HEREDITARY NONSPHEROCYTIC HEMOLYTIC ANEMIA

By William H. Crosby, Major, MC, USA

There are three well known and well defined types of hereditary hemolytic anemia: hereditary spherocytosis, sickle-cell anemia and Mediterranean anemia, or hereditary leptocytosis. In addition to these, several other types of inherited anemia have been identified in recent years. Cooley4 and later Rundles and Falls5 reported a sex-linked anemia. A familial anemia similar to this has been described,10 showing iron-staining inclusions in the erythrocytes (siderocytes). Both the sex-linked and the siderocytic anemia resemble Mediterranean anemia, for they are hypochromic and not remarkably hemolytic. Haden5 has described hemolytic hereditary anemia without spherocytosis and Thompson23 has mentioned a study of three families with hemolytic anemia, “in which the diagnosis of spherocytic jaundice might well have been made except for the absence of spherocytes.” Several other families of this sort have been reported.3, 29 In all of these nonspherocytic hereditary dyscrasias, splenectomy has not cured the anemia as it does in familial spherocytosis.

We have recently studied a form of hereditary nonspherocytic and normochromic hemolytic anemia, transmitted as a mendelian dominant and associated with brachyphalangia and porphyria. In a single instance, splenectomy was of no value. Our attention was directed to this family, which we shall describe, through one of its members, a soldier who was transferred to the Brooke General Hospital from Japan. A definition of the disease as it existed in our patient and in four generations of his family together with various studies of erythrocyte fragility and hemoglobin metabolism are the subject of this report.

MATERIALS AND METHODS

Reticulocytes were wet stained with a 1 per cent solution of brilliant cresyl blue in isotonic sodium chloride solution to which 0.4 per cent of sodium citrate was added.

Examination for abnormal forms of erythrocytes was made on Wright-stained preparations, in reticulocyte preparations and in fresh unmodified blood sealed under a coverslip as suggested by Dameshek.7 These latter preparations were incubated for seventy-two hours and examined daily for sickle cells.

Siderocyte preparations were made by fixing a thin spread of blood on a coverslip in methyl alcohol. A 2.5 per cent potassium ferrocyanide solution was acidified with concentrated hydrochloric acid until a small amount of white precipitate remained after stirring. This solution was filtered. The coverslips were immersed in it, face down, for ten minutes. The slips were then washed in water and counterstained in dilute carbol fuchsins.

Urobilinogen was determined by the technic of Sparkman.22

Urinary coproporphyrin was determined by the technic of Schwartz, Hawkinson, Cohen, and Watson,21 porphobilinogen by the technic of Watson and Schwartz.27

Chemical analyses for low concentrations of hemoglobin were carried out by the quantitative benzidine technic of Bing and Baker. Results are stated in mg. per 100 cc. Hemolysis of 1 per cent of the cells in a 10 per cent suspension yields 2.5 mg.

Survival of transfused red cells was studied by the differential agglutination technic of Ashby as modified by Young, Platzer and Rafferty.30

From the Medical Service, Brooke General Hospital, Fort Sam Houston, Texas
HEREDITARY NONSPHEROCYTIC HEMOLYTIC ANEMIA

CASE HISTORY

The patient was born in 1923 of mixed English and French antecedents and raised in southern Louisiana. His personal history prior to entering military service in 1943 was essentially negative. He had worked as a lumberman in Louisiana. Except for an acute febrile illness without jaundice when an infant, he had always been well. The patient was in an Army hospital in 1944 and 1945 for pain in the feet. The red blood cell count at that time was 3.5 million. In July 1946 he was taken ill with severe polyarticular arthritis and he was hospitalized at an Army general hospital in Tokyo. At the time of the admission, no jaundice was noted; his spleen was not palpable. He had acute gonorrheal urethritis.

In August 1946, examination of the blood showed R.B.C. 3.6 M, hemoglobin 60 per cent, hematocrit 25 per cent, W.B.C. 7,000 with 70 per cent granulocytes.

The patient was transferred from Japan to the Brooke General Hospital on August 30, 1946. Physical examination revealed a thin, pale individual appearing chronically ill and complaining of stiffness of the right wrist and swelling, stiffness and tenderness of both ankles and both knees. Blood counts at that time were essentially unchanged. Additional laboratory work was reported as follows: platelets 132,000; reticulocytes 7.6 per cent. His blood was group A, Rh negative. Osmotic fragility test: patient, 0.40–0.28: control 0.41–0.30. Serologic test for syphilis negative. Urinalysis normal. Liver function tests including cephalin-cholesterol flocculation, prothrombin time and bromosulphalein retention were normal. Total serum proteins and albumin-globulin ratio were within normal limits. Icterus index 16; serum bilirubin indirect 1.7 mg. per 100 cc.; total blood serum cholesterol 150 mg. per 100 cc. X-ray examination of the skeleton was negative except for evidence of early rheumatoid arthritis. X-rays of the chest, a gastrointestinal series, barium enema and a gall bladder series were normal.

On one occasion the patient was given an intravenous injection of typhoid vaccine. His febrile reaction was moderate but during the next three days he suffered from left upper quadrant pain, his spleen enlarged and he excreted "black" urine, slightly positive for bile but negative for hemoglobin. His jaundice did not deepen; his hematocrit fell 2 mm. This reaction was unexpected, it was not carefully observed and its nature is not known. The patient was given no more typhoid vaccine.

In September 1947 the patient was ambulatory. He was transferred to the general medical section of the Brooke General Hospital for evaluation of his anemia and was studied for several months. The results are presented in other sections of this report.

After the diagnosis of familial hemolytic anemia was established, and the patient's general physical condition was considered sufficiently good, splenectomy was performed on April 18, 1948 by Lt. Colonel Sanford W. French.* No accessory spleens were found. The patient tolerated the operative pro-

* Pathologic examination by Major G. B. Stansell, MC.: "The spleen measures 13 x 10 x 6.5 cm. and weighs 735 grams. Capsule is smooth and tense; on section the parenchyma bulges slightly. The color of the parenchyma is bright chartreuse and contains an increased amount of reticulum. The follicles are indistinct. Microscopic section reveals marked reticuloendothelial hyperplasia. The lymphoid follicles have large germinal centers. Many mitoses are noted in the reticulum cells in these centers. In the cytoplasm are small, irregular fragments of nuclear debris. The red pulp shows a large amount of hemosiderin pigment and great numbers of red blood cells with frequent normoblasts. No erythropagia is found. No spherocytosis is evident. Touch preparations (made at the time of surgery) reveal normal appearing lymphocytes, swollen reticulum cells, erythrocytes and occasional normoblasts. A section through a lymph node taken from the hilus of the spleen reveals reticulum hyperplasia both in the germinal centers and the lymphatic cords. The lymph channels contain some lymphocytes and large numbers of neutrophils. There is no hemosiderin, and no abnormal red cells are found."
William H. Crosby

235 cedure well. Postoperatively a small area of atelectasis developed in the base of the left lung, and gradually disappeared.

