillin have no effect on the fever. Splenectomy and irradiation are contraindicated as they reduce the compensatory hemopoietic mechanism and probably hasten death. Streptomycin offers the only hope in the treatment of this disease. Recent reports indicate that certain cases of generalized tuberculosis and tuberculous meningitis are benefited by adequate treatment with streptomycin. When the diagnosis is made, it would seem logical to give 2 to 3 Gm. of streptomycin daily over a prolonged period of time. Since the disease is characterized by spontaneous remissions, one must be guarded in interpreting therapeutic results.

Summary

Myelofibrosis (fibrotic bone marrow and, usually, an increase in megakaryocytes) is characterized by generalized pains, weakness, loss of weight, enlargement of the liver and spleen and a leuko-erythroblastic anemia.
Four cases of myelofibrosis associated with generalized tuberculosis have been reviewed in detail. Autopsy examination of the 4 cases revealed acute, caseating tuberculosis which was considered to be responsible for the bone marrow and generalized fibrosis observed. A similar type of tuberculosis occurred in 7 of 91 cases of myelofibrosis reviewed in the literature. The pathogenesis of myelofibrosis associated with tuberculosis is discussed.

In the diagnosis of this syndrome, attention is called to the importance of obtaining a bone marrow biopsy and making a complete bacteriologic and pathologic study of this tissue for tuberculosis.

The 4 tuberculous cases here reported as compared with cases of idiopathic type, are younger, have hyperpyrexia, less splenic but greater lymph node enlargement and run a shorter course before death.

ACKNOWLEDGMENT

The authors wish to thank Dr. Guy P. Youmans and Mrs. Elizabeth Williston of the Department of Bacteriology, Northwestern University Medical School, for their assistance in the bacteriologic studies, and Dr. Richard H. Young for permission to study and report case 1 (C. B.).

REFERENCES

MYELOFIBROSIS ASSOCIATED WITH TUBERCULOSIS

MYELOFIBROSIS ASSOCIATED WITH TUBERCULOSIS: A REPORT OF FOUR CASES

HOWARD W. CRAIL, HOWARD L. ALT and WALTER H. NADLER