Hereditary elliptocytosis

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Hereditary elliptocytosis was first recognized as a genetically transmitted red cell abnormality in 1929.[1, 2] Since then many family studies have shown that the disorder is transmitted as an autosomal dominant trait. The expression of this genetic abnormality is usually limited to the incidental finding of elliptical or oval-shaped red cells in the peripheral blood. Approximately 5% of affected individuals have a hemolytic anemia that usually presents during childhood and is of mild or moderate severity.[3] Less frequently, neonatal jaundice[4, 5] or aplastic crisis[6, 7] may be the first evidence of the hemolytic process. An associated enzyme deficiency[8, 9] or abnormal hemoglobin[10-12] may account for the hemolysis in some patients. There is evidence that the asymptomatic patients with normal hemoglobin levels have a compensated hemolytic process with a slightly shortened red cell lifespan.[13] Close linkage between the Rh blood group genome and the elliptocytosis gene has been demonstrated in some families. Those families in which no such linkage can be demonstrated appear more likely to have evidence of hemolysis.[13-17]

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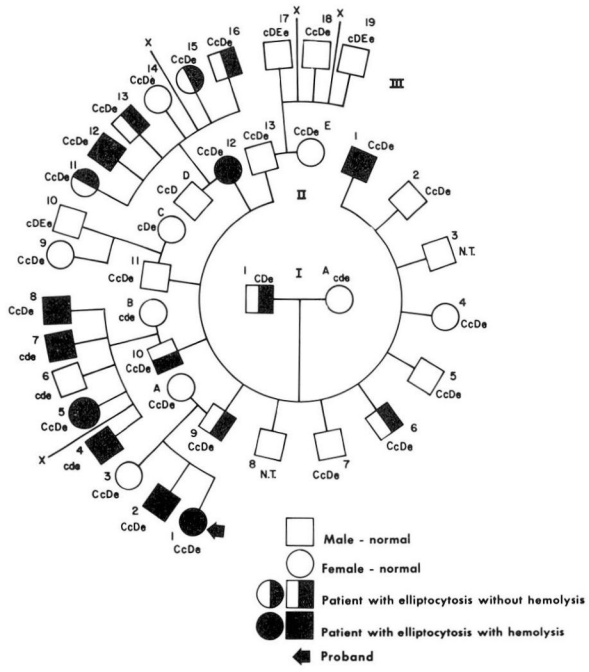

Fig. 1. Pedigree showing inheritance of elliptocytosis and the Rh blood group in three generations of family studied.

Four children from two sibships of a large family of Italian descent (*Fig. 1*) had hemolytic anemia associated with hereditary elliptocytosis but had different manifestations. A study of the patients and their families was undertaken to determine the mode of inheritance, to investigate the possibility of linkage to blood group genes, to exclude the presence of any additional red cell abnormalities, and to estimate the incidence of compensated as well as overt hemolysis.

Case reports

Patient III-1 (*Fig. 2*) was born December 28, 1964, of a full-term pregnancy and normal delivery. There was no jaundice or anemia during the neonatal period, but at age 2½ months she was found to be anemic (hemoglobin 7.2 g/100 ml). A peripheral blood smear showed marked elliptocytosis, and a bone marrow aspirate showed normoblastic erythroid hyperplasia. A diagnosis of hereditary elliptocytosis with hemolytic anemia was made. In September 1969 splenectomy was performed because of persistent anemia, and all hematologic values gradually returned to normal. However, the abnormal red cell morphology persisted.

Patient III-2 (*Fig. 3*), the brother of III-1, was born May 1, 1967, of a full-term

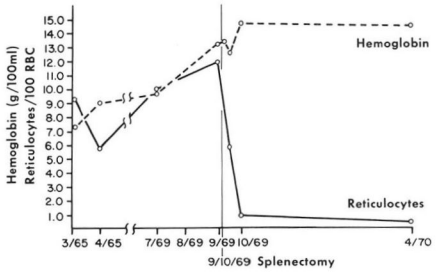

Fig. 2. (Patient III-1) Chronic hemolytic anemia relieved by splenectomy.