Another potentially serious complication was also noted. The patient had been given 3500 cc. of blood in preparation for surgery. His red cell count at the time of operation was 5.1 million. On the first postoperative day it was 4.43 M, hematocrit 43 per cent. He was given a transfusion on that day. The red cell count on the second day was 5.01 million, reticulocyte count 4 per cent. Thereafter the red cell count and reticulocyte count both fell, although the serum bilirubin was a little lower than it had been preoperatively (table 1). Both the reticulocyte count and the red cell count then gradually increased.

While suppression occurred in the erythroid series, the patient's platelets became greatly increased. On the third postoperative day the platelet count was 455,000 per cu.mm. Ten days later, when the patient returned to the Medical Service, the number of platelets could only be estimated. In wet reticulocyte preparations the proportion of platelets to red cells was far greater than 1:1. In addition, there were large clumps and platelets varying in diameter from 5 to 15 micra, some of them larger than leukocytes. During the next two weeks, the platelet count gradually diminished. When the patient left on his furlough in June, it was 120,000. In mid-August, while being checked daily, the platelet count dropped abruptly to 38,000, then in several days rose to normal levels. No purpura accompanied this drop in platelets.

The leukocyte count increased after splenectomy to 40,000, then fell and remained at about 15,000 per cu.mm. The differential count remained normal. Aspirated sternal marrow four months after splenectomy remained histologically unchanged from the presplenectomy pattern.

The peripheral reticulocyte count was 20 per cent, up from 8 per cent before splenectomy. The fecal urobilinogen level exceeded preoperative levels (table 1).

The patient was discharged from the Army on August 25, 1948. At that time he was asymptomatic. His red cell count was 3.5 million, he was mildly jaundiced and excreting dark urine. Urinary urobilinogen was 10 mg. per day.

Family Study

Study of the family was conducted in two periods of two days each over a ninety mile long area in Louisiana and eastern Texas. Most of the people who were approached consented to examination. In all, the blood of 35 relatives of the patient was examined. Work on the red cells was done of necessity on the spot. Serologic work was done at the Brooke General Hospital laboratories.

A reticulocyte count was used as a screening test, since persons with familial anemia may have a normal red-cell count. The major blood group was established in each person examined, and during the second trip Rh type was also determined. Physical examination was performed on those individuals showing reticulocytosis who submitted to it. After several instances of short fingers had been encountered in the course of the examinations, it was recognized that brachyphalangia was also a familial characteristic. X-rays of the hands were made of those with this abnormality who would consent. Careful inquiry was made concerning the hands of absent members of the family.

Results of this work are shown in figures 1 and 2.

With the information obtained we were able to construct a fair pattern of the disease as it affected members of this family. There was a low-grade normochromic anemia which did not vary greatly in intensity from one person to another. Slight jaundice was also present. The affected men were all heavy laborers, unaware of their jaundice and unhampered by their anemia. The spleen was enlarged in all cases. The liver was large in older people, the degree of enlargement apparently increasing with age. Bouts of abdominal pain had been experienced by most of those with anemia. The onset of this symptom was always after the age of 20.
HEREDITARY NONSPHEROCYTIC HEMOLYTIC ANEMIA

FIG. 1.—THE FAMILY (The numbers refer to those on the genealogical chart)

1. Mother of the family, age 73, stated that she had never been jaundiced. At the time of the examination she was hospitalized with a severe cystitis and basal-cell carcinoma of the face which had eroded into the orbit of the left eye. Physical examination revealed no enlargement of the liver or spleen. She was not jaundiced. Red cell counts on her clinical record were normal. She had normal hands. Reticulocytes 1.5 per cent. Blood group B.

2. Father of the family was of French extraction. He died at the age of 67 of a stroke of apoplexy. He was stated to have had "short fingers" but there was no recollection of his ever having been jaundiced. It is believed that the father had hemolytic anemia which, as in his sons, was unrecognized. It may be surmised from the blood groups of his wife and children that he was group A.

3. Woman, age 55, gave no history of jaundice. All fingers of both hands were short. Two of her sons, aged 16 and 17 on the chart, had severely deformed hands. She was group A, Rh positive. Reticulocytes 0.1 per cent; repeated four months later, 0.4 per cent.

4. Mother of our patient, age 54, gave a history of a bout of jaundice at the age of 2 years. No other severe jaundice, but she was mildly icteric at the time of examination. The area of splenic dullness was enlarged, but the spleen could not be palpated. The liver was enlarged, palpable 4 cm. below the costal margin before inhaling. All of the subject's fingers were short. She was group A, Rh positive. Reticulocytes 18 per cent. Red cell count, 3.18 million; hemoglobin 11.4 grams; hematocrit 30. Icterus index 16. Indirect bilirubin 1.7 mg. Kahn and Wassermann reactions positive. Quantitative Kahn 20 units. Her serum showed no increased fragility in hypotonic saline. Her serum was slightly positive for cold agglutinins. There were no other abnormal agglutinins.

5. Woman, age 45. For the past twelve years she had been treated for gall-bladder disease, with occasional bouts of jaundice, associated with abdominal pain. Six months before our examination, cholecystectomy was performed and a large number of stones was found in her gall bladder. There was also empyema of the gall bladder. About five months after this operation she had another episode of upper abdominal pain associated with jaundice. Her hands were normal. She was group A, Rh positive. Icterus index 20. Hematocrit 36. Reticulocytes 10 per cent. There was no increased fragility of her red cells in hypotonic saline. Oxalate fragility test was positive. There were no abnormal agglutinins in her serum. Serologic test for syphilis was negative. Two of her children who were examined were group A, had
The reason for the pain is not clear. In 2 persons the presence of gall stones had been diagnosed yet removal of the gall bladder in one case did not put an end to her bouts of abdominal pain. There was no history of leg ulcer nor, excepting the grandfather's cerebrovascular accident, had there been thrombotic or hemorrhagic incidents.

