FAMILIAL PANMYELOPATHESIS
Fanconi Syndrome in Adults

By KARL ROHR, M.D.

THE FOLLOWING case histories are of interest because they are the first reports of a familial panmyelopathy of the hypoplastic type occurring in adults. Two brothers were affected.

CASE REPORTS

Case 1. Sch., Franz, was born in 1921. As a boy he was nicknamed "the negro" because of marked pigmentation. He was healthy apart from bouts of eczema.

In 1939, at the age of 18 he had poliomyelitis with resulting weakness of the abdominal muscles. Anemia was discovered for the first time during this illness, with hemoglobin levels varying between 60 and 80 per cent. In April 1945, the hemoglobin was again 60 per cent. In August 1945, the hemoglobin had declined to 53 per cent and in September to 51 per cent. He was given transfusions and "Ferroedoxin" therapy and his hemoglobin rose to 80 per cent. When seen early in 1946 after accidental burning of one arm, his hemoglobin had again dropped to 48 per cent and he was transfused. In June of that year his hemoglobin was 65 per cent. He complained of being very tired and developed dyspnea with little exertion. He also complained of severe pains in the tibiae and vertebrae, slight edema and gingivitis. In November 1946, three teeth were extracted because of stomatitis and this was followed by fever ranging between 38 and 40°C; there was profuse bleeding, the hemoglobin declining to 30 per cent, and later to 2.4 per cent. Temporary improvement followed transfusions and penicillin therapy. Later that year he had bronchopneumonia and his hemoglobin was found to be only 10 per cent. He died in March 1947, at the age of 26 years.

Physical examination showed that the form and the size of the head were normal, as were the genitalia. The skin showed a marked greyish pigmentation, especially on the face, forearms and to a lesser extent on the abdomen. Petechiae were seen in the skin and mucous membranes in 1944 and in November 1946 at the time of the teeth extraction, he showed marked pallor, gingivitis, stomatitis and glossitis, and there were hemorrhages in the fundi of the eyes. The heart was found to be slightly enlarged and in September 1945, the blood pressure was 130/70. The electrocardiogram was normal at that time but in November 1946, showed signs of myocardial damage.

The urine showed urobilinogen and indican, but no porphyrin. Serum bilirubin was 0.3 mg. per cent and phosphates and phosphatase were normal. The Takata-Ara reaction was negative, the Weltman coagulation band was 0.15 (enlarged) and the serum proteins were 6.8 Gm. per cent.

Hematologic findings: The course of the anemia has already been indicated and is shown in figure 1. The red cell counts initially were between 1.7 and 3.5 million per cu. mm., later dropping to 1.1 to 1.2 million per cu. mm. and finally to 660,000 per cu. mm. The color index varied from 0.96 to 1.39, but was usually over 1.2.

The white blood cells in 1939 were 1,700 to 8,300 per cu. mm. During 1945, the count was about 4,000 per cu. mm. at first, later dropping to between 2,000 and 4,000 per cu. mm. In November 1946, the count was only 500 per cu. mm. and finally reached as low as 310 per cu. mm. The polymorphs were 65 per cent at the beginning, with 25 per cent lymphocytes. This gradually changed so that the polymorphs dropped to 38 per cent and then to 34 per cent, the lymphocytes rising to 31 per cent and later to 60 per cent. Monocytes varied between 4 and 10 per cent and the eosinophils between 1 and 3 per cent. The blood smear showed anisocytosis of marked degree throughout the illness, with macrocytosis and microcytosis, and poikilocytosis. Polychromasia was marked for a long time. Reticulocytes were 1.4 per cent in June 1946 but later declined to 0.3 and 0.4 per cent.

The platelets were noted to be diminished in August 1945 and counts during the next year lay between 4,600 and 32,000, with a drop finally to 1,000 per cu. mm.

From the Medical Department, University of Zurich, Switzerland.
The bleeding time was 5 minutes, and 1 1/2 minutes, and the coagulation time was normal on two occasions (5 minutes). The osmotic fragility test showed initial hemolysis in 0.44 per cent NaCl and complete hemolysis in 0.32 per cent NaCl.

