FAMILIAL NON-SPHEROCYTIC HAEMOLYTIC ANAEMIA*

BY

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The three accepted and well-defined types of familial haemolytic anaemia are familial spherocytic anaemia, sickle-cell anaemia, and Mediterranean anaemia. Reports have appeared of other types of familial anaemia, some of which are undoubtedly haemolytic. A family is here described in which four members in three generations were found to have non-spherocytic haemolytic anaemias.

Case Histories

Case 1.—H. J., a cable operator, was found to have a mild hyperchromic anaemia at the age of 48 when operated on for a deflected nasal septum. The indirect Van den Bergh reaction was positive and the red-cell fragility normal. For 15 years he was treated as a case of pernicious anaemia but never achieved a normal count. In addition to liver, he was given large amounts of iron. At the age of 63 he came to be examined in this department. He was an intelligent man of good physique with no apparent developmental abnormalities. His skin was dry and of a dusky yellow, the duskiness being more marked on the exposed parts. There was no buccal or genital pigmentation. His facies showed mild mongoloid features. The liver edge was palpable 2½ in. below the costal margin and felt a little firm. The spleen was not felt. There was no icterus. The main blood findings are summarized in Table I. In stained pre-

parations the red cells appear uniformly large and well coloured. Poikilocytes were rare; anisocytosis was slight; fair numbers of stippled cells were present, but polychromatic cells were not observed. Moderate numbers of target cells were seen; red-cell fragility was slightly diminished. He was group A Rh-positive. The urine contained a trace of albumin and an occasional red cell but no bilirubin. The faecal urobilinogen content was markedly raised, and the urinary urobilinogen was sometimes similarly raised. The radiological appearance of the femora, ribs, and long bones was normal, but thickening of the vault of the skull was present.

He was treated with a variety of parenteral and oral liver extracts, with folic acid, vitamin B₁₂, and crude marrow preparations, all without benefit. He remained in tolerably good health until January, 1951, when he died after a brief illness of what appeared to be bronchopneumonia and congestive cardiac failure. A post-mortem examination was not permitted.

Case 2.—V. T., aged 68, a sister of H. J., was admitted to hospital in 1946 for upper abdominal pain, and a macrocytic haemolytic anaemia was found. Ten years previously the gall-bladder had been removed for repeated gall-stone colic and pigment stones were removed. On admission she was very pale and the spleen was just palpable. The main blood findings are given in Table I. A fractional test meal showed the presence of free hydrochloric acid. The bone marrow was normoblastic and overactive. Her blood was group A Rh-positive. The direct Coombs test

TABLE I
BLOOD FINDINGS OF THE FOUR CASES

Case No.	Period of Observation	Haemoglobin (Haldane) (100% = 14.5 g./100 ml.)	R.B.C. (m./c.mm.)	M.C.V. (cu)	M.C.D. (μ)	Reticulocyte Count (% R.B.C.)	Saline Producing Maximum and Minimum Fragility (%)	Serum Bilirubin (mg.%)	Stippled Cells (% of R.B.C.)
1	June, 1948–Nov., 1950	66–90	2.3–3.67	99–125	7.9–8.9	4.5–19	0.2–0.32 0.4–0.44	0.8–2.25	0.4–9
2	Nov., 1946–Oct., 1948	54–86	1.9–3.5	113	—	9–10	0.28 0.44	1.2–2.8	Occasional
3	Oct., 1948–Mar., 1952	86–99	3.56–3.65	103–105	8.0	5.4–7.8	0.30 0.42	1.2	Not noted
4	April, 1952	105	5.5	84	6.9	24	0.22 0.44	2.1	Frequent

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FIG. 2.—Survival of red cells in 0.9% saline in Case 1. A, repeat tests at 4° C. B, repeat tests at 37° C.

strated, and the direct Coombs test was negative. Transfusion survival studies were unfortunately not possible, but *in vitro* experiments were performed. Ten per cent. sterile suspensions of washed red cells were made from both the patient and a normal control of the same group. The diluents consisted of saline, homologous plasma, and heterogenous plasma. Penicillin was added to each ampoule (approximately 200 units per ml. of suspension). The degree of haemolysis was estimated daily by direct visual comparison with individual sets of standard haemoglobin suspensions. The ampoules were shaken in a uniform manner after reading each day. In these experiments (Figs. 2 and 3) the affected subjects' cells survived longer than normal cells both in their own and in normal plasma, while they did not survive as long as normal cells in 0.9% saline.

Discussion

Each of these four cases shows the features of a mild non-spherocytic haemolytic anaemia. All have increased reticulocytes and raised bilirubin levels.

All are macrocytic except the last, which, paradoxically, showed the highest reticulocyte count. Basophilic stippling of the red cells was demonstrated in three of the cases. Splenomegaly was observed only in Case 2. Slight hepatic enlargement was present in Cases 1 and 2, both of which were older subjects. All four patients were described as being pale and sallow. Two complained of lassitude, one of slight bouts of shivering, and one of gall-stone colic. The increased rate of red cell destruction appears to be due to a defect in the red cells, of which stippling is probably an expression. The red cells of Case 1 have been shown to possess increased mechanical fragility, and to differ from normal cells in survival experiments *in vitro*. The increased survival of red cells in plasma is probably connected with their slightly flattened shape and is in keeping with their diminished saline fragility. The diminished survival of red cells in saline, with rapid initial haemolysis, may indicate an increased rate of red cell metabolism, rapid deterioration of red cells occurring when plasma nutrient is not present (Ellis and Ellis, 1950). In experimental lead poisoning it has been shown that the stippled cells are the defective cells, and that they increase greatly following splenectomy (McFadzean and Davis, 1947). In clinical lead poisoning stippled cells are more numerous in the marrow than in the peripheral blood. This was also found in Case 1. Kench, Gillam, and Lane (1942) have shown that in lead poisoning a disturbance in haemoglobin synthesis exists.

In this family the inherited defect appears to result in the production of an abnormal red cell

FIG. 3.—Survival of red cells in plasma of Case 1. A, B, and C record repeat tests at 4°C. D and E record repeat tests at 37°C.

stroma, and possibly in the presence of an abnormal haemoglobin.

Relevant Literature

A case of non-spherocytic haemolytic anaemia with splenomegaly and a suggestive family history was described by Widal and Ravaut (1902).

Thompson (1939) mentioned three families of haemolytic anaemia in which spherocytes were absent. Splenectomy was performed in several cases without benefit. Haden (1947) described two families in which eight patients were shown to have non-spherocytic haemolytic anaemias. In the first family spontaneous haemolysis was observed, while in the second a proportion of stippled cells were invariably found in affected subjects. Splenectomy in one member of the first family did not alter the course of the disease. Crosby (1950) described a family in which seven cases of normochromic and non-spherocytic haemolytic anaemia were found. The disease appeared to be transmitted as a Mendelian dominant, and to be associated in some cases with brachyphalangia and porphyria. Stippled cells were not a feature, but after splenectomy in one case the siderocyte count rose from 0.1% to 45%. Kaplan and Zuelzer (1950) described a family in which three siblings were found to have a chronic haemolytic anaemia. The red cells were normochromic yet had an increased volume. Oval cells were frequent in smears. Rundles and Falls (1946) described two families in which a hypochromic anaemia was present in association with splenomegaly and marked red cell deformity.

The family described in this paper resembles the second of Haden's two families and is similar to that of Kaplan and Zuelzer (1950), who demonstrated the presence of a red cell defect by transfusion survival experiments. They also noted hepatomegaly, thickening of the skull, and mongoloid facies, all of which were observed in Case 1. The family described by Crosby is also similar. He demonstrated a markedly impaired red cell survival time both *in vitro* and *in vivo*. The ineffectiveness of splenectomy in this type of case has been noted by Crosby and Haden.

Summary

Four cases of non-spherocytic haemolytic anaemia occurring in three generations of one family have been described, and reference has been made to five other possible cases in the family history. The red cells were macrocytic or normochromic and showed increased resistance to saline haemolysis. Stippled cells were observed in three cases. Apart from target cells, abnormal forms were not noted. In one case the mechanical fragility was found to be increased, and the survival of red cells *in vitro* was found to be abnormal. Neither sickling nor acid haemolysis could be demonstrated. Haemoglobinaemia was not found.

Clinically the condition resulted in lassitude, pallor, yellow skin, pigment stones, mild jaundice, and mild hepatomegaly. It is considered that an inherited red cell defect is present in these cases, which differs fundamentally from that present in familial spherocytic anaemia. Reference has been made to similar cases described in the literature, in some of which splenectomy was performed without benefit.

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REFERENCES

- Beebe, R. T., and Wintrobe, M. M. (1933). *Arch. intern. Med.*, **51**, 630.
 Bomford, R. R., and Rhoads, C. P. (1941). *Quart. J. Med.*, **10**, 235.
 Crosby, W. H. (1950). *Blood*, **5**, 233.
 Dacie, J. V., and White, J. C. (1949). *Journal of Clinical Pathology*, **2**, 1.
 Ellis, M. M., and Ellis, M. D. (1950). *Proc. Soc. exp. Biol., N.Y.*, **74**, 251.
 Haden, R. L. (1947). *Amer. J. med. Sci.*, **214**, 255.
 Kaplan, E., and Zuelzer, W. W. (1950). *Blood*, **5**, 811.
 Kench, J. E., Gillam, A. E., and Lane, R. E. (1942). *Biochem. J.*, **36**, 384.
 McFadzean, A. J. S., and Davis, L. J. (1947). *Glasg. med. J.*, **28**, 237.
 Ponder, E. (1934). "The Mammalian Red Cell and the Properties of Haemolytic Systems" (*Protoplasma-Monographien*, vol. 6). Borntraeger, Berlin.
 Rundles, R. W., and Falls, H. F. (1946). *Amer. J. med. Sci.*, **211**, 641.
 Shen, S. C., Castle, W. B., and Fleming, E. M. (1944). *Science*, **100**, 387.
 Singer, K. (1940). *Amer. J. med. Sci.*, **199**, 466.
 Thompson, W. P. (1939). *Bull. N.Y. Acad. Med.*, **15**, 177.
 Widal, F., and Ravaut, P. (1902). *Eull. soc. méd. Hôp. Paris*, Ser. 3, **19**, 984.