The genetic study of this large family was of interest. The anemia and deformity of the hands were transmitted as mendelian dominant characteristics. No case was normal reticulocyte counts and normal hands. Neither was jaundiced. She stated that none of her 5 children had ever been jaundiced. Her husband was group B.

6. Woman, age 40, who refused examination. She stated that she had had episodes of jaundice for the past fifteen years, associated with bouts of abdominal pain. At the time of interview her sclerae were icteric and her fingernails pale. In view of the similarity of her history to that of her sisters who were demonstrated to have hemolytic anemia it was believed that this woman had the disease.

7. Woman, age 38, who lives in California and was not available for examination. Her niece stated that she had had a severe attack of jaundice at the age of 2.0, when she was "terribly ill." She had fever and was "yellow as a pumpkin." No abdominal pain at that time. Her sister, number 5, stated: "She is jaundiced off and on all the time. She has gall bladder trouble just like I do except I don't know if she has stones." Her hands were stated to be normal. It was believed that this woman had hemolytic anemia.

8. Man, age 34, who gave no history of jaundice. Liver and spleen were not palpable. All fingers of both hands were somewhat short. Hematocrit 35. Group A, Rh positive. Reticulocytes 5 per cent. Icterus index 23. Group A, Rh positive. Reticulocytes 5 per cent. Hematocrit 35. Serologic test for syphilis negative. Van den Bergh reaction, indirect. No normal agglutinins. Four of his 5 children were examined. The oldest child was age 5 years. No deformity of their hands was noted. None had an increased reticulocyte count.

9. A twin of 8 was said to have short fingers and never to have been jaundiced. He was not examined.

10. The brother of our patient, age 34, had several spells of "acute indigestion" several years before our examination. He had at that time severe upper abdominal pain and was told that x-ray examinations showed gall stones. The fingers of both hands were short. The liver edge was down to 3 to 4 cm. below the costal margin on inspiration. His spleen was easily palpable. He was group A, Rh negative. Red cell count 3.5 million, hematocrit 37, hemoglobin 10.4 grams, reticulocytes, 7.6 per cent. Fragility of red cells in hypotonic saline was not increased. Oxalate fragility test was strongly positive. Icterus index 20. Van den Bergh indirect. No abnormal agglutinins were detected in his serum. Serologic test reaction for syphilis was doubtful. He was not aware that he was jaundiced or anemic.

11. Sister of our patient, age 25, had a congenital dislocation of her left hip. All fingers of both hands were short. There was no history of jaundice. Blood group 0, Rh positive. No reticulocytes were seen. Icterus index was less than 5. Hematocrit 45. There was no increased fragility in hypotonic saline. Osmotic fragility test was normal.

12. Our patient.

13. Sister of our patient, age 20, stated that she had always been pale but has noted a mild jaundice occasionally for the past three years. There was no history of abdominal pain. She was a pale, slightly built girl and there seemed to be a slight icteric tinge to her sclerae. Her hands were deformed and looked like those of her mother (x-ray 4). Her spleen was enlarged and quite easily palpable. It was the largest spleen in the family. Her liver was not palpable. Blood group A. Reticulocytes 10 per cent. Hematocrit 29.5. Icterus index 11.3. There were no abnormal hemolysins or agglutinins. Serologic test for syphilis was positive.


15. Girl, age 4. A healthy-looking girl though somewhat pale. Spleen was thought to be palpable, but there was some doubt as the child resisted the examination. Her hands were normal. Blood group A, Rh positive. Reticulocytes 3 per cent. Most of the reticulocytes contained very little reticulum.

16. Man, age 23, stated to have short fingers with hands that looked like his mother's. He also had abnormal feet with a hump on the instep and several short toes. He was the only person in the family with deformed feet.

17. Man, age 20, with severely deformed hands. Group A, Rh positive, reticulocytes 0.6 per cent.
Fig. 1.—Abnormality of the Hands (The numbers correspond with those in the genealogical chart, fig. 1) (Figure legend continued on facing page)
found where an unaffected person had transmitted either trait to his offspring. Application of the chi-square formula to the siblings of the patient and of his mother confirmed the mendelian dominant pattern of inheritance of both the anemia and the brachyphalangia. Though these abnormalities did occur in the same person, they also occurred independently and were not genetically linked. Neither condition was sex linked.

It appeared that the anemia was somehow associated with blood group A. Each person with demonstrated anemia was of that group. Even the father of the family, whom we must assume to have had hemolytic anemia, must also have been blood group A. (It is the only group, with his wife Group B, which could account for the children's blood groups.) Genetic linkage cannot account for the association of Group A and anemia. The degree of crossing-over required to explain the association on such a basis is not reasonable.

Our patient has three half-siblings, children of his father and of another wife. These siblings were found to be free of both anemia and brachyphalangia.

The Abnormality of the Hands.

The hands of the affected persons had a pawlike appearance which was due to a disproportion between the palm and the fingers. The palms were of normal size and normally proportioned but the fingers and the thumbs were short. Except for the hands of the boy, 17, all affected hands were normally functioning and strong.

Fig. 1.—Cont'd
3. The fingers of the hands of this woman are abnormally short, especially the first and second fingers. There is ulnar deviation of the second finger. The second phalanges show more shortening than the other bones.
4. The hands of this woman show a remarkable shortening of the first and second fingers with ulnar deviation of both. The third and fourth fingers are also somewhat shorter than would be expected in a normally proportioned hand. The metacarpals are shortened, especially those on the ulnar side, with some compensatory displacement of the carpals.
8. The fingers of this hand are all short. The length of the fingers compared with one another is approximately normal.
10. The fingers and thumb of this man's hand are shortened. Again the shortness is due primarily to the second phalanges. The shortness of the first finger on the left hand as compared with that on the right is due to shortness of the metacarpal.
11. All fingers of both hands are remarkably shortened due to extremely small second phalanges. The length of the fingers compared with one another is also abnormal.
12. The hands of our patient, showing none of the bony involvement seen in other members of his family. This film is included for comparison.
14. This 7 year old boy shows a shortening of his fingers, due especially to involvement of the second phalanges. The second phalanges of the first fingers of both hands are entirely missing. It is interesting to compare his x-rays with those of his mother, 11, and his grandmother, 4. Through these three generations the involvement of the hands becomes progressively more severe.
17. The hands of this 21 year old man are the most seriously affected of any in the family. There is severe shortening of the first two fingers of each hand, especially of the second phalanges in these fingers and also of the first phalanx in the second finger of each hand. There is fusion of the first and second phalanges in the little finger. This fusion is at a 90 degree angle so that the second phalanges on these x-rays are foreshortened. The third finger of each hand is almost normally proportioned.
On x-ray examination, the shortness of the fingers was shown to be due to shortness of the phalanges, especially of the second phalanx, together with some slight shortening of the metacarpals. Generally the first two fingers were most seriously involved. In the palm, the first metacarpal was often a little longer in proportion than the other four. In some of the hands the shortening of the latter three metacarpals was somewhat compensated by a "piling up" of the carpals (fig. 2.).

