HEREDITARY SPHEROCYTIC ANEMIA IN THE NEGRO

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HEREDITARY spherocytic anemia is a condition found rarely in Negroes. Wintrobe has reported one case in a Negro woman of undoubtedly mixed blood (1946) and in the literature we have found only six references to the incidence of this disease in Negroes, involving five families. Smith and Drake in 1944 reported a typical case in a 22 year old Negro who was successfully treated with splenectomy. Scherer and Cecil in 1945 reported the case of a 14 year old, dark-skinned Negro girl who received a good result following splenectomy; hematologic studies on 8 other members of the family revealed microspherocytes in 2 additional persons on the mother’s side, but none in the other subjects. In 1946, Stragnell and Smith reported the disease in a 21 year old Negro. Family studies revealed latent hemolytic anemia in 2 sisters, but no evidence of the disease in another sister, a brother, the mother, and a paternal aunt. In the same article they reported another case presumed to be congenital hemolytic anemia in a mulatto woman with a six-year history of jaundice, for whom splenectomy was performed with good results. This was the only such case that had been seen in twenty years in the Presbyterian Hospital in New York City, while during the same period 79 cases of the disease had been seen in white people.

Three patients in a family in South Carolina were reported in 1947 by Goodman and Cates. These were all females and in one a splenectomy was followed by good results. They noticed that all members showed strong Negroid characteristics with nothing to suggest a white ancestry and they pointed out that the previously reported cases showed an incidence of the disease of 7 females to one male.

In 1948, McCormack and Simon presented a case of congenital hemolytic icterus in a Negro woman, complicated by gall bladder disease and corrected by splenectomy. This patient was a maternal aunt of the patient previously reported by Scherer and Cecil. In 1949, Churg and Rosenbaum reported 3 cases in Negro females, a mother and her 2 daughters, ages 9 and 5. There were 6 other children in the family, none of whom was affected. This family was reported as typically Negroid as to facial features and skin color.

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In summary, then, there have been reported only 14 cases of hereditary spherocytic anemia in Negroes in the past six years, not including several so-called 'latent' cases, and only 2 of these were males. Sickle cell tests were negative in all reported families. One male and 4 females were relieved of symptoms by splenectomy and no unsuccessful results following splenectomy have been reported.

We have recently had the opportunity to study 12 persons representing four generations of a Negro family, 2 of whom appear to be typical cases of hereditary spherocytic anemia.

**CASE REPORTS**

*Case 1.* The first patient was seen in the Hematology Clinic of this hospital in February, 1946, at the age of 15. She had been well until five months previously, when during the course of a normal confinement for childbirth she was found to have a red blood cell count of 2,500,000 and a hemoglobin level of...
60 per cent. She had an uneventful postpartum course until two weeks prior to the first visit, at which
time she developed frontal headaches, weakness, fever, nausea, and vomiting.

Physical examination revealed a 13 year old Negro female who appeared quite ill. The blood pressure
was 120/58, pulse 130, respirations 24, and temperature 98.6 F. There was extreme pallor of the palms
of the hands, the conjunctivae, and the oral mucous membranes. There was no jaundice of the skin or
sclerae. The heart and lungs revealed no abnormalities. The liver edge was palpable just below the right
costal margin and the spleen extended 1 cm. below the left costal margin on deep inspiration.

The laboratory findings were as follows: Hemoglobin 4.7 grams (31
per cent), red blood cells 1,690,-
000, blood platelets normal, reticulocytes 10.8 per cent, and icterus index 6.7 units. Fragility test: The
patient showed beginning hemolysis at 0.50 and complete hemolysis at 0.36, whereas the control showed
beginning hemolysis at 0.40 and complete hemolysis at 0.34. Sickling preparations were negative. The
white cell count was 11,000, with the following differential cell pattern: metamyelocytes 7, stab neuro-
thils 1, segmented neutrophils 59, basophils 1, lymphocytes 27, monocytes 1. Urine urobilinogen was
positive in a dilution of 1:40. The bone marrow picture was that of extreme erythroid hyperplasia with
reversal of the myeloid-erythroid ratio. The red blood cells in the marrow preparation were characteristi-
cally microcytic and hyperchromic, many having an oval shape.

A diagnosis of hereditary spherocytic anemia was made and a splenectomy was performed on the
twelfth hospital day. At the
time of operation the gall bladder was normal and contained no stones and
the other abdominal and pelvic viscera appeared to be normal. The spleen
was about three times the
normal size and weighed 2.80
grams. The report on pathology of spleen sections was "splenomegaly of
hemolytic anemia."

The patient made an uneventful postoperative recovery, the blood values returned to normal, and she
has remained completely well. One year after splenectomy she gave birth to her second child after an
entirely normal pregnancy.

A study of other members of this family revealed asymptomatic microspherocytosis in the patient's
sister, two brothers, a niece, the patient's mother, and in a maternal great aunt. The family tree is illus-
trated in figure 1 and a summary of the hematologic findings in the family is given in table 1.