The sedimentation rate was first found to be high in 1944. Readings by the Westergren method showed results of 60 to 101 in the first hour and 76 to 110 in the second hour, except for readings of 30 for the first hour and 60 in the second hour after transfusions had raised the hemoglobin to 30 per cent. In the terminal stages of the illness the readings were 172 and 175 in one and two hours respectively.

Bone marrow studies during life are of interest. In 1945 smears showed abundant marrow, macroblastos is and increase of the metamyelocytes and stab forms. In 1946 the marrow showed a good deal of fat, hypocellularity with few basophilic erythroblasts and myelocytes and almost no neutrophils, but a great increase in the reticular cells of the lymphoid and plasma cell types (fig. 2). In 1947 the marrow was even poorer in the normal cell types. Lymphoid and plasma cells predominated, being seen in groups of 6 or 8. Lymphocytes were also increased, in parts a great many fibrocytes with fibril formation were seen, and there were also an unusual number of tissue mast cells, as many as 4 or 5 per field (fig. 3).

Autopsy report: The heart showed dilatation, with hypertrophy of the left side and hemorrhages into the endo- and myocardium. There was bronchopneumonia at the right lower lobe. The liver showed fatty degeneration. The brain showed slight bleeding. There were extensive hemorrhages into the mucous membranes. Generalized hemosiderosis was observed throughout the whole reticulo-endothelial system and in the liver cells. Brown, iron-free pigmentation of the skin was also observed. Rudimentary centers of blood formation with development of megakaryocytes were found in the lymph nodes and spleen. Areas of chronic inflammation were seen in the suprarenal medullae and in the interstitial tissue of the kidneys.

Case 2. Sch., Willi. The younger brother was born in 1913, and is now 25 years old. The course of his illness is shown in figure 4.

Past illnesses were whooping cough, measles, mumps and bronchitis during childhood, and appendectomy at the age of 15.

The present illness started in November 1943 at the age of 20 with a cold which was followed by pneumonia of the left lower lobe, while the patient was in military service. Following "Cibazol" therapy the pyrexia diminished, but a low-grade fever continued and a high sedimentation rate persisted, with readings of 90 mm. in the first hour and 105 mm. in the second hour (Westergren). The hemoglobin at the onset of the illness was 86 per cent, later dropping to 60 per cent.

![Fig. 1. Course of the Blood Counts in Sch. Franz](image-url)
FAMILIAL PANMYELOPOIETHESIS

Following blood transfusion therapy the hemoglobin was 86 per cent but later dropped and the anemia became even more severe. The disease continued to progress, with a hemorrhagic tendency always the most prominent feature, with especially bad bleeding following the extraction of a tooth. He continued to run a low-grade fever with temporary bouts of higher pyrexia of unexplained origin. Occasional episodes of diarrhea which were resistant to therapy occurred. In 1945, the patient began to suffer from violent pain in the bones, and had intercurrent eosinophilic infiltration of the lungs and an attack of epidemic hepatitis. At times there was spontaneous improvement in his condition. The disease was resistant to all forms of therapy, including sulfonamides, penicillin in large doses, iron and massive doses of vitamins. Temporary improvement could be brought about only by transfusions. He was given more than 70 transfusions totalling about 20 liters of blood.

Because of the failure of all other therapeutic measures, splenectomy was carried out in September 1945. Following operation, the hemoglobin increased to 70 per cent, the bleeding tendency ceased, the
general condition improved and the weight increased. However, a few weeks after operation the anemia again increased, with a recurrence of bleeding into the skin. Violent pains occurred in the bones of the legs and thighs, in the shoulder blades and the vertebral column. The skin of the legs gradually became greyish like smoke, with dark pigmented spots. At the beginning of January 1946, the patient was given high altitude therapy in the Engadine. His clinical condition became stationary, with frequent violent pains in the legs and pigmentation of the hands. The hemoglobin at this time was 65 per cent.