A narrow palate with protruding upper incisors was noted in many members of this family. This anomaly was not explored further. Even tactful questions on the point, addressed to members of the family who had artificial dentures, caused such embarrassment and hostility that it seemed fruitless to pursue the inquiry.

Hereditary bony dysplasia has been described in association with familial spherocytic hemolytic anemia. These hereditary defects associated with anemia should not be confused with the thickening of the skull and thinning of the cortex of long bones which are seen in sickle cell anemia and severe Mediterranean (Cooley's) anemia. Such bony changes are probably the end result of bone marrow hyperplasia. They are also found occasionally in hereditary spherocytosis.

The Anemia

The anemia in this family was usually not severe, although, as can be seen from the low counts of our patient during his acute arthritic episodes, it might become so. The red cells on stained spreads appeared normally filled with hemoglobin. Morphologically, the cells were normal biconcave disks (fig. 3). A very rare spherocyte and target cell were found. There was an occasional oval cell and "tailed" erythrocyte. On several examinations of the patient's blood a nucleated red cell was found; after splenectomy there was an occasional metamyelocyte. A typical example of the cellular characteristics before splenectomy was the following (September 5, 1947): R.B.C. 3.18 million, hemoglobin 12 grams, hematocrit 32 per cent, mean corpuscular volume 101 cubic micra, mean corpuscular hemoglobin 3.87; mean corpuscular hemoglobin concentration 37.5 per cent; mean cell diameter 7.76 micra. Reticulocyte count at this time was 8 per cent. The Price-Jones curve of the patient before splenectomy is shown in figure 4. In the patient and other affected members of his family the following procedures were negative: test for abnormal hemolysins and agglutinins including the Coombs antiglobulin test for incomplete antibodies, tests for cold agglutinins, cold hemolysins (Donath-Landsteiner), the Ham acid fragility test for paroxysmal nocturnal hemoglobinuria.

Recently, siderocytes, red blood cells with iron-staining inclusion bodies, have been described as occurring after splenectomy, especially in cases of acquired hemolytic anemia. They have been noted, too, in familial spherocytic anemia. In our patient before splenectomy the iron stain showed less than 0.1 per cent siderocytes in the peripheral blood. In the bone marrow, 8 per cent of mature erythrocytes had iron-staining inclusions. Inclusions were also seen in erythroblasts which contained hemoglobin but these were not included in the count. The gradual increase in siderocytes after splenectomy is shown in table 1. Four months after splenectomy the siderocyte count in the peripheral blood had risen.
Fig. 3.—(A) Peripheral blood stained with Wright’s stain (X 350), showing cells normally filled with hemoglobin. Several elliptical and "tear-drop" cells are demonstrated. (B) Fresh unmodified blood (X 700), showing normal rouleaux and normal cell thickness. (C) Wet reticulocyte preparation, showing normal biconcavity of the red cells. The four crumpled cells are reticulocytes. (D) Prussian blue stain, showing a high percentage of siderocytes, four months after splenectomy.
to 45 per cent and in the bone marrow to 56 per cent. We have noted this gradual increase in siderocytes to the same high levels in hereditary spherocytosis after splenectomy.

Effect of Splenectomy. Following splenectomy in our patient, the red-cell characteristics altered somewhat. The average size of the cell became larger, due perhaps to the reticulocytes, which increased from 8 to 20 per cent. Four months after splenectomy, when attrition had removed all of the blood which was transfused into the patient at the time of operation, the mean cell diameter had increased from 7.76 micra to 8.06 micra. The other cell characteristics were as follows: RBC, 3.47 M; hemoglobin, 13 grams; hematocrit, 38 per cent; mean corpuscular volume, 110 cubic micra; mean corpuscular hemoglobin, 37.5 y/µ; mean corpuscular hemoglobin concentration 34 per cent. There was a shift to the right in the Price-Jones curve (fig. 4). The appearance of siderocytes after splenectomy has been discussed. The effect of splenectomy on the hemolytic process is discussed in the following section on Hemoglobin Metabolism.

Studies of Hemoglobin Metabolism

When hemoglobin is destroyed, the porphyrin groups of the hemoglobin molecule are transformed into bilirubin which is excreted by the liver. In the bowel the bilirubin is transformed by bacterial action to urobilinogen. These are quantitative reactions and the total fecal urobilinogen is therefore an accurate index of blood destruction. In normal adults, the daily average is approximately 150 mg. (range 50-250 mg.). Values in excess of this are evidence of excessive hemolysis.

When hemoglobin is formed in the bone marrow, coproporphyrin I is formed
as an apparently useless by-product which is excreted in the urine. The total daily excretion of coproporphyrin in a normal individual is less than 100 gamma. Urinary coproporphyrin is increased in conditions other than increased blood regeneration; but in the absence of these conditions, coproporphyrin excretion is believed to be an index of the amount of hemoglobin formed.24

Our patient's daily excretion of fecal urobilinogen and of urinary coproporphyrin was repeatedly measured, one time for a period of fifty-one consecutive days. Urinary coproporphyrin excretion was excessive, averaging about 400 gamma per day. Uroporphyrin was never found, though repeatedly sought. Fecal urobilinogen excretion was erratic, but always very high. For several days there would be 500 to 1000 mg. of urobilinogen excreted, then one day there would be 2000 or 4000 mg. with a subsequent return to the lower level. These wide swings were not reflected by changes in the blood count or in coproporphyrin excretion and may have been due to alterations in the hepatic clearance of bilirubin from the blood.

During this period of observation the patient was submitted to several sorts of stress to determine their effect on his hemolytic process. 

Epinephrin has been noted to impede hemolysis in some circumstances.14, 18, 24 In our patient, 0.5 cc. of epinephrin given subcutaneously every four hours for four days had no effect on his red cell count, urinary coproporphyrin or fecal urobilinogen excretion.

Mild alkalosis induced by feeding 4 grams of sodium bicarbonate every four hours for four days was also ineffective.