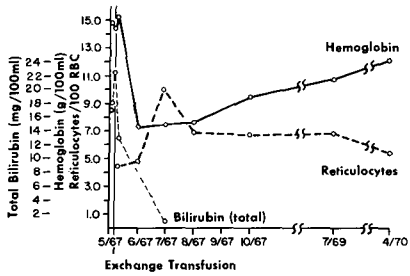

Fig. 3. (Patient III-2) Neonatal hyperbilirubinemia treated by exchange transfusion, with ensuing chronic hemolytic anemia.

pregnancy and normal delivery. Two days after birth he became deeply jaundiced; the serum bilirubin level was 17.0 mg/100 ml and the blood hemoglobin level, 14.8 g/100 ml; the direct Coombs' test was negative. The peripheral blood smear contained macrocytes, burr cells, helmet cells, and spherocytes. The patient underwent exchange transfusion on May 5, 1967. One month later the patient was anicteric but anemic; the hemoglobin level was 7.2 g/100 and the reticulocyte count, 4.8%; a peripheral blood smear showed elliptocytosis. In July 1969 the hemoglobin level was 10.8 g/100 ml, reticulocyte count, 6.9%; and the spleen was palpable 3 cm below the left costal margin. Splenectomy was performed on February 14, 1973.

Patients III-4 and III-7 (*Fig. 4*), brothers aged 7 years and 3 years, respectively, are cousins of III-1 and III-2. Patient III-7 had severe, neonatal jaundice requiring exchange transfusion at another hospital, but subsequently had been in good health. Patient III-4 had mild neonatal jaundice, and his mother states that at age 5 years, he was anemic. In January 1970 the two brothers and most of the immediate family had febrile flu-like illnesses. In early February, 1 week apart, III-4 and then III-7 were found to be anemic but anicteric with palpably enlarged spleens, reticulocytosis, and elliptocytosis. A bone marrow aspiration from III-4 showed erythroid hyperplasia. These patients were considered to be recovering from hyporegenerative crises secondary to a viral illness. Both patients recovered from these crises, and on April 1, 1970, splenectomies were performed which resulted in restoration of normal hematologic values.

Family study

Forty-two members of the family were studied and 17 had morphologic evidence of elliptocytosis, as judged by the presence of 25% or more elliptical red cells. The degree of elliptocytosis was variable, but tended to be most pronounced in those patients who were symptomatic. Elliptocytosis was more marked in the third generation (*Fig. 5*) than in the second (*Fig. 6*), and least marked in the first (*Fig. 7*). The results of some of the laboratory tests are listed in the *Table*.

As can be seen in the pedigree (*Fig. 1*), the elliptocytosis trait is inherited as an autosomal dominant, without linkage to the Rh or other tested blood groups. Independent segregation from the Rh locus is best demonstrated by the sibship of III-4 to III-8. Since I-A is cde/cde, II-10 must have the Rh genotype CDe/cde. If the elliptocytosis locus were linked to the Rh locus, it should segregate with either CDe or with cde in all the progeny of II-10 and

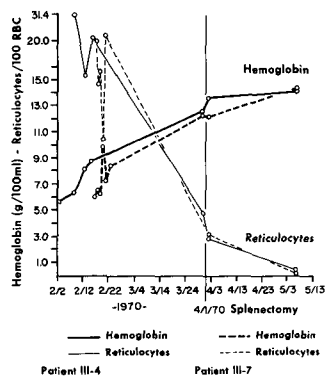

Fig. 4. (Patients III-4 and III-7) Recovery from aplastic crisis.