The clinical condition remained unchanged up to the end of April 1947. The patient had been able to do some light work for several months. He often complained of violent boring pain in the bones of legs,
the cervical vertebrae, the shoulder blades and the bones of the jaw. After preparation by blood transfusions, 11 decayed teeth were extracted without any severe bleeding. Only rare bleeding into the skin and epistaxis had occurred and there had been no hematuria. The temperature had been only slightly elevated, except during an influenzal infection. The hemoglobin on March 30, 1947, was 59 per cent. Liver and folic acid therapy were without effect.

Physical examinations done at various times during the illness, showed striking pigmentation of the skin, especially around old scars, as well as brownish spots of pigmentation on the mucous membrane of the mouth. The skin was delicate and decidedly smoke-grey in color, particularly on the legs and thighs, and to some extent on the arms and body. In a few places some darker spots were noticed. It was observed that the patient had a slender skull and x-rays revealed a thin skull with a small sella turcica. The structure of the body was somewhat asthenic and gave the impression of being slightly infantile. There were few hairs on the body, with hardly any beard growth and feminine genital hair distribution (fig. 5). He was found to be intellectually normal. No abnormalities were found by x-ray in the pelvic bone, femur or humerus.

The urine gave a slightly positive test for urobilin and occasionally showed a few isolated red cells. Free hydrochloric acid was present in the stomach. The stools contained increased amounts of fats, but no increase of urobilin. X-rays showed the stomach and intestines to be normal. The electrocardiogram showed deflection of the T wave in the second lead but was otherwise normal. The basal metabolic rate was +4 per cent.

Blood chemistry showed total proteins varying from 7.0 to 7.8 gm. per 100 cc., cholesterol 147 to 173 mg. per 100 cc., serum iron 172-125 gamma per 100 cc., calcium 9.5 mg. per 100 cc., nonprotein nitrogen 27 mg. per 100 cc., the uric acid 4.1 mg. per cent and the bilirubin 0.3 mg. per cent except during the attack of epidemic hepatitis when it rose to 6.3 mg. per cent. The Takata-Ara reaction was negative and the Weltman coagulation band was 0.1 (enlarged).

The Wassermann, Pirquet and Mantoux reactions were negative, and repeated blood cultures were also negative.

Hematologic findings: The hemoglobin varied between 59 and 65 per cent except after transfusions and a rise to 70 per cent following splenectomy. The red cell count varied from 2.4 to 3.0 million per cu. mm.
FIG. 5. SCH. WILLI

Note the slight infantile aspect, the feminine hair growth and the pigmentation of the skin, especially on the legs. Status after splenectomy.

and the color index from 1.0 to 1.3. The white cell count showed leukopenia, 2,800 to 4,500 except after transfusions and after splenectomy when it rose to 5,500. Neutrophils were 39.5 to 45.5 per cent, co-
Fig. 6. Blood Picture of Sch. Willi

Microphotographic enlargement (X 1,000). Note the enormously developed anisocytosis in (a) macrocytic and microcytic (schistocytes) forms, and in (b and c) the target cells.

sinophils 0.5 to 5.0 per cent, basophils 0.0 to 0.5 per cent, monocytes 9 to 12 per cent, lymphocytes 40 to 57 per cent with a rise to 63 per cent following splenectomy and 1.5 per cent plasma cells were seen on one occasion. The platelets were markedly reduced, 25,000 to 46,000, except immediately after splenectomy when they were 66,000. The reticulocytes were 1.1 to 2.3 per cent. Blood smears (fig. 6) showed
anisocytosis with very large and very small cells, poikilocytosis, polychromasia, and even before splenectomy erythroblasts and Howell-Jolly bodies were present.

The bleeding time was 6 minutes with a temporary rise to 93 minutes in 1945. The prothrombin time was 40 per cent, later 100 per cent. The coagulation time was 1 to 12 minutes. The osmotic fragility test showed initial hemolysis in 0.5 per cent NaCl and complete hemolysis in 0.1 per cent NaCl.