Mild acidosis (6 grams of ammonium chloride every four hours for four days) had no effect on the fecal urobilinogen but produced a marked fall of urinary coproporphyrin excretion to less than 50 gamma per day. The phenomena suggested bone marrow suppression. After a brief rise there was also a fall in the reticulocyte count to the lowest level observed in this patient before splenectomy (4 per cent). The effect was produced on two occasions. The fall and recovery of coproporphyrin were gradual. It may have been due to acidosis or perhaps to an increase in the "nitrogenous waste" from the ammonium radical. One is reminded of the anemia resulting from bone marrow suppression which occurs in uremia.

Effect of Transfusion and Splenectomy. The patient was given 2500 cc. of whole blood at the time of splenectomy. The effect of this large transfusion on his hemoglobin metabolism was obscured by the simultaneous splenectomy. However, four months later when all of the transfused blood was gone the hemolytic process was intensified, as indicated by an increase in the reticulocyte count and in the fecal urobilinogen values (table 1.). Immediately following splenectomy there was a temporary drop in the fecal urobilinogen and the urinary coproporphyrin excretion, but during the subsequent four months both slowly increased as did the reticulocyte count. It seems probable that the large transfusion caused this temporary slowing of the hemolytic-hematopoietic process. It reduced the demand on the bone marrow, thus lowering the coproporphyrin excretion and reticulocyte count; it also reduced the volume of the patient's own fragile cells in his circulation, thus reducing total hemolysis per day and causing a lower urobilinogen excretion.

Following splenectomy and just prior to his discharge, the patient's urine was
tested for porphobilinogen and was found to be positive. The finding was confirmed on several subsequent occasions. Porphobilinogen is an abnormal urinary pigment which has been stated to occur only in acute idiopathic porphyria. Assuming the specificity of this pigment, its presence in the urine of our patient poses a problem. Does his disease and that of his family represent an association of porphyria and hemolytic anemia or is the hemolytic anemia merely a phase of a larger syndrome including disorders of hemoglobin and porphyrin?

Acute idiopathic porphyria, an hereditary disease, is manifested clinically by abdominal symptoms and nervous system changes. In our patient and his family

<table>
<thead>
<tr>
<th>Date</th>
<th>R.B.C.</th>
<th>Hemoglobin—grams</th>
<th>Hematocrit</th>
<th>Reticulocytes per cent</th>
<th>Siderocytes per cent</th>
<th>W.B.C.</th>
<th>Thrombocytes per cu. mm.</th>
<th>Serum Bilirubin mg./100 cc</th>
<th>Fecal Urobilinogen mg/per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 Apr. 46</td>
<td>2.6</td>
<td>8</td>
<td>25</td>
<td>7.6</td>
<td>0.1</td>
<td>7000</td>
<td>112,000</td>
<td>2.6</td>
<td>1150</td>
</tr>
<tr>
<td>1 Sept. 46</td>
<td>2.1</td>
<td>10</td>
<td>20</td>
<td>6.0</td>
<td>0.1</td>
<td>11000</td>
<td>112,000</td>
<td>2.6</td>
<td>1150</td>
</tr>
<tr>
<td>1 Sept. 47</td>
<td>3.18</td>
<td>12</td>
<td>32</td>
<td>8.0</td>
<td>0.1</td>
<td>7600</td>
<td>9400</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>18 Feb. 48</td>
<td>3.94</td>
<td>11.5</td>
<td>35</td>
<td>9.3</td>
<td>0.1</td>
<td>9400</td>
<td>8350</td>
<td>2.6</td>
<td>1150</td>
</tr>
<tr>
<td>19 Apr. 48</td>
<td>3.9</td>
<td>12.5</td>
<td>36</td>
<td>9.6</td>
<td>0.1</td>
<td>8350</td>
<td>112,000</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>28 Apr. 48</td>
<td>5.1</td>
<td>14.3</td>
<td>45</td>
<td>2.0</td>
<td>0.1</td>
<td>9900</td>
<td>112,000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>29 Apr. 48</td>
<td>4.43</td>
<td>13.5</td>
<td>43</td>
<td>2.0</td>
<td>0.1</td>
<td>33000</td>
<td>112,000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>1 May 48</td>
<td>5.01</td>
<td>14.8</td>
<td>45</td>
<td>4.0</td>
<td>0.1</td>
<td>40600</td>
<td>455,000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>3 May 48</td>
<td>3.56</td>
<td>12.5</td>
<td>37</td>
<td>2.0</td>
<td>0.1</td>
<td>40600</td>
<td>455,000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>5 May 48</td>
<td>3.56</td>
<td>12.5</td>
<td>37</td>
<td>2.0</td>
<td>0.1</td>
<td>40600</td>
<td>455,000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>7 May 48</td>
<td>4.09</td>
<td>13.5</td>
<td>39</td>
<td>2.7</td>
<td>0.1</td>
<td>40600</td>
<td>455,000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>8 May 48</td>
<td>4.77</td>
<td>13.5</td>
<td>39</td>
<td>2.7</td>
<td>0.1</td>
<td>40600</td>
<td>455,000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>10 May 48</td>
<td>4.67</td>
<td>13.5</td>
<td>39</td>
<td>2.7</td>
<td>0.1</td>
<td>40600</td>
<td>455,000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>14 May 48</td>
<td>4.88</td>
<td>13.5</td>
<td>39</td>
<td>2.7</td>
<td>0.1</td>
<td>40600</td>
<td>455,000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>15 May 48</td>
<td>4.32</td>
<td>13.5</td>
<td>39</td>
<td>2.7</td>
<td>0.1</td>
<td>40600</td>
<td>455,000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>2 July 48</td>
<td>4.31</td>
<td>13.5</td>
<td>39</td>
<td>2.7</td>
<td>0.1</td>
<td>40600</td>
<td>455,000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>13 July 48</td>
<td>4.01</td>
<td>13.5</td>
<td>39</td>
<td>2.7</td>
<td>0.1</td>
<td>40600</td>
<td>455,000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>17 July 48</td>
<td>4.2</td>
<td>13.5</td>
<td>39</td>
<td>2.7</td>
<td>0.1</td>
<td>40600</td>
<td>455,000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>20 Aug. 48</td>
<td>3.69</td>
<td>13.5</td>
<td>39</td>
<td>2.7</td>
<td>0.1</td>
<td>40600</td>
<td>455,000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>21 Aug. 48</td>
<td>3.57</td>
<td>13.5</td>
<td>39</td>
<td>2.7</td>
<td>0.1</td>
<td>40600</td>
<td>455,000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>27 Dec. 48</td>
<td>3.3</td>
<td>13.5</td>
<td>39</td>
<td>2.7</td>
<td>0.1</td>
<td>40600</td>
<td>455,000</td>
<td>1.2</td>
<td></td>
</tr>
</tbody>
</table>

there was no evidence of nervous system disease, but the bouts of severe abdominal pain which occurred in several of the family have not been explained.

