The Life Span of the Elliptocyte

Hereditary Elliptocytosis and Its Relationship to Other Familial Hemolytic Diseases

By ARNO G. MOTULSKY, M.D., KARL SINGER, M.D., WILLIAM H. CROSBY, Lt. Col., MC, USA, and VERNON SMITH, Capt., MC, USA

Hereditary Elliptocytosis is often a benign hereditary condition manifested by the presence of oval and elliptical red cells, discovered in routine blood examinations.* While the condition is usually harmless, 12 per cent of all patients have been demonstrated by conventional methods to have increased hemolysis.1, 2 Severe hemolytic anemia with hereditary elliptocytosis is infrequent, but such cases have been recorded.1, 3-6 A useful classification of hereditary elliptocytosis is that of Heilmeyer.7 He divides the cases into three categories: (1) Hereditary elliptocytosis with no signs of hemolysis; (2) hereditary elliptocytosis with hemolysis but no anemia, a “compensated” hemolytic disease; such a patient may have splenomegaly, reticulocytosis, icterus, and increased fecal urobilinogen; (3) hereditary elliptocytosis with hemolytic disease and anemia. The average life span of circulating red cells is abnormally short in any hemolytic disease. The work to be reported here deals with the life span of elliptocytes and the results appear to sustain Heilmeyer’s classification.

Several investigators8-11 have attempted to establish the life span of elliptocytes by transfusing the blood into normal recipients and plotting the disappearance of the abnormally shaped erythrocytes. Because of technical difficulties of such procedures, no consistent data have been obtained. Recently, Hedestedt and Berlin12 combined a careful photographic visual technic with the generally accepted method of differential agglutination (Ashby) to study one patient with hereditary elliptocytosis. Agreement between these two methods was not obtained.

During the present investigations, we transfused elliptocytes from three donors of different families and followed survival of the transfused cells by the method of differential agglutination as well as by a special visual method. Patients with sickle cell anemia were selected as recipients in two instances. Following transfusion, sickle cell preparations helped to place the nonsickling elliptocytes into sharp contrast, thus facilitating counting. Our results are compared with similar data in the literature and the general relation of hereditary elliptocytosis to other hereditary hemolytic syndromes is discussed.

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Submitted May 2, 1953; accepted for publication June 6, 1953.

* The term “elliptocytosis” will be used in this paper to designate the hereditary condition. The characteristic red cell will be named “elliptocyte.” The term “ovalocytosis” (and “ovalocyte”) will be used for oval red cells seen in many types of anemia.
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MATERIAL AND METHODS

Ashby Survival Time Studies

Whole blood from elliptocytic donors was transfused into recipients within two days after venesection. Serial counts were performed using the method previously described from the Chicago laboratory. The inagglutinable count twenty-four to forty-eight hours after transfusion is taken to be 100 per cent.

Sickling

Sickling was elicited by the bacterial method or by sodium metabisulfite. The elliptical cells stood out in sharp contrast against the typical sickled cells. Many red cells in stained blood films of sickle cell anemia patients appear oval and rod-shaped. Ordinarily such cells are difficult to differentiate from true elliptocytes, but anoxia transforms almost all sickle cell erythrocytes into the characteristic sickle and oat-shaped forms which are quite distinct from the nonsickling elliptocytes. It has been shown that elliptocytes cannot be made to sickle.

Donors

Case 1. M. H., a 33 year old Negro lieutenant of the Women’s Army Corps, was admitted to Walter Reed Army Hospital for a severe upper respiratory infection which cleared rapidly. Routine blood studies revealed significant anemia and elliptocytosis (tables 1 and 2). The patient’s sister showed a similar blood picture with many ovalocytes and elliptocytes. No other family members could be tested. Serum iron was 55 γ per cent. Radioiron tracer studies revealed markedly accelerated plasma clearance and complete utilization of labeled iron by the red cells. These findings were interpreted as evidence of iron deficiency and the patient was treated with ferrous sulphate. The patient responded to this treatment, and after three months the hemogram was stabilized as shown in table 1. Elliptocytosis persisted. On paper electrophoresis, the patient’s hemoglobin moved as one