The sedimentation rate was persistently elevated. Early in the disease it was 45 mm. in the first hour and 75 mm. in the second hour by the Westergren method, rising to 70 mm. and 110 mm. in the first and second hours respectively, except for readings of 8 and 15 respectively during a remission in the anemia. In April 1946, the readings varied from 18/39 to 26/45 and in March 1947 the result was 28/47.

Histologic findings. The spleen histologically showed moderate thickening of the capsule and trabeculae, as well as thickening and hyalinization of the intima of the follicular arteries. The pulp contained copious amounts of red cells, with a moderate number of lymphocytes, some neutrophils and eosinophils, numerous hemosiderin-containing pulp cells and some plasma cells. The venous sinuses were also enlarged. A diagnosis of chronic splenomegaly and hemosiderosis was made.

Sections of a growth excised from the subcutis of the leg showed perivascular lymphatic infiltrations with some isolated polymorphs. Numerous hemosiderin-containing cells were found in the connective tissue as well as in the corium.

Sections of the bone marrow also showed numerous hemosiderin-containing macrophages and a few lymph follicles. The bone marrow was also studied by sternal puncture done seven times during the course of the disease. The corticalis was moderately hard. At first the marrow was rather abundant, but later became scarce. The most consistent finding was an increase of the immature myelocytes and of big ba-
sophilic erythroblasts, while megakaryocytes were seen rarely. In several punctures many reticular cells, especially larger and smaller plasmocytic forms were present. On one occasion tissue mast cells were remarkably abundant and they were seen in a few other instances especially in places where the bone marrow was thick.

**Family History.** The maternal grandparents died at 70 and 84 years of age, both of cancer of the stomach. The father is 56 years old. The mother is 6 years old and suffers from mild hypertension but is otherwise well. Of 8 paternal uncles and aunts, one has tuberculosis and 2 suffer from chronic polyarthritis. Two brothers are living and well. There were twin sisters, one of whom was stillborn and the other died one hour after birth.

Of 40 relatives examined, only 1 showed hematologic abnormalities. In 2 otherwise healthy brothers, with hemoglobins of 100 and 102 per cent and red cell counts of 4.8 and 5.0 million per cu. mm. respectively, the Price-Jones curves showed a tendency to widening of the base, both to the macro- and microcytic sides (fig. 7). Their reticulocytes sometimes rose to 1.0 and 1.4 per cent and the serum iron concentrations were 140 and 165 gamma per 100 cc. Osmotic fragility tests showed initial hemolysis in 0.48 and 0.46 per cent NaCl respectively and complete hemolysis in 0.30 per cent NaCl in both.

The second patient and the parents were Rh positive.

**Discussion**

One of the notable features of the disease in these two brothers lies in their strikingly analogous clinical symptomatology. The features common to both cases may be listed as follows.

1. **Age of onset of symptoms.** In the case of the elder brother, symptoms began when he was 2.4 years old, although signs were already present five years earlier. The younger brother became ill at the age of 20.

2. **Pigmentation.** In both patients an abnormal pigmentation of the skin attracted attention, showing sometimes a brown, sometimes a more smoky-grey color. Pigmentation was present in one brother even before other manifestations of the disease appeared, and in the other patient the degree of pigmentation was greater than could be accounted for by the hemorrhagic diathesis or by the numerous blood transfusions.

3. **Hemosiderosis.** In both cases, histologic examination revealed an abnormally marked hemosiderosis in the reticulo-endothelial system.

4. **Pain in the bones.** Both patients complained at times of violent pain in the bones.

5. **Panhemocytopenia.** In both cases the entire bone marrow was affected from the very beginning, with resultant anemia, leukopenia and thrombocytopenia.

6. **Hematologic findings.** Both patients had a hyperchromic type of anemia, with a color index between 1.1 and 1.4. The erythrocytes revealed unusually marked anisocytosis with large macrocytes and some abnormally small microcytes (so-called schistocytes). Furthermore, in both cases there was a tendency to poikilocytosis, occasional target cell formation and to an abnormal amount of polychromasia. The number of reticulocytes was almost constantly above normal in both patients. The serum bilirubin was normal, the Takata-Ara test negative and the Weltman coagulation band enlarged and the Wassermann test negative.