It is well known that increased urinary porphyrins are associated with various anemias. In hemolytic anemia and in pernicious anemia, excretion of coproporphyrin I is increased. In lead poisoning with its associated anemia and in some cases of aplastic anemia the excretion of coproporphyrin III is increased. These changes are believed to be associated with abnormalities of hemoglobin formation and do not represent a primary disturbance of porphyrin metabolism. This is porphyrinuria, not porphyria. Uroporphyrin and porphobilinogen are not excreted. On the other hand, cases of true porphyria may show an anemia which is sometimes quite severe. The nature of this anemia has not been extensively studied.
Waldenström states that in cases of porphyria the usual symptoms of hemolysis seem always to be absent. Hemoglobin by its derivation is intrinsically bound with the metabolism of the porphyrins. As more is learned of these compounds the group of diseases characterized by pathologic alterations of the metabolism of hemoglobin and other porphyrins will become clearly defined, and diseases now recognized but poorly understood will be found to fit into the scheme. It is possible that the disease which affects our patient and his family will find a place not only on the spectrum of blood dyscrasias, but also among the ill defined disorders of porphyrin metabolism.

Studies of Red Cell Fragility and Survival

Osmotic Fragility. This study was repeatedly performed by the usual method of placing drops of blood or of packed red blood cells in sodium chloride solutions of varying hypotonicity. Results showed the patient's cells to have a normal resistance. Indeed, on several occasions the resistance was slightly greater than that of the control. The results of a more elaborate procedure are shown in figure 5.
Again, the patient showed normal resistance. Three other affected persons in the patient's family were tested and showed normal osmotic resistance.

**Mechanical Fragility.** A 10 per cent suspension of washed red cells was prepared in three different media: isotonic sodium chloride solution, serum of the blood from which the cells were taken, 20 per cent bovine albumin. Each cell suspension was divided among a series of 20-cc. culture tubes, 1 cc. of the suspension together with three glass beads being placed in each tube. The tubes were shaken on a Kahn shaker at room temperature. At the end of each hour one tube of each sort was removed, the cell suspension centrifuged and the supernatant fluid removed and chemically analyzed for hemoglobin. Controls which were not shaken showed no hemolysis. The results are shown in figure 6.

Another modification of the mechanical fragility test was the following: The cells from gently centrifuged and heparinized blood were drawn up to fill red cell counting pipets. The pipets were shaken on a mechanical shaker for three hours. The cells from each pipet were then discharged into a small test tube. The pipet was refilled with isotonic saline solution and the saline discharged into the same test tube. Cells and saline were mixed and centrifuged. The supernatant saline was then analyzed for hemoglobin. Results: The patient showed 16.2 mg. per 100 cc.; normal control showed 19.4 mg.; spherocytic control showed 43 mg. These values
are averages of several pipets of each sort of blood. There was very little difference
(2 to 3 mg.) between the pipets of any subject.

"Vacuum" Fragility. The plasma was removed from gently centrifuged hepar-
inized blood and used to rinse a clean, small Van Slyke gas analysis apparatus.
The cells from the blood were then drawn into the pipet, the pipet was closed and
the mercury slowly lowered to the middle of the bulb and locked there for ten
minutes. The cells were then expelled into a graduated centrifuged tube, and iso-
tonic saline solution was added to double the volume. Saline and cells were mixed
and centrifuged. The supernatant saline was removed and chemically analyzed for
hemoglobin. Results: Patient showed 4.8 mg. per 100 cc., normal control 4.8 mg.,
spherocytic control 12.2 mg.

<table>
<thead>
<tr>
<th>Tube</th>
<th>Cells</th>
<th>0.05 cc.</th>
<th>0.05 cc.</th>
<th>0.05 cc.</th>
<th>Result: Mg. Per</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1/3N HCl</td>
<td>2/3N HCl</td>
<td>1/3N NaOH</td>
<td>100 cc. Hemog!obin</td>
</tr>
<tr>
<td>1</td>
<td>P</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5.8</td>
</tr>
<tr>
<td>2</td>
<td>P</td>
<td>x</td>
<td>-</td>
<td>-</td>
<td>9.6</td>
</tr>
<tr>
<td>3</td>
<td>P</td>
<td>-</td>
<td>x</td>
<td>-</td>
<td>63.4</td>
</tr>
<tr>
<td>4</td>
<td>P</td>
<td>-</td>
<td>-</td>
<td>x</td>
<td>10.0</td>
</tr>
<tr>
<td>5</td>
<td>C</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.6</td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>x</td>
<td>-</td>
<td>-</td>
<td>4.8</td>
</tr>
<tr>
<td>7</td>
<td>C</td>
<td>-</td>
<td>x</td>
<td>-</td>
<td>13.8</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>-</td>
<td>-</td>
<td>x</td>
<td>7.2</td>
</tr>
<tr>
<td>9</td>
<td>P</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.6</td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.1</td>
</tr>
</tbody>
</table>

In each tube was placed 1 cc. of fresh plasma (heparin) from the normal group-compatible
control. The cells were washed three times in isotonic sodium chloride solution. Red cells were
added to each tube to make a 10 per cent suspension. To assure uniformity, the HCl and NaOH
were mixed with the plasma in 2 cc. aliquots and then divided. The tubes were overlaid with mineral
oil and incubated fifteen hours at 40 C. A hemoglobin value of 25 mg. per 100 cc. represents the
lysis of approximately 1 per cent of the cells in a 10 per cent suspension. Tubes 9 and 10 are plasma
controls.

"Acid" and "Alkali" Fragility.* By addition of small amounts of dilute acid and
alkali, the pH of serum in vitro was altered. Incubation of the patient's red cells
in these sera showed increased fragility as compared with normal controls (table
2.). The sensitivity to acidity of the red cells in paroxysmal nocturnal hemoglo-
binuria is not analogous. The hemolytic reaction in PNH is very rapid, occurring
in a matter of minutes; the hemolytic reaction is blocked by oxalate. In the case
reported here, oxalate increased the amount of hemolysis.