<table>
<thead>
<tr>
<th>Table 1.—Summary of Significant Hematologic Data of Elliptocytic Donors</th>
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</thead>
<tbody>
<tr>
<td><strong>Case 1, M. H.</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>Blood type</td>
</tr>
<tr>
<td>Recipient’s blood type</td>
</tr>
<tr>
<td>Red blood cell count, (X 10⁶)</td>
</tr>
<tr>
<td>Hemoglobin, (Gm. per 100 cc.)</td>
</tr>
<tr>
<td>Hematocrit</td>
</tr>
<tr>
<td>Reticulocytes</td>
</tr>
<tr>
<td>(Total number of reticulocytes)</td>
</tr>
<tr>
<td>White blood cell count</td>
</tr>
<tr>
<td>Sickling</td>
</tr>
<tr>
<td>Osmotic fragility</td>
</tr>
<tr>
<td>Serum bilirubin</td>
</tr>
<tr>
<td>Fecal urobilinogen* (mg./24 hr. 4 day collection)</td>
</tr>
<tr>
<td>Hemolytic index (60) (Normal 10-20)</td>
</tr>
<tr>
<td>Survival time</td>
</tr>
</tbody>
</table>

* Before iron administration.
† Three months after iron administration. Elliptocytosis persisted after treatment of the anemia.
TABLE 2.—Distribution of Degree of Elliptocytosis in Dried Preparations (at Least Two Hundred Cells Counted)

(RED CELLS ARE ARBITRARILY DIVIDED (SEE DISCUSSION) INTO FOUR GROUPS: I NORMAL ROUNDERYTHROCYTES; II OVAL ERYTHROCYTES; III ELLIPTICAL ERYTHROCYTES; AND IV ROD SHAPED ERYTHROCYTES)

<table>
<thead>
<tr>
<th>Patient</th>
<th>ROUND</th>
<th>OVAL</th>
<th>ELLIPTICAL</th>
<th>ROD SHAPED</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. H.*</td>
<td>55%</td>
<td>32%</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>L. J.</td>
<td>10%</td>
<td>6%</td>
<td>76%</td>
<td>8%</td>
</tr>
<tr>
<td>E. B.</td>
<td>3%</td>
<td>34%</td>
<td>50%</td>
<td>13%</td>
</tr>
</tbody>
</table>

* After three months treatment with iron.

Component with normal mobility.17 No increase in fetal hemoglobin could be demonstrated by the method of alkaline denaturation.18 The presumable source of the iron deficiency was menorrhagia due to multiple uterine fibroids. Hysterectomy was performed at a later date. It should be pointed out that the red cells of this patient were transfused for this study before iron treatment was started.

Case 2. L. J., a 28 year old Negro woman, was seen at Michael Reese Hospital, Chicago, because of amenorrhea and a possible ovarian cyst. Physical examination was negative. There was no jaundice or splenomegaly. Routine blood studies revealed marked elliptocytosis (table 2). No relatives could be examined. In view of the extreme degree of elliptocytosis and the absence of other hematologic disease, a diagnosis of hereditary elliptocytosis was made. Hematologic data are summarized in table 1. The reticulocytosis of 3.4 per cent (absolute count 163,000), the elevated hemolytic index, and the bilirubin in the upper normal range should be noted (table 1). No increase in the amount of fetal hemoglobin was detected. Plasma volume (Evans-Blue method) was 2850 cc. Total blood volume was 4600 cc. Amenorrhea disappeared spontaneously.

Case 3. E. B., a 42 year old white woman, was admitted to Michael Reese Hospital for surgical treatment of menorrhagia due to uterine fibroids. Routine blood studies revealed marked elliptocytosis (table 2). The family could not be studied. A large number of elliptical and rod-shaped blood cells in the absence of anemia suggested hereditary elliptocytosis rather than symptomatic ovalocytosis (see discussion). The mild elevation of reticulocytes was explained by the preceding episodes of bleeding.

Recipients

The red cells of case 1 (M. H.) were transfused into a normal volunteer. Recipients of the blood of cases 2 and 3 were both 8 year old boys (R. W. and O. H.) with classical sickle cell anemia who had been transfused periodically. It has previously been shown that normal red cells transfused into patients with sickle cell anemia survive normally.19 In addition, recipient R. W. had been transfused with normal blood about a year previously and normal survival of the normal donor cells had been found. This finding helped to strengthen further the validity of the shortened survival time of L. J.'s (case 2) red cells in this recipient.