7. **The morphology of the bone marrow.** At the beginning of the illness, only the signs of maturation arrest were apparent. Later, hypoplasia of the marrow parenchyma appeared which progressed to almost complete aplasia of the marrow in the patient who died. Moreover, in both cases, striking changes were present in the
stroma. There was marked increase of small as well as larger forms of plasmocytic reticular cells (plasmocytosis), constant increase of the fibrocytes (fibrosis), and in addition unusually exuberant growth of the so-called tissue mast cells (mastocytosis), with as many as 4 to 5 such cells per field in some areas.

Additional features of the disease are as follows: (a) The younger, still living patient showed certain signs not observed in his brother, namely slight infantilism with deficient hair growth, microcephaly, a small hypophysis and hypogenitalism. (b) In one patient the osmotic fragility of the red cells was increased at the beginning of the illness, while it was normal at the beginning of the illness of the other. (c) In one patient a few Howell-Jolly bodies and erythroblasts were seen in the peripheral blood even before splenectomy. (d) The level of serum iron was continuously high in one patient, but was not determined in the other. (e) There have been no previous reports in the literature of the occurrence in adults of a similar familial form of panhemocytopenia accompanied by such striking pigmentation. Many cases of familial anemia, agranulocytosis and panmyelophthisis have been reported, especially by Gaennslen and Huber. However, the clinical picture of the two patients reported here seems to bear more resemblance to the constitutional panmyelopathy of children, described first by Fanconi in 1927 and known as anemia perniciosiformis constitutionalis, or the Fanconi syndrome. This disease has also been described by Uehlinger, Zellweger and Zollinger and by Dameshek and associates. The condition is characterized by a refractory macrocytic anemia with leukopenia and thrombopenia, brown pigmentation of the skin, microcephaly, atrophy of the testes and a tendency to deformities of the skeleton.

Hematologically, we are apparently dealing with the same anomaly in the patients reported here. Furthermore, as reported in the disease in children, these patients showed pigmentation of the skin, due apparently chiefly to hemosiderosis. The infantile features were less pronounced here, though they could be seen distinctly in one of the patients. The less pronounced degree of these changes seems to be connected with the relatively late development of the disease, which set in after the completion of puberty in both patients.

Unlike the known aplastic anemias which are either normochromic or show a tendency to macrocytosis, it is of considerable interest to find in these patients an unusually marked anisocytosis with, on the one hand, very large macrocytes, and on the other hand, very small microcytes (so-called schistocytes), as well as poikilocytosis and target cell formation. The reticulocytes were increased up to 1.0 to 3.0 per cent, whereas they are usually lacking in typical cases of aplastic anemia. Although there was little or no increase of bilirubin in the serum, and the urobilin elimination in the urine was insignificant, there were various other factors which indicated pathological hemoglobin metabolism. One indication was increased hemolysis, suggested by the high concentration of serum iron, the abnormal osmotic fragility of the erythrocytes and the number of reticulocytes. Another was the pathologic iron storage throughout the reticuloendothelial system, as indicated by the hemosiderosis of the various organs.* The increase of

* This may have been due, at least in part, to the effects of multiple transfusions; it is curious that "exogenous" hemochromatosis seems to develop much more extensively in cases of hypoplastic anemia than in some other cases of anemia given numerous transfusions. Editor.
hemolysis might be explained by assuming that a more exact balance of hemoglobin metabolism existed.

The pathologic functioning of the reticulo-endothelial system in the two patients studied manifested itself not only in the generalized hemosiderosis, but also in changes in the bone marrow. As mentioned above, the changes in the reticulum and in the stroma of the marrow were especially remarkable, consisting of marked growth of the reticular cells, especially of the large and small plasmocytes, of the tissue mast cells and of the fibrocytes. These pathologic changes can be summed up with the designation "reticulo-fibrosis of the bone marrow." The changes in the stroma seem to represent the primary disturbance, the first changes being plasmocytosis and mastocytosis. This results in maturation arrest of the normal marrow parenchyma which follows as the next stage of the process. With the evolution of the disease there ensues a kind of cicatrization process, an increase of the fibrosis with a gradual destruction of myeloid tissue and marrow atrophy is a still later stage of the process.