"Oxalate" Fragility. Heparinized blood in 2-cc. aliquots was placed in small
tubes containing 0.1 cc. of 2 per cent potassium oxalate. This was overlaid with
mineral oil and after the blood and oxalate were mixed by twirling, the tubes

* Fragility to acid and alkali has been reported in patients with increased osmotic fragility.11 The
technic used was addition of acid or base to unbuffered isotonic sodium chloride solution. In such a solu-
tion prepared with hydrochloric acid, our patient's cells showed the same resistance as normal controls.
were incubated for twenty-four hours at 37 C without resuspending the cells. Heparinized blood without oxalate was treated in the same way. At the end of the incubation the cells were gently resuspended and immediately centrifuged. The plasma was removed and chemically analyzed for hemoglobin. The results are shown below:

<table>
<thead>
<tr>
<th>Patient*</th>
<th>Oxalated Blood</th>
<th>Heparinized Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>39.8</td>
<td>21.4</td>
</tr>
<tr>
<td>Normal control</td>
<td>11.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Spherocytic control</td>
<td>256</td>
<td>84</td>
</tr>
</tbody>
</table>

Two other affected persons in the patient’s family gave similar results. Unaffected persons in the patient’s family gave normal results.

**Table 3. Cross Incubation**

<table>
<thead>
<tr>
<th>Tube</th>
<th>Fresh Plasma 1 cc.</th>
<th>Washed Cells 0.5 cc.</th>
<th>Result: Hemoglobin mg./100 cc.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td>1</td>
<td>C</td>
<td>C</td>
<td>9.4</td>
</tr>
<tr>
<td>2</td>
<td>P</td>
<td>C</td>
<td>9.8</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>P</td>
<td>38.0</td>
</tr>
<tr>
<td>4</td>
<td>P</td>
<td>P</td>
<td>38.0</td>
</tr>
<tr>
<td>5</td>
<td>C</td>
<td>—</td>
<td>3.8</td>
</tr>
<tr>
<td>6</td>
<td>P</td>
<td>—</td>
<td>2.8</td>
</tr>
</tbody>
</table>

P: Patient. C: Group-Compatible Control. Fresh plasma (heparin) was used.
Cells were washed three times. Tubes were overlaid with mineral oil. (1) Incubated at 40 C. for fourteen hours. (2) Incubated at 40 C. for twenty-eight hours.

**Discussion**

In the tests which involved mechanical, vacuum and osmotic injury the cells of the patient showed normal resistance. The single exception was their behavior when shaken with beads in isotonic sodium chloride solution. We have no explanation for this seeming aberration.

The fragility tests which involved incubation showed uniformly an increased sensitivity of our patient’s cells as compared with those of normal controls, but compared with spherocytic controls the sensitivity was not so great.

Cross incubation experiments were done (table 3) which showed the patient’s cells to be equally sensitive in his own serum or that of a group-compatible control. Preliminary heating of the serum for ten minutes at 52 C reduced the hemolytic potency about 50 per cent (table 4). It could not be reactivated by the addition of guinea pig complement. This suggests the presence of a heat-labile hemolytic factor present in serum to which the patient’s red cells were sensitive. Such a

* These values seem small, but the differences were real and reproducible. In over 100 normal controls we have found no value in excess of 25 mg. per 100 cc.
### Table 4.—The Inactivation of Serum by Heat

<table>
<thead>
<tr>
<th>Tube</th>
<th>Fresh Plasma 1 cc.</th>
<th>Deactivated Plasma 1 cc.</th>
<th>Washed Cells 1 cc.</th>
<th>Complement 0.05 cc.</th>
<th>Result: Hemoglobin mg./100 cc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P</td>
<td>—</td>
<td>P</td>
<td>—</td>
<td>33.8</td>
</tr>
<tr>
<td>2</td>
<td>P</td>
<td>—</td>
<td>P</td>
<td>x</td>
<td>53.2</td>
</tr>
<tr>
<td>3</td>
<td>—</td>
<td>P</td>
<td>P</td>
<td>—</td>
<td>16.6</td>
</tr>
<tr>
<td>4</td>
<td>—</td>
<td>P</td>
<td>P</td>
<td>x</td>
<td>13.8</td>
</tr>
<tr>
<td>5</td>
<td>Plasma control</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2.0</td>
</tr>
</tbody>
</table>

P: Patient. Plasma (heparin) was deactivated by heat in 10 minutes at 52°C. Cells were washed three times. Complement was freshly reconstituted, lyophilized guinea pig serum. Tubes were overlaid with mineral oil and incubated thirteen hours at 40°C.

**Fig. 7.—Cross Survival Transfusion.** (A, Patients' cells in AB, Rh— subject; B, O, Rh— cells in patient.) The patient's cells when transfused into a normal subject were gone from the circulating blood in twelve days. Extension of curve B shows that normal cells transfused into the patient survive normally, approximately 110 days.
reaction rather than a "structural" weakness may be the basis of the short survival
time the red cells in this disease. We have obtained similar results with these
procedures in hereditary spherocytosis.

Survival transfusions were performed with our patient and a normal volunteer.
The results are shown in figure 7. The patient's cells survived only twelve days
when transfused into a normal, compatible recipient. When normal, compatible
cells were transfused into the patient, attrition occurred at a normal rate. This
agrees with the results of the cross incubation experiments; the fault resides in the
red cell. The nature of the defect is obscure.

Differential Diagnosis

Sickle-cell anemia was excluded by the absence of the sickling trait in the pa-
tient and 35 of his relatives whose bloods were examined.

Mediterranean anemia is a hypochromic disease which is not especially hemolytic
except in severe cases. In the same family, affected members often vary considerably
in the severity of their disease. In our patient before splenectomy and in his family
there were no target cells or stippled cells.

In recent years there have been described several other forms of hereditary
anemia which are refractory to treatment by liver, iron, vitamins or splenectomy.
Cooley and later Rundles and Falls described an hereditary sex-linked anemia,
the hematologic features of which are more comparable to those of severe Medi-
terranean anemia than to any other recognized entity. . . . Evidence of increased
red cell hemolysis . . . were minimal or absent." Haden has described two
families having "a new type of hereditary hemolytic jaundice without spherocy-
tosis." In each family the blood had a remarkable characteristic which distin-
guished it. The first family showed a powerful autohemolytic mechanism which
could be demonstrated in vitro; the second family showed basophilic stippling
of the red cells of affected members even without splenectomy. Mills and Lucia
have described a familial siderocytic anemia which resembles that found in the
families of Rundles and Falls. This anemia, too, was not hemolytic, but severely
hypochromic. It was characterized by iron-staining inclusions in the red cells after
splenectomy. The quantity of iron-staining matter in each cell was greater than
was found in our patient and in cases of hereditary spherocytosis.