RESULTS

Differential Agglutination Studies

Figure 1 shows the results of the red cell life span studies by the Ashby method. Survival time of the transfused elliptocytes was normal in cases 1 and 3 (M. H.
Fig. 1.—Survival time of transfused elliptocytes from patients with hereditary elliptocytosis. (Control transfusion of normal red cells into sickle cell anemia recipient R. W. revealed normal survival time.) One hundred per cent values: L. J.—R. W.: 873,000 inagglutinable cells—blank count 36,500, E. B.—C. H.: 1,188,000 inagglutinable cells—blank count 37,500, M. H.—C. Ha.: 320,000 inagglutinable cells—blank count 8,000.

(Black circle = donor L. J.—recipient, sickle cell anemia patient R. W.; white circle = donor E. B.—recipient, sickle cell anemia patient C. H.; X = donor M. H.—recipient, normal patient.)

and E. B.). The elliptocytes of case 2, however, had a definitely shortened life span of about forty-five days. The Ashby curve in this case was straight or possibly slightly convex. This is interpreted as steady decay of this patient’s short-lived red cells with all erythrocytes having an average life span of about forty-five days.

M. H.’s (case 1) red cells presumably were iron deficient† when withdrawn from the donor. Since they survived normally, it may be concluded that mildly iron deficient cells have a normal life span. This is in keeping with known hematologic and pigment excretion data in patients with mild iron deficiency.

* An uneven rate of red cell production will give rise to uneven distribution as far as erythrocyte “age” is concerned. A preponderance of young red cells will be found in the transfused blood if red cell production of the donor increased shortly before venesection. The Ashby curve of such blood will be convex since a large segment of young erythrocytes will not be destroyed in the first few weeks after transfusion. 29

† Although the absence of hypochromia on repeated examinations is not explained.
Fig. 2.—Inagglutinable elliptocytes on chamber of Ashby count on eighty-second day following transfusion (M. H. to C. Ha.). Arrows point to elliptocytes.

Special attention was paid to the shape of the cells in the counting chamber while doing differential agglutination tests. Allowing for the recipient’s blank count, the number of inagglutinable elliptocytic cells agreed approximately with the degree of elliptocytosis of the various donors (table 2). A photograph was obtained of the counting chamber on the eighty-second day after transfusion of M. H.’s cells (case 1) into the normal recipient. Elliptocytes were clearly discernible (fig. 2). It should be recalled that only about 13 per cent of this donor’s erythrocytes were elliptical or rod-shaped. The presence of elliptocytes in the counting chamber on the eighty-second day after transfusion is therefore significant.

Mild reticulocytosis, a bilirubin in the upper normal range, and the elevated hemolytic index (table 1) further corroborated the existence of a mild hemolytic process in the patient with the diminished survival time. However, no anemia was present. These findings help to point out the difficulty of recognizing well-compensated hemolytic disease unless survival time determinations are carried out. It has recently been shown that an uninhibited bone marrow may increase hemoglobin output 6 to 8 times over normal, and anemia occurs when the mean life span of red cells is reduced to fifteen to eighteen days. Knowing L. J.’s total circulating hemoglobin (635 Gm.), survival time (forty-five days), and weight (55 Kg.), one can calculate the amount of hemoglobin per Kg. destroyed daily \( \left( \frac{44.5}{3} \right) = 14.1 \) Gm. of hemoglobin. \( \frac{14.1}{5} = 0.25 \) Gm. of hemoglobin per Kg. Normal: 0.09 Gm. hemoglobin per Kg.). In a steady chronic hemolytic state the rate of hemoglobin production equals that of destruction; therefore, this patient was producing about 2\( \frac{1}{2} \) times as much hemoglobin as normal.
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TABLE 3.—Percentage of Elliptocytes in Sickle Cell Preparation Following Transfusion Compared with Ashby Count

(Initial count: 200 Elliptocytes per 1000 cells. Note rough agreement)

<table>
<thead>
<tr>
<th>Day after transfusion</th>
<th>Percentage of E. B.'s elliptocytes in sickle cell preparation</th>
<th>Percentage of E. B.'s inagglutinable cells on Ashby count</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>92</td>
<td>89</td>
</tr>
<tr>
<td>15</td>
<td>86</td>
<td>78</td>
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<tr>
<td>26</td>
<td>75</td>
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<td>33</td>
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<td>57</td>
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<td>44</td>
</tr>
<tr>
<td>76</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>90</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>

Increased production explains the absence of anemia. This was compensated hemolytic disease.