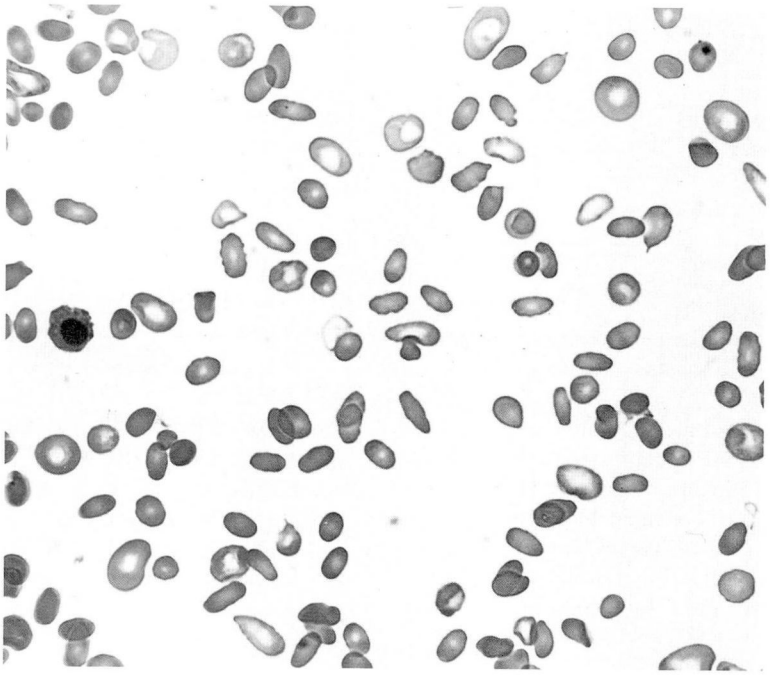

Fig. 5. Peripheral blood smear of Patient III-4 prior to splenectomy showing marked elliptocytosis, reticulocytosis, and a nucleated RBC (×640).

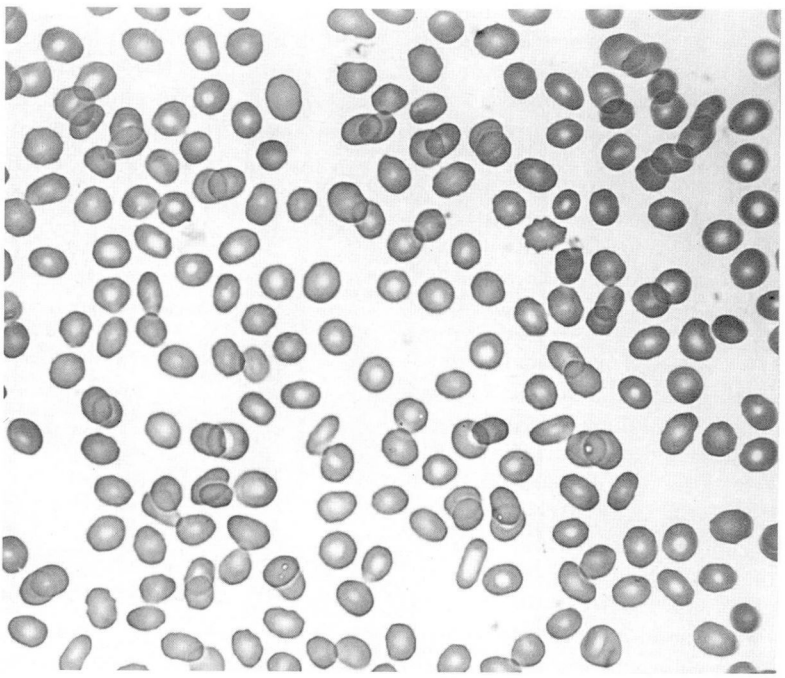

Fig. 6. Peripheral blood smear of II-9 showing moderate elliptocytosis (×640).

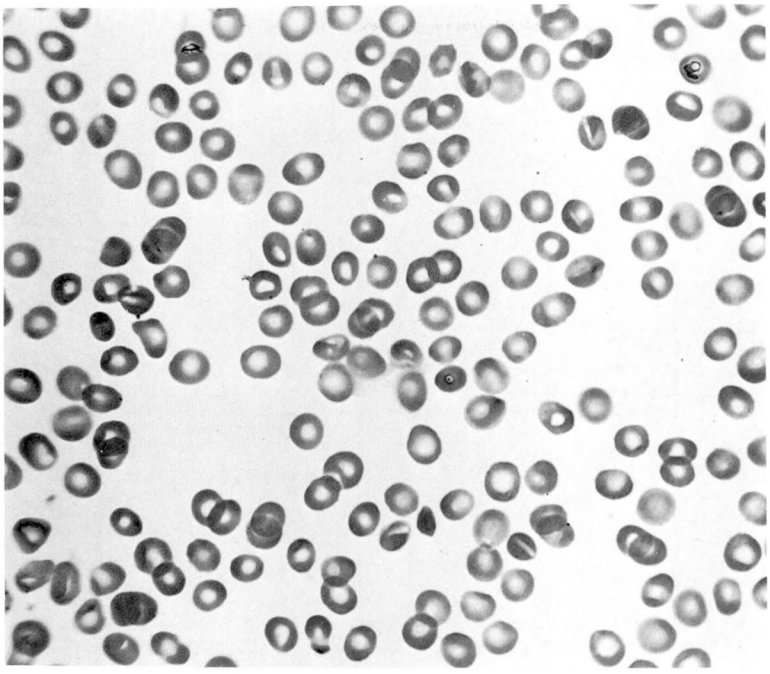

Fig. 7. Peripheral blood smear of I-1 showing mild elliptocytosis (×640).

