the patient's mental symptoms as being due to the "ulcer type" or that he is being "difficult" after the operation.

Finally, it is emphasized that the diagnosis is difficult to establish in many cases in spite of a healthy clinical suspicion. Present-day "normal" levels of serum vitamin B₁₂ are inadequate to cope with a wider concept of deficiency of the vitamin, but blind administration is to be deprecated unless injections are to be continued for life if the patient improves.

Summary

Attention is drawn to the pre-macrocytic (? pre-megaloblastic) state, and six cases are presented to illustrate the pitfalls in diagnosis.

Apart from the mental state, an abnormal E.E.G. may be the only positive finding and suggest exclusion of the diagnosis.

Much larger doses of vitamin B₁₂ are needed when treating this type of case, and care must be taken to ensure that an associated encephalopathy is not missed in a patient who presents with severe anaemia. Attribution of the mental symptoms to the anaemia may result in undertreatment, with subsequent cerebral demyelination as the physician's reward.

It is probable that both exogenous and endogenous factors may modify the body's need and demand for vitamin B₁₂. The role of smoking as a possible factor in the production of syndromes other than tobacco amblyopia is worth future consideration. Our present concept of normal levels of the vitamin needs constant re-scrutinization and evaluation in order that treatment may be planned on a scientific basis.

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On August 31 this year, the number of children in the care of London County Council was 8,830 (5,083 boys and 3,747 girls). This figure was 200 more than on August 31 last year. The largest increase was in children under 5 years of age (2,100 compared with 1,999 on August 31, 1959). Of the children in care 939 were "short stay" children—that is, they were in care for such temporary causes as the illness or confinement of a parent—compared with 852 "short stay" children last year. Considerable success has been achieved in finding foster homes. This year it was possible to board out 2,061 children compared with 1,884 last year. (L.C.C. Council Meeting, November 22, 1960.)

MILD HEREDITARY SPHEROCYTOSIS —A FAMILY STUDY

BY

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The clinical features and laboratory findings of typical hereditary spherocytosis are well known and have been reviewed by Dacie (1954). The condition may also occur in a mild form, when clinical and laboratory findings are minimal (Gänsslen, Zipperlen, and Schütz, 1925; Campbell and Warner, 1926). Families suffering from mild hereditary spherocytosis have been described by Discombe (1948) and by Young, Izzo, and Platzer (1951). Affected members in these families showed similar manifestations of the disease.

There is fairly general agreement in the medical literature that the disease, whether in the severe or the mild form, is transmitted as a Mendelian dominant characteristic (Race, 1942). However, some families show irregularity in the pattern of inheritance. Thus Race found a significant shortage of affected sibs compared with the expected ratio. Young (1955) described five families in each of which both parents of an affected child seemed to be haematologically normal. In at least two of these families, mutation could be excluded as another member of the kindred also suffered from spherocytosis. Young concluded that carriers might occur in families with hereditary spherocytosis who could transmit the genetic defect but themselves appear normal. Ham (1955) confirmed Young's observations, and pointed out that minor increases in mean corpuscular haemoglobin concentration or osmotic fragility of incubated red cells might be important in detecting the carrier state.

The present paper describes three generations of a large family with mild hereditary spherocytosis. In this family two carriers were identified who appeared to be haematologically normal when first examined. Repeated testing of one of these carriers disclosed an abnormality on the fourth occasion. The difficulties in diagnosis offer one explanation for the shortage of affected sibs found by Race.

Family Study

The proband was a 26-year-old man (Fig. 1, Subject II 4) with no significant past history except "failure to thrive." He was admitted to hospital suffering from a fractured pelvis sustained in a motor-vehicle accident. The amount of blood loss was uncertain, as a large haematoma of the thigh was present. The haemoglobin value of his blood three days after admission was 7.6 g./100 ml. and he was given a transfusion of 1 litre of whole blood. At this time spherocytes were noted in the blood film. No operative procedures were performed. Four days later the haemoglobin value was 9.4 g./100 ml., haematocrit 27%, and reticulocytes 8.6%. The serum bilirubin was 1.5 mg./100 ml. and red-cell osmotic fragility was increased. The direct Coombs test on his red cells gave a negative reaction. Further clinical examination revealed slight icterus; the spleen was not palpable. Apart from short stature, the patient was normally developed.

No specific therapy was given for the anaemia after the initial blood transfusion, and the haemoglobin value returned to normal during the next few weeks. However, reticulocytosis, spherocytosis, and increased osmotic

fragility persisted. The Table shows a representative blood count performed six months later.

With the co-operation of the patient, a study was made of available relatives, most of whom consented to clinical and laboratory examination. No member of this family had been diagnosed as suffering from hereditary spherocytosis.

Methods of Family Study.—Clinical study included history, general inspection, and palpation of the abdomen. Venous blood was obtained for haemoglobin value, haematocrit, reticulocyte percentage, blood-film examination, and red-cell osmotic fragility according to the methods described by Dacie (1956). In two members the osmotic fragility of incubated red cells was determined.

Results

The findings in those members of the family who were examined are shown in the Table. The code numbers refer to the individuals listed in the family pedigree in Fig. 1. Four members of generation I were examined. One member (Subject I 5), the father's sister, was diagnosed as suffering from hereditary spherocytosis. She had splenomegaly, reticulocytosis, spherocytosis, and increased red-cell osmotic fragility. This patient also had a palpable liver and a past history of gall-bladder colic. She was not anaemic. Neither parent of the proband (Subjects I 2 and I 3) had clinical or laboratory evidence of hereditary spherocytosis. They were both in good health and neither

had any significant past history of disease. Subject I 7 was dead; there was a history of jaundice while in the Army.

As it seemed likely that the father (Subject I 3) was indeed a carrier, he was re-examined with similar normal clinical and haematological findings. On this occasion the osmotic fragility of red cells incubated at 37° C. for 24 hours was determined and found to be normal. The curve for freshly drawn red cells is shown in Fig. 2 and for incubated cells in Fig. 3. This member has since died, and it was not possible to carry out further tests.

FIG. 2.—Osmotic fragility curves of freshly drawn blood. From left to right, the carrier father (Subject I 3); an affected cousin (Subject II 8) who showed an abnormal curve after repeated testing; the proband (Subject II 4).

FIG. 3.—Osmotic fragility of incubated blood. From left to right, an affected cousin (Subject II 8) who subsequently showed increased osmotic fragility, and the carrier father (Subject I 3).

FIG. 1.—Pedigree of family. □ Normal male. ○ Normal female. ◻ and ◯ Affected male and female respectively. ◻ and ◯ Members not examined. The proband is represented by a black square.

Clinical and Laboratory Findings in the Family Studied

Subject	Sex and Age	Haemoglobin (g./100 ml.)	P.C.V. (Wintrobe) %	Reticulocytes %	Spherocytes	Osmotic Fragility	Splenomegaly
I 2	F 64	14.4	45	1.4	—	Normal	—
I 3	M 68	14.6	44	1.6	—	Normal	—
I 5	F 65	13.6	38	5.4	+	Increased	+
I 6	F 62	15.1	43	2.4	—	Normal	Not examined
II 1	F 35	13.6	40	10.0	+	Normal once; increased once	+
II 2	F 32	13.2	40	3.8	+	Increased	+
II 3	F 30	13.6	40	3.0	—	Normal	—
II 4	M 26	15.6	45	4.6	+	Increased	—
II 5	M 25	15.7	47	1.6	—	Normal	—
II 6	F 22	15.4	45	4.4	—	"	—
II 7	F 20	15.0	46	1.0	—	"	Not examined
II 8	F 45	14.3	46	1.5	—	Normal three times; increased once	—
II 9	M 44	15.1	46	1.1	—	Normal	—
II 10	M 33	16.6	45	3.5	+	Increased	—
III 7	F 7	12.6	38	1.6	—	Normal	—
III 14	M 21	15.7	49	0.2	—	"	—
III 15	M 18	15.2	47	1.4	—	"	—
III 16	F 16	15.0	45	0.8	—	"	—
III 17	F 10	12.6	36	12.8	+	Increased	+
III 18	M 13	13.6	44	1.3	—	Normal	—
III 19	M 11	13.5	41	1.2	—	"	—
III 20	F 7	12.8	39	0.6	—	"	Not examined
III 21	M 11	13.3	39	2.1	+	Increased	+
III 22	M 9	12.3	37	3.7	+	"	—

All the members of generation II were examined. Five, including the proband, were diagnosed eventually as suffering from hereditary spherocytosis. Subject II 1 was not anaemic and had no symptoms of ill-health. She showed splenomegaly, spherocytosis, and reticulocytosis. On the first examination the red-cell osmotic fragility was normal; when retested one year later the curve was just beyond the normal range (M.C.F. 0.455%). Subject II 2 was clearly affected, showing splenomegaly, spherocytosis, reticulocytosis, and increased red-cell osmotic fragility. There was a vague past history of anaemia in childhood, but the haemoglobin value was normal at the time of examination. Subject II 6 has not been included in the affected group, as, although she showed a reticulocyte count of 4.4%, there were no spherocytes present in the blood film, the osmotic fragility of the red cells was normal, and the spleen was not palpable. Subject II 8 was considered initially to be unaffected, even though she was the mother of an affected child. Laboratory findings representative of the first three examinations were haemoglobin 14.3 g./100 ml., haematocrit 46%, reticulocytes 1.5%, and absence of spherocytes in the stained blood film. Osmotic fragility of both fresh and incubated cells was normal (Figs. 2 and 3). She suffered

from menorrhagia, for which hysterectomy was performed. When re-examined some months later she showed 4% reticulocytosis and osmotic fragility of both fresh and incubated cells was definitely increased. Subject II 10 had spherocytosis, reticulocytosis, increased osmotic fragility, but no splenomegaly. He was not anaemic and had no symptoms of ill-health.

Ten members of generation III were examined. Three were diagnosed as suffering from hereditary spherocytosis. Subject III 17 showed reticulocytosis, spherocytosis, increased red-cell osmotic fragility, and splenomegaly. Her reticulocyte count was the highest recorded in this family study. She was recovering from a pyrexial illness at the time of examination. There was no anaemia or any significant past history. Subject III 21 showed splenomegaly, spherocytosis, and increased red-cell osmotic fragility. The reticulocyte count was 2.1% and there was no anaemia. He was stated to have been jaundiced at birth, but was a premature baby. Subject III 22 was considered by his mother to be delicate and was taking "blood tonics." He showed reticulocytosis, spherocytosis, and increased red-cell osmotic fragility. The spleen was not palpable and there was no anaemia.

Discussion

Nine of 24 members examined in this family appear to be suffering from hereditary spherocytosis, and one (Subject I 3) seems to have been a haematologically normal carrier. It is possible that further testing would have eventually detected an abnormality in this individual as it did in Subject II 8; he died from coronary occlusion while this study was in progress. With the exception of the proband, no subject was found to be anaemic, indicating the mild nature of the disease. The anaemia shown by the proband could have been accounted for by blood loss only, although it is also possible that he suffered from an "aplastic crisis" after the injury to his pelvis. Unfortunately, reticulocyte counts were not performed until the seventh day after the injury, at which time he showed reticulocytosis and the haemoglobin value was rising.

Seven of the eight subjects who showed spherocytosis had reticulocytosis greater than 3%. Subject III 21, who had spherocytosis, increased red-cell osmotic fragility, and splenomegaly, had a reticulocyte percentage of only 2.1%. The highest reticulocyte percentage (12.8) was shown by Subject III 17, who was recovering from an unexplained fever at the time of examination. Subject II 6 had 4.4% reticulocytes, but no other findings to suggest hereditary spherocytosis, and has not been included among the affected members.

Red-cell osmotic fragility was found to be abnormal in all nine affected members, but only on repeated testing in two of these (Subjects II 1 and II 8). It was of particular interest that initially the osmotic fragility of incubated red cells was normal in Subject II 8. The red cells showed mild hypochromia at this time due to menorrhagia. After hysterectomy the osmotic fragility of freshly drawn cells was definitely abnormal, as also was the fragility of incubated cells.

Splenomegaly was found in five subjects. In four the degree of enlargement was such as to be just detected clinically; Subject III 17 was found to have a firm enlargement of the spleen which extended 3 cm. below the left costal margin.

The family pedigree (Fig. 1) suggests transmission of the disease as an autosomal dominant characteristic, with variable expression of the affected gene. The family findings indicate the necessity for a full investigation when studying inheritance. The proband

might have been considered an example of mutation if his parents only had been investigated; the same might have been said of Subject III 17 if repeated laboratory investigations had not demonstrated eventually the disorder in her mother.

The inheritance of mild hereditary spherocytosis appears the same as that for the classical disease. The similar severity of the clinical findings in affected members of this family suggest that the gene for hereditary spherocytosis may occur in allelomorph form. In this family an iso-allele may be responsible for a mild disease. The other possibilities are that the condition described in this paper is a different one from typical hereditary spherocytosis, or that each affected member is revealing incomplete penetrance of the gene responsible for the typical disease. Both these possibilities appear unlikely.

The disease in this family is so mild that no treatment seems to be indicated.

Summary

A large family suffering from symptomless hereditary spherocytosis in three generations is described. The diagnosis was established in affected members on clinical and laboratory findings.

No haematological abnormality could be detected in one member who, on genetic grounds, was transmitting the disease. All ten members of the second generation were examined and five were found to be affected. In one affected member of this generation haematological abnormalities were detected only after repeated testing.

It is suggested that the gene responsible for hereditary spherocytosis occurs in allelomorph form.

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The University of Nigeria occupies a large site at Nsukka, near Enugu in Eastern Nigeria, where accommodation has already been provided for over 270 students who came into residence on October 12. Princess ALEXANDRA performed the formal ceremony of laying the foundation stone during her visit to the recent Independence celebrations. The Senate of London University has agreed to enter into a tripartite association, for a period whose length is to be decided in due course, with Michigan State University and this new University. The new University will from the outset grant its own degrees, but will benefit from British and American assistance and advice both in its planning and in such matters as staffing and examining. The British contribution will come partly through the Inter-University Council, which will arrange a number of secondments to the new University, and partly through the University of London, whose role will be to advise on academic matters in association with Michigan State University, and to suggest the names of members of the University of London to be invited to serve on the council, to visit Nigeria, and to join boards of examiners. (*University of London Gazette*, October, 1960.)