Elliptocyte Counts in Sickle Cell Preparations

Table 3 summarizes the results of the survival of "normal" elliptocytes (E. B.) in a sickle cell recipient as obtained by counting the number of elliptocytic cells per 1000 erythrocytes in sickle cell preparations at various intervals after transfusion. A good straight line could not be fitted to the serial counts, but the values roughly parallel the results obtained with the Ashby technic (table 3). A similar rough check of the two methods was obtained with short-lived elliptocytes of L. J. In L. J.'s survival study no transfused cells remained by the Ashby technic on the forty-fifth day. However, 5 per cent morphologically identifiable elliptocytes could still be identified by the visual counting technic at that time.

Our results do not indicate that any significant change in shape of elliptocytes occurs at any time during their life span.

DISCUSSION

Hereditary Elliptocytosis vs. "Symptomatic" Ovalocytosis

Erythrocytes from patients with hereditary elliptocytosis may be divided arbitrarily into four groups depending upon the degree of elliptocytosis. (I) normal, round erythrocytes; (II) oval erythrocytes; (III) elliptical erythrocytes; (IV) rod or cigar-shaped erythrocytes (table 2). European authors have devised careful mathematic calculations to estimate exactly the degree of elliptocytosis and have established such subdivisions based on measurements of red cell length and diameter.5, 22

There appear to be wide variations in the proportions of elliptocytes in the various affected families, so that no categorical statement can be made as to the number of oval (II), elliptical (III), and rod-shaped (IV) red cells necessary for a diagnosis of hereditary elliptocytosis. This is important since hereditary elliptocytosis must be carefully distinguished from "symptomatic" ovalocytosis. A significant increase in the number of oval and elliptical red cells may occur in
many conditions where anisocytosis and poikilocytosis is prominent. Such “symptomatic” ovalocytosis is not uncommon in pernicious anemia, severe iron deficiency anemia, Cooley's anemia, and severe anemia associated with infection, leukemia, and cancer. A demonstration of family occurrence of elliptocytosis is practically always confirmatory of the hereditary condition. The presence of a predominance of very deformed cells (group IV) strongly favors the diagnosis of hereditary elliptocytosis. On the other hand the association of deformed cells that are not elliptical—tear drop cells, etc.—is more indicative of symptomatic ovalocytosis.

Occasionally patients with hereditary spherocytosis may develop a superimposed symptomatic ovalocytosis. Such patients respond favorably to splenectomy. Since ovalocytosis in such patients may be more striking than spherocytosis, reports of hemolytic elliptocytosis cured by splenectomy may actually represent instances of hereditary spherocytosis with symptomatic ovalocytosis. Recently, an increasing number of cases of congenital hemolytic disease not associated with any significant red cell shape anomaly have been studied (hereditary nonspherocytic hemolytic disease, atypical congenital hemolytic anemia). Some of these patients had “symptomatic ovalocytosis” on blood films. In occasional instances the differential diagnosis between true hereditary hemolytic elliptocytosis and hereditary nonspherocytic hemolytic disease may be quite difficult and even impossible without extensive family study. The characteristic clinical and hematologic findings usually differentiate the other listed anemias. Since the number of oval cells of a given subdivision (groups II to IV) necessary to make the diagnosis of hereditary elliptocytosis may vary, every case must be judged on its own merits.