At present no definite answer can be given to the question of the physio-pathologic importance of the enormous increase of the plasmocytes and mastocytes. However, it is known that both cellular forms should be classified in the reticulo-histiocytic system and that they belong to the so-called active mesenchyma. The plasma cells undoubtedly play an important part in the formation of globulin, particularly of gamma globulin, and hence in the development of antibodies. Thus, a relationship between plasma cells and certain immunity reactions appears to be important. On the other hand, the mastocytes, which show a genetic relation to heparin and amyloid, presumably have some connection with anaphylactic processes. It is theoretically possible that these particular plasmocytic and mastocytic changes of the bone marrow are an expression of an anaphylactic-allergic process of the bone marrow. In the light of these facts, it is noteworthy that in both patients the whole clinical picture developed in connection with an infectious disease (poliomyelitis and pneumonia respectively). Such a pathologic reaction of the reticulo-histiocytic system not only explains the primary reaction of the stroma of the bone marrow with a tendency to fibrosis of the marrow, but also accounts for the abnormal blood picture.*

Other pathologic conditions of the reticulum or mesenchyma are known to be accompanied by even greater disturbances of the blood picture. This is true especially of osteosclerosis and osteomyelosclerosis, where the principal disturbances originate in the osteogenic reticulum; and in Cooley's anemia, where it is the disturbance of the myelogenic reticulum which seems to be chiefly responsible for the disturbances in the formation of blood. In these blood diseases, similar morphologic changes of the erythrocytes are found, namely marked aniso-, micro-, macro-, poikilocytosis, and target cells. These changes are much more pronounced in Cooley's anemia. In both these diseases there is not only a disturbance in the formation of blood but also a disturbance in the development of the bones. One

* We have found tissue mast cells in the bone marrow in but a dozen cases and only in hypoplastic and aplastic anemias of various etiology (benzol poisoning, leukemia, myeloma, infections, and in idiopathic forms).*
disturbance is not the consequence of the other, but pathologic changes occur in both organs from the beginning. In Cooley's anemia, however, the pathologic blood formation is more striking, and in osteosclerosis the pathologic bone formation dominates the clinical picture.

It is not difficult to explain generalized hemosiderosis and pigmentation of the skin and mucous membranes as a consequence of pathologic functioning of the reticulo-histiocytic system. Abnormal hemolysins or agglutinins were not detectable in the two patients reported here. The parents and the patient who is still living are all Rh+.

**Summary**

An account is given of a similar and hitherto unknown clinical-hematologic syndrome in two adult brothers with marked hemorrhagic diathesis, diffuse pigmentation of the skin, violent pain in the bones and panhemocytopenia. In the younger brother, there is also a certain degree of infantilism. The elder brother died with all the symptoms of an intensive aplastic anemia; in the younger brother, the condition was stabilized after splenectomy. The blood picture in both patients was characterized by a hyperchromic anemia with remarkable micro- and macrocytosis, and an increased number of reticulocytes. In the younger brother, increased fragility of the red blood cells and an elevated serum iron content were observed. In both cases, an unusual increase of the plasmocytic and reticular cells and of the tissue mast cells was noticed in the bone marrow and, in the final stages of the disease, the marrow showed marked fibrosis.

The disease is believed to be a variety, in adults, of the syndrome first described by Fanconi as a constitutional panmyelopathy occurring in children. The illness is the result of a hereditary pathologic reaction of the reticulo-histiocytic system and seems to have been caused by an anaphylactic-allergic phenomenon. The possibility is discussed that genetic connections may exist between this condition and other diseases, such as certain osteoscleroses and Cooley's anemia, which are characterized by simultaneous disturbances of the bone and bone marrow and by a similar blood morphology.

**REFERENCES**

FAMILIAL PANMYELOPHTISIS: FANCONI SYNDROME IN ADULTS

KARL ROHR

Updated information and services can be found at:
http://www.bloodjournal.org/content/4/2/130.full.html
Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml