Atypical Familial Hemolytic Anemia

By R. K. Smiley, H. Dempsey, P. Villeneuve and J. S. Campbell

With the technical assistance of Barbara Best

The various types of familial hemolytic anemia are characterized by an intrinsic abnormality of the red cell which can be demonstrated by failure of the red cells to survive a normal length of time in the circulation of the patient or a normal recipient. This type of erythrocyte defect is suspected when the cells show certain morphologic features such as spheroctosis, leptoctosis, elliptocytosis or the sickling phenomenon, although the presence of a morphologic abnormality of the erythrocyte does not imply a shortened life span under all circumstances. Familial hemolytic anemia due to an intraerythrocytic defect unassociated with any typical morphologic abnormality of the red cells has been reported under the titles “atypical” or “nonspheroctytic” familial hemolytic anemia. This paper presents the results of genetic, clinical and laboratory studies of a family in which two siblings had severe hemolytic anemia without characteristic morphologic abnormalities of the red cells.

Material

Studies of two siblings (R.B. and S.B.) in January 1953 revealed a chronic hemolytic anemia with atypical features. Plans were made to observe the clinical course of the siblings in detail and to perform an extensive family study. Since that time 134 members of this family have been examined by the methods to be described. After the initial studies had been made, the older affected sibling (R.B.) was splenectomized and both siblings observed at regular intervals for the next 22 months. Splenectomy was then performed on the second sibling (S.B.) and periodic observations continued for a further six month period.

Methods

Red cell counts, hemoglobin estimations, the volume of packed red cells, reticulocyte and platelet counts were determined by standard methods. Serum bilirubin was determined by the method of Ducci and Watson; quantitative urine and stool urobilinogen estimations were performed according to King. Osmotic fragility of the red cells has been studied repeatedly on sterile defibrinated blood both fresh and after 24 hours incubation at 37 C. “Quantitative” measurements have been made of the degree of hemolysis at various saline tonicities. Mechanical fragility of the red cells was measured by a modification of the method of Shen et al. in which the tonometer flasks were rotated at 57 r.p.m. for one hour by means of a Fisher-Kendall mixer. The degree of hemolysis of fresh normal blood ranges from 1.8 to 4.7 per cent, with a mean value of 2.5 per cent and standard deviation of 0.95. The mechanical fragility of normal red cells after 24 hours incubation at 37 C., corrected for autohemolysis, ranges from 8.2 to 11.1 per cent, with a mean value of 10.3 per cent and standard deviation of 1.3.

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The method used to estimate the degree of autohemolysis was based on the principles outlined by Shen et al. for the estimation of mechanical fragility. Defibrinated blood, 0.6 cc., was placed in a tube containing 3 cc. of distilled water (Tube C) which yielded complete osmotic lysis, and an additional 0.6 cc. of the blood was placed in a tube containing 3 ml. of 0.85 per cent sodium chloride (Tube A). After 24 hours incubation of 2 ml. of the defibrinated blood in stopped tubes at 37 C, the blood was mixed by inversion, and 0.6 ml. transferred to a third tube containing 3 ml. of 0.85 per cent saline (Tube B). Tubes A, B and C were centrifuged for 10 minutes at 2000 r.p.m. and the amount of hemoglobin in the supernatant estimated in a photometric colorimeter. The percentage autohemolysis was calculated from the formula: \[ \frac{B - A}{C - A} \times 100 \]. Normal values ranged from 0.37 to 2.3 per cent with a mean value of 1.2 per cent and a standard deviation of 0.69.

The method Singer et al. was used to determine the amount of hemoglobin resistant to alkali denaturation. Paper electrophoresis of hemoglobin solutions was performed by Dr. Herbert Lichtman of Kings County Hospital, Brooklyn.

Studies of red cell survival were done by the method of De Gowin et al. The family studies were carried out in the home by a series of field trips. A brief history included specific questions about past jaundice, anemia, leg ulcers or gallbladder disease. Eye color, the shape of the hands and skull and the presence or absence of palpable splenomegaly or hepatomegaly were noted. Oxalated blood was taken for the determination of the volume of packed red cells, the icterus index and reticulocyte count. Direct blood smears were made. The major blood group and the Rh type (Rho, D) were determined. In very young children, blood smears only were taken.

Case Reports

R. B.—III—50. This girl was born January 19, 1949, one of six siblings of a French Canadian family. A normal full term pregnancy was followed by an uncomplicated home delivery. The diet was adequate and supplemented with vitamins. The first medical record was obtained when the child was hospitalized in August 1950 at the age of 18 months because of lethargy and pallor. Examination revealed a pale, listless, nonicteric child. Small lymph nodes were palpable in the posterior cervical triangles and the spleen was felt at the level of the umbilicus. The hematologic findings at that time and since are shown in table 1. The patient was transfused and sent home without a definitive diagnosis or further study. The same sequence of events was repeated in January 1951 and July 1952. Each time the physical findings were unchanged except that the liver was noted to be palpable two fingerbreadths below the costal margin. In January 1951 several small cervical lymph nodes were removed (see Results).

In January 1953 examination revealed a pale child with an adenoidal facies and prominent frontal bossing. The tip of the spleen extended to the left iliac crest and the firm edge of the liver could be palpated two inches below the right costal margin. There were no skeletal abnormalities and the child was within normal limits of height and weight for her age. The urine was normal and the serologic test for syphilis was negative. A chest x-ray showed slight generalized cardiac enlargement. After the initial family and laboratory studies were completed the patient was prepared for operation with blood transfusions, and splenectomy was performed on March 16, 1953, by Dr. J. B. Ewing. The postoperative course was uneventful and the child was discharged on March 27, 1953.

Three months after splenectomy little benefit seemed to have resulted from the procedure. Moderate anemia with reticulocytosis and elevated serum bilirubin levels persisted. The child was again transfused. Since that time the hemoglobin level has remained at 10 grams per cent for two years without transfusion. Reticulocytes are present in greater numbers than before splenectomy but the circulating nucleated red cells have disappeared. The bone marrow has a greater proportion of erythroid cells than normal but this proportion is much less than before splenectomy (table 1). The mother finds that the child is able to join in all activities of children her own age without undue fatigue and we have found her to be alert and active during the numerous admissions since June 1953.

S. B.—III—51. The younger sister of R. B. was born at home February 11, 1952. At
### Table 1.—Hematologic Data of Patients R.B. and S.B.

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<th></th>
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<th>S.B.</th>
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<tr>
<td>Date</td>
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<td>4.4</td>
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<td>Jan. 1951</td>
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<td>Mar. 27, 1953</td>
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<tr>
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<td>Oct. 1953</td>
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**Splenectomy and Transfusion**

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<th>Date</th>
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<th>HGB Gm %</th>
<th>VPFC %</th>
<th>MCV</th>
<th>MCHC</th>
<th>Retic. %</th>
<th>Serum* Bilirubin (Mg %)</th>
<th>WBC (X 10^9)</th>
<th>Platelets (X 10^9)</th>
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<td>7.3</td>
<td>26</td>
<td>106</td>
<td>28</td>
<td>2.3 (7.9)</td>
<td>1.4 (0.0)</td>
<td>12.0 (NRC)</td>
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<td>32</td>
<td>0.1</td>
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<tr>
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<td>8.3</td>
<td>22</td>
<td>91</td>
<td>33</td>
<td>8.8</td>
<td>2.2 (0.0)</td>
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<tr>
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<td>10.0</td>
<td>32</td>
<td>99</td>
<td>31</td>
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<td>3.5</td>
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<td>91</td>
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(NRC) = Nucleated red cells present, 4-16 per 100 leukocytes.
NB = Normoblastic marrow.
* = Figures in brackets indicate one minute value.
† = Immediate post-splenectomy value.
birth she weighed 6 1/2 pounds and "seemed normal" but because of progressive pallor and lethargy she was admitted to hospital in July 1952, at the age of 6 months. Apart from pallor no abnormal physical findings were recorded. The hematologic data available are shown in table 1. After blood transfusions the child was discharged but was readmitted in October 1952 because of severe anemia. At that time the spleen was reported palpable three fingerbreadths below the costal margin. In January 1953, at the age of 11 months, S. B., along with R. B., came under our observation. She was found to be listless, very pale and slightly icteric. The spleen extended 7 cm. and the liver 3 cm. below the costal margin. The remainder of the physical examination was not remarkable. In March 1953, when the older sibling (R. B.) was splenectomized as described previously, S. B. was transfused. Since that time the two children have been admitted every 3 to 6 months for study. The course of the hematologic findings and treatment are presented for comparison in table 1. On December 20, 1954, S. B. was splenectomized and the observations have been continued.

Results

Family Studies

The pertinent findings of the family study are presented in figure 1. R. B. and S. B. (III—50 and III—51) have four siblings. One of these (III—48) is a girl aged five who has marked splenomegaly. The volume of packed red cells is 31 per cent, the icterus index is 15 and the reticulocyte count 3.1 per cent. The remaining three siblings have lesser degrees of splenomegaly without other clinical or hematologic abnormalities. The mother of the children (II—23) and her nine living siblings were examined. Five of these ten people including the mother have palpable spleens. Almost identical findings prevailed in the first generation where three of the seven members examined, including the maternal grandmother, had palpable spleens. None of these individuals have anemia, icterus or reticulocytosis and the red cells in stained blood smears appeared normal. Examination of the father and the maternal grandfather revealed no clinical or hematologic abnormality.

Figure 1.—Family tree (see text).
Eighty-six individuals who are descendants of the members of the first generation other than I—5 were examined but are not shown in figure 2. These people showed no abnormalities by the methods of examination outlined except for ten persons in whom the spleen tip may have been palpable. These individuals were scattered throughout the second and third generations without relationship to the members of the first generation who had splenomegaly. The trend towards disappearance of any evidence of abnormality can be seen in figure 1 in the descendants of members of the second generation other than II—23.

These data suggest a dominant type of inheritance with variable penetrance and low expressivity. An alternative explanation would be that inheritance is dominant and expressivity low, but that a modifying gene was contributed by the father. We can present no evidence to support the latter assumption.

**Blood and Bone Marrow**

Wright stained smears of peripheral blood* (fig. 2) showed moderate anisocytosis due to the presence of polychromatophilic macrocytes, normal red cells, slightly oval forms and occasional frank elliptocytes. The number of stippled cells present is not unusual in view of the severe hemolytic process. Three to 16 normoblasts per hundred white cells have been present at different times prior to splenectomy, but none has been found postoperatively. Very rare cells could be considered microspherocytes and wet preparations formed normal rouleaux. The sickling phenomenon could not be demonstrated.

Bone marrow aspirations in both children prior to splenectomy revealed very cellular material with an intense normoblastic response. From 63 to 78 per cent of the nucleated cells were normoblasts in all stages of development. The

* In both siblings.
Table 2.—Results of Mechanical Fragility and Autohemolysis Studies

<table>
<thead>
<tr>
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<th>MECHANICAL FRAGILITY (%)</th>
<th>AUTOHEMOLYSIS 24 Hours (%)</th>
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<td></td>
<td>Fresh</td>
<td>Incubated</td>
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<tr>
<td><strong>NORMAL</strong></td>
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<tr>
<td>Mean</td>
<td>2.5</td>
<td>10.3</td>
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<tr>
<td>S.D.</td>
<td></td>
<td>2.5</td>
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<tr>
<td>S.B.</td>
<td></td>
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</tr>
<tr>
<td>Pre-Splenectomy</td>
<td>5.8</td>
<td>15.0</td>
</tr>
<tr>
<td>Post-Splenectomy</td>
<td>2.6</td>
<td>12.6</td>
</tr>
<tr>
<td>R.B.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Splenectomy</td>
<td>2.8</td>
<td>13.9</td>
</tr>
<tr>
<td><strong>SPHEROCYTIC CONTROL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsplenectomized</td>
<td>5.8</td>
<td>30.7</td>
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The proportion of normoblasts has ranged from 32 to 45 per cent since splenectomy (table 1).

Fragility Studies

a) Osmotic. Repeated studies on fresh or incubated sterile defibrinated blood of both patients failed to reveal a definite difference in the resistance of the red cells to osmotic lysis when compared with controls. Before splenectomy hemolysis of fresh blood from both patients was detected in most tests at a saline tonicity of 0.48 per cent, while in most controls hemolysis began at 0.46 per cent. After incubation hemolysis began at the same tonicity (0.56 per cent) as the control blood, or in some determinations 0.04 per cent higher. Since splenectomy the blood of both patients begins to show hemolysis, both before and after incubation, in the same tube as the control blood or may show slightly more resistance to osmotic lysis than normal (unsplenectomized) controls.

b) Mechanical Fragility. The results of these studies on the two siblings, on normal blood and the blood of a child with typical congenital spherocytic disease who was not splenectomized, are presented in table 2. Fresh blood from S. B. (before splenectomy) and from the spherocytic control show a moderate increase in mechanical fragility. After incubation the mechanical fragility of S. B.'s blood is increased slightly above the normal range for these values (i.e., to 15 per cent) while the incubated blood of the spherocytic control is increased greatly (30.7 per cent). In both R. B. and S. B., after splenectomy, the mechanical fragility of the red cells, fresh or incubated, is within the normal range.

c) Autohemolysis. The amount of autohemolysis after 24 hours incubation was increased in S. B. (presplenectomy) and in the spherocytic control (table 2). In both S. B. and R. B. all determinations of the degree of autohemolysis have been within normal limits since splenectomy.

Abnormal Hemoglobins

Paper electrophoresis of the hemoglobin of both patients showed a normal pattern. The percentage of hemoglobin resistant to alkali denaturation ranged from 1.4 to 2.4 per cent. The value of 2.4 per cent was obtained on the blood of
S. B. at the age of thirty months, while all other determinations have been less than 2 per cent. These figures include both pre- and post-splenectomy observations.

**Pigment Studies**

The results of serial estimations of the serum bilirubin are included with the hematologic data in Table 1.

Urinary and fecal urobilinogen estimations were done on 24 hour urine and four day stool collections of S. B. before and after splenectomy. Before splenectomy the urinary excretion of urobilinogen was 0.48 mg. per cent (2.3 mg. per 24 hours) and after splenectomy 1.2 mg. per cent (4.4 mg. per 24 hours). The fecal urobilinogen excretion was 728 mg. per 100 Gm. of feces (239 mg. per 24 hours) before splenectomy. Two separate four day stool collections averaged 138 mg. per 100 Gm. of feces (52 mg. per 24 hours) exactly four months after splenectomy.

**Tissue Studies**

Pathologic changes in the resected spleens of both patients were nonspecific but showed features in common. The spleen of R. B. weighed 240 Gm. (normal 39 Gm.) and that of S. B. 300 Gm. (normal 47 Gm.). The cut surfaces of these spleens were brownish.

Paraffin embedded formalin and Zenker fixed tissues were stained by hematin, phloxine and saffron, by silver impregnation for reticulum and by Mallory’s aniline blue connective tissue stain. Prussian blue reactions were studied microscopically. Abundant hemosiderin was seen microscopically within macrophages and extracellularly. Erythrocytophagocytosis and leukocytophagocytosis were demonstrable. The pattern of sinusoids and the sinusoidal endothelium was unremarkable. The sinusoids and the somewhat widened pulp spaces were the seat of abundant erythrocytic and leukocytic hemopoiesis. Megakaryocytes were inconspicuous. There was a striking absence of pulp congestion. The pulp showed an increase in the number of reticulum fibers, but no demonstrable increase in collagen. Lymphoid follicles showed slight germinal center proliferation with trizonal arrangement of lymphocytes. The capsules and trabeculae were intact.

The resected accessory spleens (one in R. B. and two in S. B.) measured 0.5 to 1 cm. in maximal diameters and showed histologic changes similar to those described above.

Similar histologic changes were observed in a slide from a surgically resected spleen loaned to us by Lt. Colonel William Crosby from one of his previously reported cases.2

A liver biopsy taken from S. B. showed a pronounced degree of liver cell hemosiderosis with a slight amount of leukocytic and erythrocytic hemopoiesis in the portal areas.

Seven cervical lymph nodes removed from R. B. measured 0.3 to 1.2 cm. in maximal diameters and showed active hemopoiesis. The presence of numerous eosinophils and megakaryoblasts imparted to some nodes a spurious resemblance to Hodgkin's disease. Capsules, trabeculae, sinuses and germinal centers were well preserved; some nodes showed moderate hyperplasia of sinus endothelium.
and germinal centers. There was a minimal degree of hemosiderosis and little erythro- or leukocytophagocytosis.

A specific histologic diagnosis could not be reached from examination of the above tissues. The absence of pulp congestion together with easily demonstrable splenic hemopoiesis constitute the most outstanding differences from the usual histologic findings in congenital spherocytic disease.

Radiologic Studies

X-rays of the hands, long bones and skull were taken in both patients. The only abnormality seen was in the skull of the older sibling, R. B. (fig. 3), where there is moderate cortical thickening with vertical striations.

Red Cell Survival

Transfusion of normal cells into the older sibling (R. B.) was not done until after splenectomy. These cells survived a normal length of time (fig. 4). The survival of normal cells in the circulation of S. B. prior to splenectomy was shortened (half survival time 32 days), but after splenectomy, as in R. B., a normal life span was found. These results indicate that an extracorporeal
hemolytic mechanism existed before splenectomy but disappeared after operation.

Studies of the survival of the cells of the patients in a normal recipient have not been performed.

Miscellaneous Observations

No history suggestive of gall bladder disease was obtained in any of the members of the family. There was no relationship between the presence of splenomegaly, with or without anemia, and eye color. No other congenital anomalies were noted in the patients or their relatives, and no porphobilinogen was found in the urine of either sibling. There was no correlation between the presence of splenomegaly and A B O or RH0 (D) blood factors, but the three anemic members of the family were type A, RH0 (D). Presumptive tests for warm, cold and acid agglutinins and hemolysins were negative in both siblings, as were direct and indirect Coombs tests. No antibodies could be detected which would agglutinate trypsinized normal red cells. A ten day period of oral Cortisone therapy in R. B. prior to splenectomy had no effect on the clinical or hematologic findings.

Discussion

The two siblings who provided the basis for this report were found to have a severe chronic hemolytic process manifested by normocytic or slightly macrocytic anemia, slight icterus, reticulocytosis with circulating nucleated red blood cells, intense normoblastic hyperplasia of the bone marrow and increased excre-
tion of fecal urobilinogen. The hemolytic disease was present at birth or began within the first year of life. The hereditary and familial features suggest that an intrinsic abnormality of the red cells with a decreased life span may be the fundamental defect although red cell survival studies to establish this point were not done. The extracorpuscular hemolytic mechanism present in S. B. prior to splenectomy has been demonstrated in other familial hemolytic diseases with intrinsic defects of the red cell. Normal survival of normal red cells in the circulation of both patients after splenectomy while excessive blood destruction continued provides indirect evidence of a basic defect in the erythrocytes of the two children. There is no characteristic morphologic abnormality of the red cells and no abnormality of the hemoglobin fraction could be demonstrated with the technics used.

The principal features which differentiate our patients from patients with hereditary spherocytosis are: (a) absence of spherocytes in stained smears and the formation of normal rouleaux in wet preparations; (b) only a slight increase in osmotic fragility of the red cells even with incubation together with complete disappearance of this tendency after splenectomy; (c) failure of the red cells to show a marked increase in mechanical fragility after incubation; (d) incomplete arrest of the hemolytic process by splenectomy; (e) absence of marked congestion of the splenic pulp spaces in histologic sections. The results of the studies of osmotic and mechanical fragility differ sharply from the results reported by Young in his extensive studies of patients with hereditary spherocytosis before and after splenectomy.

Other authors have discussed in detail the hemolytic diseases which must be differentiated from "atypical" or "nonspherocytic" hereditary hemolytic anemia. It should be emphasized that patients with this type of hemolytic disease may be thought to have acquired hemolytic anemia without demonstrable antibodies unless careful family studies are performed. Because of the low penetrance and expressivity of the trait it is possible that no abnormalities could be detected in other members of a family, and it would be necessary to demonstrate by red cell survival studies that the defect was intracorpuscular rather than extracorpuscular.

We have found seven reports in the literature on atypical hemolytic anemia which include descriptions of patients with varying degrees of similarity to our own. Most of these authors have expressed the opinion that this group of patients is not homogeneous, but Dacie has produced the first definite evidence in support of this assumption by the study of his cases. In type 1 nonspherocytic hemolytic anemia autohemolysis is not increased, but the addition of glucose does not reduce the amount of hemolysis to the degree that it does in control blood. In type 2 there is an increased degree of autohemolysis which is not prevented by the addition of glucose. The degree of autohemolysis in both our patients was normal after splenectomy, although elevated in the one patient studied prior to splenectomy. A single group of observations have indicated that the normal degree of autohemolysis is unaffected by the addition of glucose or adenosine.

Inheritance studies in the families which have been reported are incomplete but some form of dominant inheritance has been postulated. The present studies
suggest dominant inheritance but emphasize the features of low penetrance and expressivity of the trait. The patients of three\textsuperscript{2, 3, 17} of the seven reports quoted above have French or French Canadian ancestors and in other ways are most similar to our patients except for the presence of congenital anomalies and porphobilinogen in the family reported by Crosby.\textsuperscript{2} Thickening of the bony trabeculae of the skull similar to patient R. B. (fig. 3) has been noted by three authors.\textsuperscript{3, 17, 19} Chemical or electrophoretic abnormalities of the hemoglobin have not been demonstrated in any patients of this group, although electrophoretic abnormalities are not excluded by the techniques used.\textsuperscript{20} While no correlation was found between the presence of splenomegaly and blood type, all three patients with anemia in this study were type A. A review of the blood types of the patients in the seven reports mentioned previously revealed that all were type A with one exception.\textsuperscript{17} The association of hereditary nonspherocytic anemia with blood group A was noted first by Crosby.\textsuperscript{2}

From the data we have presented it would appear that splenectomy benefited the two patients of this family. The volume of packed red cells has stabilized at 30 per cent and the necessity for blood transfusions has disappeared. A marked fall in fecal urobilinogen output after splenectomy was demonstrated in S. B. and the proportion of normoblasts in the bone marrow of both patients decreased greatly. Evidence of continued excessive blood destruction persists in the form of mild anemia, reticulocytosis of 10 to 20 per cent (greater than before splenectomy) and moderately normoblastic bone marrows. Patient S. B. has a serum bilirubin of 2.0 mg. per cent and the daily excretion of fecal urobilinogen is 52 mg. or approximately 54 mg. per hundred Gm. of hemoglobin if the blood volume is assumed to be 70 ml. per Kg. of body weight. The cases of Lipton\textsuperscript{17} have shown a similar response to splenectomy with a decrease in the severity of the anemia, but the majority of authors\textsuperscript{2, 4, 16, 18} have reported no beneficial effect from the operation. At present there are no criteria by which to select patients with atypical familial hemolytic anemia who will benefit from splenectomy. We selected the elder of the two severely affected siblings for splenectomy and decided to proceed with the operation on the second sibling only after a prolonged period of parallel observations. Operation on the third sibling (III—48) who has no symptoms and a mild degree of anemia is not contemplated. It is possible that alleviation of the disease in our patients resulted from removal of the extracorpuscular hemolytic mechanism demonstrated in patient S. B. Further observations may indicate that an extracorpuscular hemolytic mechanism, as demonstrated by red cell survival studies, must exist before benefit can be expected from splenectomy.

**Summary**

1. The genetic, clinical and hematologic features of an atypical chronic hemolytic anemia in two siblings of a French Canadian family have been described.
2. The anemia is normocytic, normochromic and not associated with any characteristic morphologic abnormality of the red cells.
3. Slight increases in osmotic and incubated mechanical fragility, as well as a more definite increase in autohemolysis were found which could not be demonstrated after splenectomy.
4. The survival time of normal red cells was shortened before splenectomy in one patient. Normal red cell survival was demonstrated in both patients after splenectomy.

5. The features which differentiate this hemolytic anemia from hereditary spherocytosis are discussed.

6. French or French Canadian ancestry has been noted in some of the reported patients most similar to our own.

7. The association of this type of hemolytic anemia with blood group A has been confirmed in our patients.

8. Splenectomy decreased the severity of the hemolytic process in both patients. This benefit may have resulted from removal of an extracorpuscular hemolytic mechanism.

**SUMMARY IN INTERLINGUA**

1. Es describite le aspectos genetic, clinic, e hematologic de un atypic chronic anemia hemolytic in duo fraternos de un familia franco-canadian.

2. Le anemia es normocytic, normochromic, e non associate con ulle characteristic anormalitate morphologic del erythrocytos.

3. Esseva constatate leve augmentos del fragilitate osmotic e del fragilitate mechanic post incubation e etiam plus marcate augmentos de autohemolyse. Iste augmentos non esseva demonstrabile post splenectomia.

4. In un del patientes le superviventia de normal erythrocytos esseva reducite. Normal superviventia erythrocytico esseva demonstrate in ambe patientes post splenectomy.

5. Es discutite le aspectos que differentia iste anemia hemolytic ab spherocytosis hereditari.

6. Inter le reportos de casos simile al nostres, ancestres francese o franco-canadian esseva notate repetitemente.

7. Le association de iste typo de anemia hemolytic con le grupo sanguinee A esseva confirmate in le caso de nostre patientes.

8. Splemectomia reduceva le severitate del processo hemolytic in ambe patientes. Iste beneficio ha resultate possibilmente ab le ablation de un mecanismo hemolytic extracorpuscular.

**REFERENCES**


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Atypical Familial Hemolytic Anemia

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