II-B (III-4 through III-8). Inference of the inheritance of the Rh locus is simplified because the mother (II-B) has the Rh genotype cde/cde. In III-4 and III-7, who are cde/cde and have elliptocytosis, the elliptocytosis locus might be linked to the paternal (II-10) cde locus. However, III-6 also has the Rh genotype cde/cde but does not have elliptocytosis, indicating that the elliptocytosis locus is inherited independently of the paternal cde genome. Moreover, III-5 and III-8 have elliptocytosis and both must have inherited the CDe genome from the father. This demonstrates that the elliptocytosis locus is inherited independently from CDe and cde loci, and therefore is not linked to any of the Rh loci.

It was not feasible to test the entire family for the presence of the red cell enzymes glucose-6-phosphate dehydrogenase and glutathione reductase, deficiencies of which have been implicated as causing hemolysis in otherwise benign elliptocytosis,[8, 9] but the four symptomatic patients with hemolytic anemia were screened for G-6-PD deficiency[18] and two of them were tested for GSH reductase.[19] The values for these enzymes were normal.

Hb-A_2 measured by starch-gel electrophoresis[20] was normal in the four patients and no abnormal hemoglobin was detected.

Cumulative frequency distribution curves were constructed for levels of total and indirect serum bilirubin, reticulocyte counts, and hemoglobin concentration. Individuals with elliptocytosis (more than 25% elliptical red cells) were compared with those whose red cell morphology was normal.

As can be seen in the *Table* and *Figure 8*, there was little difference in the hemoglobin concentrations between

Table. Results of laboratory studies performed at the time of the family study

Pt.	Age	RBC*	Blood type				Hb. g/ 100 ml	Hct %	RBC × 10^6/ mm^3	Retics/mm^3	Bilirubin mg/100 ml (T/I)†
			ABO	Rh	Kell	Duffy					
I-1	57	E	A	CDe	–	–	14.8	44.3	4.96	49,600 (1.0%)	.7/.1
I-A	56	N	A	cde	–	–	14.7	41.7	4.55	109,000 (2.4%)	.7/.1
II-1	10	E	A	CcDe	–	–	15.4	45.2	5.21	104,200 (2.0%)	.8/.1
II-2	17	N	A	CcDe	–	–	15.6	45.3	5.12	41,000 (0.8%)	.7/.1
II-3	21	N	----------N.T.‡----------				14.8	42.2	4.79	57,400 (1.2%)	.6/.2
II-4	21	N	A	CcDe	–	–	14.1	39.6	4.43	31,100 (0.7%)	.5/.1
II-5	23	N	O	CcDe	–	–	15.5	46.1	5.18	67,500 (1.2%)	.9/.2
II-6	24	E	A	CcDe	–	–	16.8	45.6	5.21	73,000 (1.4%)	1.4/.3
II-7	26	N	A	CcDe	–	–	16.7	49.2	5.74	101,800 (1.8%)	.8/.1
II-8	N.T.										
II-9	30	E	A	CcDe	–	–	15.7	43.2	4.92	54,100 (1.1%)	1.2/.3
II-10	32	E	A	CcDe	–	–	15.5	43.7	5.24	47,000 (0.9%)	1.0/.1
II-11	33	N	A	CcDe	–	–	16.4	47.8	5.29	68,500 (1.3%)	1.1/.3
II-12	36	E	A	CcDe	–	–	15.1	43.4	4.95	182,300 (3.7%)	.5/.1
II-13	38	N	A	CcDe	–	–	16.6	49.4			
II-A	28	N	O	CcDe	–	+	14.8	44.3	4.77	47,700 (1.0%)	.7/.2
II-B	31	N	O	cde	–	–	14.0	41.2	4.59	18,300 (0.4%)	1.3/.6
II-C	32	N	A	cDE	–	+	12.8	37.6			
II-D	40	N	A	CcD	–	+	15.2	43.2	4.94	29,600 (0.6%)	.6/.1
II-E	38	N	O	CcDEe	–	+	14.6	42.6	4.59	27,500 (0.6%)	.8/.3
III-1	4	E	A	CcDe	–	+	13.8	38.9	4.83	24,200 (0.5%)	.6/.2
III-2	3	E	A_2	CcDe	–	–	10.7	28.9	3.55	254,000 (5.9%)	1.1/.5
III-3	1	N	A	CcDe	–	+	13.5	39.7	4.75	18,900 (0.4%)	.9/.1
III-4	7	E	A	cde	–	–	13.6	37.5	4.98	19,400 (0.2%)	.5/.1
III-5	6	E	A_2	CcDe	–	–	13.4	36.3	4.44	173,000 (3.9%)	1.0/.5
III-6	4	N	O	cde	–	–	12.5	36.7	4.44	13,300 (0.3%)	.7/.3
III-7	3	E	O	cde	–	–	13.1	35.4	4.69	42,300 (0.9%)	1.0/.4
III-8	½	E	A_2	CcDe	–	–	10.9	30.7	3.79	335,000 (11.5%)	1.5/.6
III-9	8	N	A	CcDe	–	+	13.2	38.7			
III-10	3	N	O	cDEe	–	+	13.6	39.3			
III-11	16	E	A	CcDe	–	+	13.9	40.4	4.87	24,400 (0.5%)	1.4/.6
III-12	14	E	A	CDe	–	–	16.1	44.9	5.14	134,000 (2.6%)	.7/.1
III-13	13	E	A	CDe	–	–	15.1	43.4	5.11	25,600 (0.5%)	2.1/.8
III-14	12	N	A	CDe	–	–	12.9	37.4	4.37	30,500 (0.7%)	.7/.1
III-15	11	E	A	CDe	–	+	12.9	36.6	4.38	17,500 (0.4%)	.6/.1
III-16	4	E	A	CcDe	–	+	13.4	37.3	4.58	32,000 (0.7%)	.5/.1
III-17	9	N	A	cDEe	–	+	13.1	37.7	4.49	26,800 (0.6%)	.7/.2
III-18	7	N	A	CDe	–	–	14.1	40.1	4.66	80,200 (1.7%)	.6/.2
III-19	5	N	A	cDEe	–	–	13.4	37.7	4.46	22,300 (0.5%)	.7/.1

* E = elliptocytosis present; N = normal red cell morphology.
† T = total bilirubin; I = indirect reacting bilirubin.
‡ N.T. = not tested.

the two groups, indicating that most hemolysis is well compensated.

There was a tendency to higher total and indirect serum bilirubin levels in patients with elliptocytosis, although the difference was not statistically significant (*Fig. 9*). Reticulocyte counts were higher in the persons with elliptocytosis than in those with normal cells. This difference is statistically significant at the .05 level (*Fig. 10*).

Patients with elliptocytosis had lower serum haptoglobin levels than those with normal red cells. This difference was also statistically significant at the .05 level. Of the 14 patients with untreated elliptocytosis, 13 or 93% had serum haptoglobin levels of 25 mg or less hemoglobin-binding capacity per 100 ml serum. However, the haptoglobin levels of many "normal" members of the family were below the normal range; hence the validity of this observation and its use-

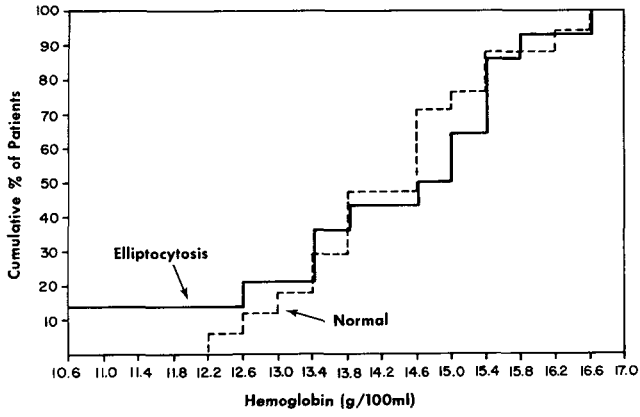

Fig. 8. Cumulative frequency distributions of hemoglobin concentrations.

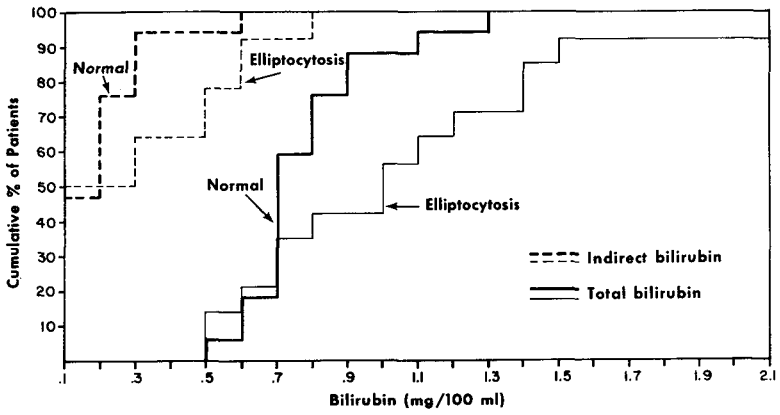

Fig. 9. Cumulative frequency distributions of indirect and total serum bilirubin levels.

fulness as a means of detecting hemolysis are doubtful.

Discussion

The great variability in the mode of presentation and the severity of the disease is one of the intriguing aspects of hereditary elliptocytosis. This has led investigators to look for genetic linkage to other traits and to look for variants of the elliptocytosis gene or its penetrance between families. The family we report contains members with and without elliptocytosis. Those with elliptocytosis show a wide clinical spectrum from the asymptomatic trait to neonatal hemolytic anemia. Assuming that only one elliptocytosis gene is inherited in this family, then one gene can evidently underlie widely varying clinical manifestations, presumably an indication of varying penetrance. An intriguing observation in this family is the increasing severity of the hemolysis, though not its incidence, with each generation.

In a family of Italian descent the possible coinheritance of a gene for thalassemia[12] must be considered; however, there was no evidence of a thal-

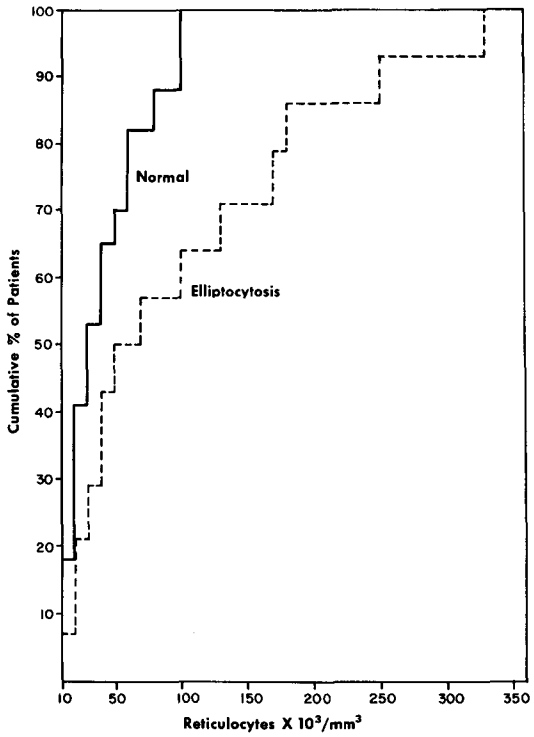

Fig. 10. Cumulative frequency distributions of reticulocyte counts.

assemic blood picture in any member and in the four patients Hb-A_2 was normal.

We have not found any other red cell defect that might increase the likelihood of hemolysis in this family. The lack of linkage between the Rh locus and the elliptocytosis is consistent with the impression of others that hemolysis is more common in such families.

The incidence of hemolysis, defined as a shortened red cell lifespan, cannot be judged for certain without red cell survival studies. However, the data obtained in this family from the reticulocyte counts, serum bilirubin levels, and possibly the haptoglobin levels are consistent with the belief that elliptocytosis is associated with hemolysis in most, if not all, affected individuals.

Summary

The cases of four related children with symptomatic hereditary elliptocytosis are reported. Splenectomy was performed with beneficial results in each patient. Seventeen of 42 members of the family had hereditary elliptocytosis. The elliptocytosis trait was not linked to the ABO, Rh, or Duffy blood group systems. No associated enzyme defect or hemoglobin abnormality was detected. Of the 17 members of this family with morphologic evidence of hereditary elliptocytosis, at least 9 (53%) had evidence of hemolysis.

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