Without family study, case 3 might be questioned as a true case of hereditary elliptocytosis. The very large number of oval and elliptical cells (50 per cent and 13 per cent respectively) in the absence of anemia, suggests true hereditary elliptocytosis. The rather small number of elliptical and rod-shaped cells (groups III and IV) in case 1 is interesting. It should be noted that a large proportion of the red cells are mildly oval (group II). In this instance definite proof of the familial nature of the condition was available since the patient's sister had the same red cell anomaly with similar numbers of elliptical and rod forms. The patient with definite evidence of hemolysis (case 2) had the largest percentage of extremely oval (group III) and rod-shaped (group IV) cells (76 per cent and 8 per cent respectively). These red cells were morphologically indistinguishable from similar oval and elliptical erythrocytes in the other two patients. It is questionable whether the degree of deformity of the red cells is any index of their viability since large-scale family studies do not suggest that there is a correlation between marked degree of elliptocytosis and increased hemolysis.

**Elliptocyte Survival Time Studies in the Literature**

The striking shape of the elliptocyte suggested its use for survival time studies to early workers. Several investigators transfused elliptocytes into normal patients and followed their disappearance by periodic inspection of the recipient's blood films or of photographs of such preparations. Red cell survival time values obtained with these methods ranged from twelve to thirteen days.
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(from cases with the “compensated” hemolytic syndrome) to twenty-six to thirty-four days. Since the number of elliptocytes in a recipient’s blood sample following a transfusion is very small, any visual method is inaccurate and the above data underestimate the true life span of such erythrocytes.

The first survival time study of elliptocytes with the Ashby method was performed by Trillsick who reported one hundred to one hundred ten day survival of blood from a patient with 90 per cent elliptocytes. Very recently Berlin and Hedenstedt reported simultaneous differential agglutination and photographic survival time studies using erythrocytes from a patient with elliptocytosis. The Ashby curve was straight with normal life span of transfused elliptocytes (as in our cases 1 and 3). In the same experiment, results with the photographic technic yielded an exponential (concave) curve reaching the base line at about sixty-four days. These authors explained the discrepancy between the two technics by postulating a change from elliptocytic into normal shape near the end of the life-span of elliptocytes. In contrast, our data indicate rough agreement between both Ashby method and visual counting technic under the special conditions of our study. Similarly, our Ashby counts showed the expected number of inagglutinable cells to be elliptical throughout their life span (table 3).

Relationship and Similarities to Other Hereditary Hemolytic Syndromes

The demonstration of diminished erythrocyte life span in a case of hereditary elliptocytosis places this condition more securely into the group of hereditary hemolytic diseases associated with red cell shape anomaly. Table 4 summarizes recent information on the pathophysiology of the various hereditary hemolytic syndromes and their mild and nonanemic manifestations (“trait” etc.) as contrasted with hereditary elliptocytosis. The characteristic finding in diseases such as sickle cell anemia, hereditary spherocytosis, and thalassemia major is a morphologic deformity of the red cell associated with shortened life span. Shape anomaly alone does not imply decreased life span since sickle cell trait erythrocytes and target cells from patients with thalassemia minima survive normally. Hereditary elliptocytosis is an analogous disease. Similar to the conditions observed in the sickle cell trait and thalassemia minima patients, the majority of patients with elliptocytosis have no hemolytic disease in spite of abnormally shaped red cells.

Genetic patterns are of great importance in the pathogenesis of the hereditary hemolytic diseases. The trait for elliptocytosis as that for sickling and hereditary spherocytosis is inherited by both sexes as a mendelian dominant. Both parents of patients with sickle cell anemia or thalassemia major are heterozygous for the sickling or thalassemia gene respectively. A double dose of the pathologic gene results in severe hemolytic disease in both instances. Since the gene for hereditary elliptocytosis is distributed less frequently (0.04 to 0.1 per cent) among the population at large than the genes for sickling (10 per cent of Negroes) and thalassemia (4 per cent of some Mediterranean populations), homozygosity for elliptocytosis may be predicted to occur rarely. One such in-

* Patients with hereditary spherocytosis are known to exist where both parents are normal hematologically and clinically. Doubtful paternity and incomplete expressivity of the hereditary spherocytosis gene or mutation may be invoked to explain these cases.
stance was reported by Wyandt, Bancroft, and Winship. Their patient was the
daughter of parents who both had marked nonhemolytic elliptocytosis. The pa-
tient (the only one of five children examined hematologically) had definite
hemolytic anemia with splenomegaly and jaundice. A noteworthy finding in this
case was the presence of microspherocytes and markedly increased osmotic
fragility in addition to elliptocytosis. Microspherocytosis in this instance could
be seen in the published illustration and was probably due to red cell fragmenta-
tion. A few spherocytes and increased osmotic fragility are also found in thalas-
semia major where erythrocyte fragmentation is outstanding. Other cases of
hemolytic elliptocytosis with striking fragmentation, spherocytosis, and mark-
dedly increased osmotic fragility have been published by Holst-Larsen and by
Dacie and his co-workers. In these cases only one parent carried the trait for
elliptocytosis, and it was also present in siblings of the patients.

The cases of Dacie and of Holst-Larsen indicate that heterozygosity for the
gene of elliptocytosis may be associated with normal as well as diminished life
span of the elliptocyte. Homozygosity would presumably always be associated
with a sharply diminished life span. This is exactly what is found in thalassemia
major. The red cells of most individuals who are heterozygous for the thalas-
semia gene, however, survive normally (thalassemia minima). In other heter-
ozygous patients, mild to moderate shortening of the red cell survival time
is found (thalassemia minor). The variable hematologic picture of hetero-
yzous carriers of thalassemia or elliptocytosis is usually explained by postulat-
ing incomplete penetrance of the respective gene.

The view of recent genetic data, an alternative hypothesis to the “expres-
son” theory may be suggested. The combination of the genes for sickling
and thalassemia, inherited from a sickle cell trait and thalassemia minor
parent, produces a hemolytic syndrome known as microspherocytosis (table
4). The mating of sickle cell trait carriers (heterozygous sickling gene) with
heterozygous hemoglobin C carriers causes a distinct variant of sicklemia,
characterized by a mild course (table 4). Hemoglobin C is an electrophoreti-
cally distinct hemoglobin, and the disease cannot be detected by usual hema-
tologic methods. It is possible that hemolytic elliptocytosis, in cases in which
only one parent has elliptocytosis, may represent the combination of the ellipto-
cytic trait with another gene which cannot be detected by ordinary clinical and
hematologic examinations.

It is of interest that elliptocytosis has been reported in association with the
sickling phenomenon in the same patient. No family studies were carried out.
Although the patient was not anemic, the data given do not exclude a com-
pensated hemolytic process. Of great interest is the finding that the elliptocytes
of this patient could not be made to sickle.

The demonstration of specific, genetically determined abnormalities of hemo-
globin synthesis has further clarified our understanding of the various mani-
festations of thalassemia and of sicklemia (table 4). Methods used in the
investigation of abnormal hemoglobins are beginning to be applied in heredi-
tary elliptocytosis. Paper electrophoretic study of the hemoglobin of our (non-
hemolytic) case 1 revealed normal adult hemoglobin. Similar findings have been
reported by others. Alkaline denaturation tests for the detection of fetal hemo-
<table>
<thead>
<tr>
<th>Red cell shape</th>
<th>Severe condition</th>
<th>Mode of inheritance</th>
<th>Race</th>
<th>Hemoglobin abnormality of severe condition</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Mild or nonanemic forms of condition</th>
<th>Red cell life of mild or nonanemic form of condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherocyte</td>
<td>Hereditary spherocytosis</td>
<td>Dominant</td>
<td>All</td>
<td>Occasional small increase of fetal Hemoglobin (HbF)</td>
<td>a) Osmotic fragility increased \ b) Spherocytosis \ c) Positive family history</td>
<td>Splenectomy always cures</td>
<td>“Compensated” hereditary spherocytosis</td>
<td>Diminished</td>
</tr>
<tr>
<td>Elliptocyte</td>
<td>Hereditary, hemolytic elliptocyte</td>
<td>Dominant</td>
<td>All</td>
<td>None found yet \ a) Elliptocytosis \ b) Positive family history</td>
<td>Splenectomy successful</td>
<td>Hereditary nonhemolytic elliptocytosis</td>
<td>“Compensated” hereditary hemolytic elliptocytosis</td>
<td>Normal \ Diminished</td>
</tr>
<tr>
<td>Red cell shape</td>
<td>Severe condition</td>
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<td>Red cell life of mild or nonanemic form of condition</td>
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<tr>
<td>Sickle cell</td>
<td>Sickle cell</td>
<td>2 heterozygotes for sickle gene produce offspring with sickle cell anemia</td>
<td>Negro</td>
<td>Derangement of globin synthesis. 76-100% sickle; (Hb-8) 0-24% fetal hemoglobin; (HbF)</td>
<td>a) Positive sickle cell test b) Severe hemolytic anemia c) Positive family history</td>
<td>Transfusion in hematologic crises</td>
<td>Sickle cell trait Sicklem Hb C Sicklem Hb D Sicklem-Thalassemia disease. (Microdyspancytosis)</td>
<td>Normal Diminished Unknown Diminished</td>
</tr>
<tr>
<td>Fragmented cell—leptocye</td>
<td>Thalassemia major</td>
<td>2 heterozygotes for thass. gene produce offspring with Thalassemia major</td>
<td>Medit.</td>
<td>Failure of incorp. of Fe into heme. 40-100% fetal hemoglobin (HbF)</td>
<td>a) Marked RBC fragmentation and aniso cytosis b) Very high HbF value c) Positive family history</td>
<td>a) Transfusions b) Splenectomy may help occasionally</td>
<td>Thalassemia minima Thalassemia minor</td>
<td>Normal Transitions from normal to diminished</td>
</tr>
</tbody>
</table>
globin revealed normal values in cases 1 and 2, (case 3 was not studied) as well as in five additional patients with nonhemolytic elliptocytosis. To our knowledge no case of hemolytic elliptocytosis has as yet been studied electrophoretically; further investigations are required.