Acquired hemolytic anemia may present a picture very similar to that described
in our patient. It has been shown that in most cases of acquired hemolytic anemia, an
antibody can be demonstrated using either the Coombs antiglobulin technic or
bovine albumin. In the affected members of this family who were tested by both
methods no antibodies were demonstrated. Acquired hemolytic anemia may occur
without a demonstrable antibody. Normal red blood cells transfused into such cases
show a shortened survival time. In our patient the survival of transfused blood was
normal (fig. 7). Family study is another differential factor. It is negative in
acquired hemolytic anemia with or without demonstrable antibody. Another

...
a positive family study is conclusive. In the case of this family the results of questioning the patient and even correspondence with his mother concerning a history of anemia or jaundice were repeatedly negative. Not until Captain Harry J. Sacks, passing through Louisiana, visited their homes and kindly obtained for us samples of blood was the familial nature of the anemia established.

Hereditary Spherocytosis: The differential diagnosis would seem to be easily made on the presence of spherocytes and the results of the osmotic fragility test. But familial hemolytic spherocytic anemia does occasionally show itself in an individual who has no spherocytes. Gaensslen reports normal hypotonic fragility in 10 per cent of affected persons in the families he studied. Cade reports a patient with a hemolytic anemia and normal erythrocytic osmotic resistance who had two anemic daughters whose red cells showed decreased resistance. We have had an

Table 5.—Comparative Studies of Hereditary Nonspherocytic Hemolytic Anemia and Hereditary Spherocytosis

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherocytosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmotic Fragility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical Fragility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fecal urobilinogen (mg. per day)</td>
<td>1000</td>
<td>400</td>
<td>500</td>
</tr>
<tr>
<td>Reticulocytes per cent</td>
<td>9</td>
<td>4.5</td>
<td>6</td>
</tr>
<tr>
<td>Hyperplastic bone marrow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythrocyte count (millions)</td>
<td>3.7</td>
<td>4.1</td>
<td>4.7</td>
</tr>
<tr>
<td>Red-Cell Survival in normal recipient</td>
<td>12 days</td>
<td>18 days</td>
<td>Not done</td>
</tr>
<tr>
<td>Circulating antibodies (Coombs technique)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure by splenectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Case 1: The patient described in this report.
Case 2: Hemolytic patient without spherocytes from a family of hereditary spherocytosis.
Case 3: Typical hereditary spherocytosis.
* Repeated determinations over a period of six months in three different laboratories.

opportunity to study such an individual. He was a young flight officer with hemolytic anemia without spherocytosis whose infant son had typical spherocytic anemia. We also studied a third patient, a soldier with classic familial spherocytosis. The 3 adult patients were studied simultaneously for several months (table 5). All, including the son of the officer, were subjected to splenectomy. Only our patient from the nonspherocytic family failed of cure.

It is of interest that in the artificial in vitro fragility tests the red cells of the patient from the nonspherocytic family were more resistant than the cells of patients from spherocytic families. On the other hand, within the circulatory system these cells were the more fragile. This is shown by the higher reticulocyte count and high daily fecal urobilinogen excretion (table 5) indicating a faster turnover of red blood cells. These cells also showed a shorter survival time in the transfusion experiments. This difference of fragility in vitro and in vivo, together with the failure of splenectomy, suggests a profound difference in the hemolytic mech-
HEREDITARY NONSPHEROCYTIC HEMOLYTIC ANEMIA

Anism of this nonspherocytic hemolytic anemia and the commoner spherocytic type.

SUMMARY AND CONCLUSIONS

1. An hereditary hemolytic anemia is described which is normocytic and normochromic, transmitted as a mendelian dominant and not cured by splenectomy. In the family studied, the anemia was associated but not genetically linked with brachyphalangia. Acute idiopathic porphyria may also have been associated. All anemic members were of blood group A.

2. Neither the degree of anemia nor the rate of hemolysis was favorably influenced by splenectomy.

3. Various studies of erythrocyte fragility and hemoglobin metabolism are presented.

4. Although the red cells in this anemia were more resistant to fragility tests in vitro than the red cells of hereditary spherocytosis, they were more rapidly destroyed in vivo.

5. The disease is differentiated from other hereditary and hemolytic anemias. Of the hereditary anemias, this disease seems most closely to resemble hereditary spherocytosis. Yet the differences of cellular survival in vivo and in vitro and the failure of splenectomy in hereditary nonspherocytic hemolytic anemia suggest a difference in the hemolytic mechanism.

6. The demonstration of porphobilinogen in this patient suggests a possible relationship of this hereditary hemolytic anemia to hereditary porphyria.

ACKNOWLEDGMENTS

This has been the work of many hands. I especially wish to express my gratitude to Major Donald M. Goss, MSC, Miss Addelia Peterson, M.T. and Mrs. Jane C. Neff, B.S. of the Chemistry Section, Fourth Army Area Laboratory, for the many chemical determinations which were done; to Major Joseph H. Akeroyd, MSC, and Miss Constance Pollack for the tests for abnormal agglutinins, the mechanical fragility test and the cross survival transfusion studies; to Mrs. Joy Cornell for the osmotic fragility tests; to Mr. Philip Lund for many blood counts, to Dr. S. R. Henry of Crowley, Louisiana, for the x-rays of the hands of this family; and to Colonel John G. Knauer, MC, Chief of Medical Service, Brooke General Hospital for his advice, encouragement and help throughout the course of this work. Dr. Marvin Bloom suggested the diagnosis of hereditary porphyria in this case, and Dr. William Dameshek brought to my attention the significance of this finding in association with hemolytic anemia. I wish also to express my thanks to Dr. Dameshek for his valued advice in the preparation of the manuscript.

All photographs were made at the Photographic Laboratory of the Pathology Service, Brooke General Hospital.

REFERENCES

WILLIAM H. CROSBY

HEREDITARY NONSPHEROCYTIC HEMOLYTIC ANEMIA

WILLIAM H. CROSBY, MAJOR

Updated information and services can be found at:
http://www.bloodjournal.org/content/5/3/233.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