Case 2. The patient's great aunt gave a history of recurrent episodes of weakness and only fair general
health. She denied ever having jaundice, indigestion, or intolerance to fatty foods. She had never had

Table 1.—Laboratory Data on Members of Family

| Relationship      | Age | M.C.D. | Retics. | Hgb. | R.B.C. | W.B.C. | Fragi-
|-------------------|-----|--------|---------|------|--------|--------| gility |
| Maternal great    | 47  | 6.4    | 9.7     | 12.0 | 3.96   | 13,100 |
| aunt              |     |        |         |      |        |        | +      |
| Maternal second   | 8   | 7.5    | 0.4     | 13.0 | 4.39   | 9,050  |
| cousin            |     |        |         |      |        |        | o      |
| Maternal aunt     | 41  | 7.5    | 0.3     | 14.5 | 4.70   | 8,750  |
| Mother*           | 34  | 6.0    | 4.6     | 11.5 | 4.09   | 11,850 |
| Brother           | 9   | 7.6    | 0.3     | 14.5 | 4.70   | 7,100  |
| Brother           | 11  | 6.5    | 1.2     | 11.0 | 4.23   | 7,200  |
| Brother           | 17  | 6.2    | 0.4     | 11.7 | 4.69   | 8,500  |
| Sister            | 20  | 6.4    | 5.8     | 12.0 | 3.93   | 7,600  |
| PATIENT           | 18  | 6.3    | 0.5     | 13.5 | 4.58   | 14,100 |
| Niece             | 3   | 6.3    | 4.1     | 13.0 | 4.41   | 12,300 |
| Nephew            | 4   | 7.7    | 0.5     | 13.0 | 4.34   | 12,300 |
| Nephew            | 2   | 8.0    | 0.1     | 12.0 | 4.68   | 10,100 |

* Father of the patient not available for study. †† indicates increased, N indicates normal. Note:
Sickling was not noted in any members of the family.
bloody, tarry, or clay-colored stools. On physical examination there was no clinical jaundice and the liver was not palpable. The spleen was enlarged, firm, and nontender 5 cm. below the left costal margin. The laboratory findings, including reticulocytosis and increased fragility test, are recorded under Patient 1 in table 1.

The patient was advised to return for a more complete evaluation, but has not done so.

Because of the laboratory and physical findings, we feel that this is also a patient with hereditary spherocytic anemia who has never yet had a hemolytic crisis, although the reticulocytosis and large spleen indicate that the disease is active. Questioning disclosed that she remembered clearly a sister who died at the age of 16 years of "low blood and swollen ankles."

DISCUSSION

Spherocytic anemia has always been stated to be transmitted as a simple mendelian dominant factor. Gates8 suggests the possibility that the gene is allelic to the more severe recessive gene of Mediterranean anemia. Wintrobe1 has stated that both sexes are affected equally.

In 1942, Race9 studied twenty-six European families comprising 183 members and confirmed the dominant inheritance mechanism. He was unable to demonstrate linkage of the disease with the ABO blood groups, M, N, the secretor factor, eye color, attached ear-lobe, or phenyl-thio-carbamide tasting.

In connection with the "latent cases" encountered by other observers as well as ourselves, it is interesting to note that Campbell and Warner10 in 1926 suggested that a "carrier state" exists. They described 3 persons who led normal lives, but whose red cells showed a marked increase in fragility to hypotonic saline solutions. One of these had an enlarged spleen.

In our series, 5 of the persons showing microspherocytosis and increased red cell fragility were completely asymptomatic and appeared in good health. It is our belief that carriers are represented in the family trees reported by Goodman and Cates,5 Scherer and Cecil,3 and Stragnell and Smith.4

With regard to the genetic mechanism involved, the presence of three recognizable categories—viz., cases, carriers, and normals—indicates at once that a simple single-gene dominant-recessive relationship is not the explanation. It would at first appear that a single pair of genes with no dominance could be responsible. Neel11 and Pauling12 have recently presented good evidence that this applies to sickle cell anemia. On this basis, patients with the disease should be homozygous for the causative gene, carriers should be heterozygous, and normal persons should possess both normal genes. That such a mechanism is not responsible for spherocytic anemia in the Negro is shown by the fact that persons with the disease may bear normal children, and also by the fact that patients with the disease frequently have one normal parent. Presumably, then, a multiple factor system must be operative, but we have been unable to recognize a definite pattern of inheritance in the available data.

In screening a number of genetic mechanisms for application to the observed data, we found that a system of three allelomorphs at a single gene locus gives a satisfactory explanation of the observed results when sex is not considered. If we let "A" represent the normal gene, "B" a factor for susceptibility to hemolysis of spherocytes, and "C" the factor producing spherocytosis, the following com-
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Binations would be possible: AA, normal; AB, normal; AC, carrier; BB, normal; BC, case; CC, carrier.

When this hypothesis is applied to the available data, the calculated results agree favorably with those actually observed when sex is not considered. However, the incidence of the disease in 12 females, as opposed to 2 males, is statistically "significant" and may indicate some other method of inheritance perhaps involving sex-linkage or sex-modification of factors. It is hoped that more data will become available for statistical study of the inheritance mechanism.

SUMMARY

1. A family study is presented in which 12 persons representing four generations of a Negro family were observed. Of these, 2 were cases of spherocytic anemia, 5 were normal and 5 appeared to be carriers of the disease.

2. Several genetic mechanisms are discussed and the suggestion is made that spherocytic anemia in the Negro is due to multiple factors. The high incidence of the disease in females is again pointed out.

REFERENCES

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