Some clinical similarities of hereditary elliptocytosis to the other hereditary syndromes are of interest. Infants with hereditary elliptocytosis at birth have few elliptical cells. The number of elliptocytes gradually increases during the first three to four months of life. A similar phenomenon occurs in infants with sickleemia. Only a few red cells sickle at birth. As erythrocytes with a large proportion of fetal hemoglobin become replaced by others that contain sickle cell hemoglobin, almost all red cells can be made to sickle. It is not yet known whether the analogous phenomenon in elliptocytosis is related to the disappearance of fetal hemoglobin.

Mild erythrocytosis may occur in thalassemia minor and in hereditary spherocytosis and has been reported in hereditary elliptocytosis. Bone changes such as cranial and maxillo-facial-dental abnormalities have been described in patients with hereditary elliptocytosis. Leg ulcers have also been seen. As in hereditary spherocytosis, nucleated red cells and reticulocytes in elliptocytosis do not show the characteristic shape anomaly. For this reason, it has been suggested that the degree of elliptocytosis increases with aging of the red cell. Our results do not support such hypothesis.

**Treatment**

No treatment is required for patients with nonhemolytic elliptocytosis. The condition is benign and by itself is of no medical significance. Compensated hemolytic elliptocytosis also requires no treatment except for careful surveillance during infection when bone marrow production may fail to keep pace with continued increased destruction.

Splenectomy has been successful in all eight cases of hereditary hemolytic elliptocytosis where this operation was performed. As discussed above, symptomatic ovalocytosis associated with true hereditary spherocytosis cannot be ruled out in three of these patients. Osmotic fragility in all but two of the eight cases subjected to splenectomy was increased. In one of the patients with normal fragility many spherocytes appeared following the operation. These findings are significant since increased osmotic fragility is not characteristic of nonhemolytic elliptocytosis. In all cases, elliptocytosis and the associated microspherocytosis where it was mentioned, remained or increased after the operation even though the patients' red cell values returned to normal.

Since the hemolytic mechanism of elliptocytosis is unknown, no information is available to explain why splenectomy benefits these patients. It is quite likely, however, that at least part of the hematologic improvement was due to increased life span of the “fragmentation-spherocytes” which had been selectively destroyed by the spleen. The favorable response to splenectomy of an occasional patient with thalassemia major may be explained in a similar manner since “fragmentation-spherocytes” also occur in this disease. It is well known that removal of spherocytes by the spleen is the basic hemolytic mechanism of heredi-
Hereditary spherocytes in the absence of the spleen have a normal life span. In view of the favorable effect of splenectomy, we feel that the operation should be performed in cases of “decompensated” hemolytic elliptocytosis. Careful study of such patients with red cell survival time determinations before and after splenectomy will contribute much to further understanding of hereditary elliptocytosis and hemolytic mechanisms in general.

**SUMMARY**

1. Red cells from three patients of different families with hereditary elliptocytosis were transfused and their survival followed by the Ashby technic of differential agglutination.

2. Life span of elliptocytes was normal in two cases.

3. A life span of forty-five days was obtained with the elliptocytes of a third patient who presented other evidence of hemolysis in the absence of anemia.

4. In two recipients with sickle cell anemia the survival of the transfused elliptocytes was also followed by counting the number of elliptocytes in sickle cell preparations. Rough agreement between the results of the Ashby and visual technics was obtained. There was no evidence of transformation from the elliptocytic into normal shape.

5. Elliptocytes from patients with hemolytic elliptocytosis were morphologically indistinguishable from elliptocytes with normal life span.

6. No hemoglobin abnormalities have yet been demonstrated in hereditary elliptocytosis. The basic defect responsible for hemolytic elliptocytosis remains unknown.

7. Symptomatic ovalocytosis occurs in many types of anemia, and must be differentiated from hereditary elliptocytosis.

8. The place of hereditary elliptocytosis in the classification of familial hemolytic diseases is discussed (table 4) and similarities to the other hereditary hemolytic anemias are pointed out. It is shown that the red cell life span (and genetic) pattern of hereditary elliptocytosis resembles closely that found in thalassemia. As in thalassemia major, spherocytosis and increased osmotic fragility due to red cell fragmentation may occur in cases of hemolytic elliptocytosis. Increased life span of these “fragmentation–spherocytes” after splenectomy may partially explain the success of the operation in hemolytic elliptocytosis.

9. No treatment is required for hereditary nonhemolytic elliptocytosis. Splenectomy is advised for “decompensated” hemolytic elliptocytosis.

**Summario in Interlingua**

1. Erythrocytas de tres patientes de differente familias con elliptocytosis hereditari esseva transfundite e lor superviventia observate per medio del technica Ashby de agglutination differential.

2. Le duration de vita del elliptocytes esseva normal in duo casos.

3. Un duration de vita de quaranta-cinque dies esseva obtenite pro le elliptocytes de un tertie patiente, le qual presentava altere symptomas de hemolyse in le absentia de anemia.
4. In duo recipientes con anemia a cellulas falciforme le supervivencia del elliptocytas transfundite eseva etiam sequite per contar le numero de elliptocytas in preparationes de cellulas falciforme. Un accordo approximate inter le resultatos del technica Ashby e del technica visual eseva constatate. Nulle indication de transformation del forma elliptocytic al forma normal eseva observe.

5. Elliptocytas ab patientes con elliptocytosis hemolytic eseva morphologicamente indistinguibile de elliptocytas de duration de vita normal.

6. Usque nunc nulle anormalitates de hemoglobina ha essite demonstrate in elliptocytosis hereditari. Le defecto fundamental responsable pro elliptocytosis hemolytic remane inecognoscite.

7. Ovalocytosis symptomatic occurrre in multe typos de anemia e debe esser distinguite de elliptocytosis hereditari.

8. Le loco de elliptocytosis hereditari in le clasification de morbos hemolytic familial es discutite, e similitates al altere hereditari anemias hemolytic es signalate. Il es monstrate que in re duration de vita del erythrocytes e etiam geneticamente, elliptocytosis hereditari ha un configuration simillime a illo de thalassemia. Como in thalassemia major, microspherocytosis e augmentate fragilitate osmotic debite a fragmentation del erythrocytes pote occurrer in casos de elliptocytosis hemolytic. Un augmentate duration de vita de iste “spherocytes fragmentational” post splenectomia pote explicar in parte le successo de iste operation in elliptocytosis hemolytic.


REFERENCES
(References marked with an asterisk (*) are excellent reviews of hereditary elliptocytosis)


LIFE SPAN OF THE ELLIPTOCYTE


The Life Span of the Elliptocyte: Hereditary Elliptocytosis and Its Relationship to Other Familial Hemolytic Diseases

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