between haemoglobins A and S (see Fig.). In phosphate buffer at pH 7.8 two components were still discernible, the abnormal haemoglobin having the greater mobility, but complete separation did not occur. At pH 6.5 in phosphate buffer, however, the abnormal haemoglobin was not separable from haemoglobin A, but trailed behind it.

The solubility of Mrs. L. M.'s haemoglobin was 1.57 g. per litre in 2.58 M phosphate buffer, by the method of Itano (1953). After ten weeks' storage at about -25°C . no precipitate was formed in a haemolysate that contained 8 g. per 100 ml., and no change was observed in the proportion of the abnormal haemoglobin after this period of freezing.

Haematological Findings

The relevant findings in Mrs. L. M. and three of her children are given in the Table. None of these subjects showed sickling, malaria was absent in all, reticulocytes did not exceed 0.2% in any subject, the serum bilirubin was normal in all, and alkali-resistant haemoglobin was absent in every case—less than 2% by the method of Singer *et al.* (1951). No changes were observed in wet preparations in saline, dithionite, and cresyl blue.

Haematological Findings in the M. Family

	Mrs. L. M., Mother	T. M. (16), Daughter	P. M. (14), Son	N. M. (13), Son
Haemoglobin (g./100 ml.)	15.06	12.57	14.9	14.67
Erythrocytes (mil. c.mm.)	6.15	5.91	5.5	5.55
M.C.V. (cubic microns)	77.2	66.8	76.4	79.0
M.C.H.C. (%)	31.8	31.8	35.4	33.7
Plasma Fe ($\mu\text{g.}/100\text{ ml.}$)	73	235	—	—
Osmotic Limits	0.42–0.3	0.34–0.24	0.42–0.3	0.42–0.3
fragility 50%	0.37	0.29	0.36	0.35

The stained blood film of Mrs. L. M. showed no abnormality except that a very occasional oval erythrocyte could be found. The films of the two younger children were quite normal, and, though the M.C.V. recorded in these three members was rather low, this did not appear to represent any abnormality. The daughter (T. M.), however, displayed definite abnormalities, her erythrocytes showed considerable variation in size and shape, there were many elliptocytes, target cells were numerous, but no polychromatic staining was seen. These findings accord with the lowered cell volume (66.8 cubic microns) and the increased resistance to hypotonic saline, and are suggestive of thalassaemia minor. The plasma iron of this girl was high (method of Ramsay, 1953), which is in favour of the same diagnosis. Presumably the inheritance was through T. M.'s father, who unfortunately was not available for examination. The presence of the thalassaemia gene in this family must be a coincidence, but it is not a surprising one, for thalassaemia is by no means rare in the Indian immigrants in Uganda.

Discussion

Several human haemoglobins having greater mobility than haemoglobin A at pH 8.6 have been described.

The present haemoglobin differs from haemoglobin H (Rigas *et al.*, 1956) in its cathodal mobility at pH 6.5, its stability when frozen, and the absence of any associated disease. It differs from haemoglobin I (Rucknagel *et al.*, 1955) and from the haemoglobin described by Cabannes *et al.* (1955), in that it appears to be less mobile at pH 8.6.

Haemoglobins J and K are less mobile than H and I. Exactly which haemoglobin should be designated K has been the subject of some confusion. The letter was originally reserved by Itano (1955) for a component reported by Battle and Lewis (1954), but subsequently he could not confirm that this was a distinct variant (Itano *et al.*, 1956). At the sixth International Congress of Haematology it was suggested that K might describe another haemoglobin reported from Algeria by Cabannes *et al.* (1956), and one of the new variants (Liberia II) found by Robinson *et al.* (1956) in Liberia.

Fortunately haemoglobin J is a clearly defined entity. Described by Thorup *et al.* (1956) in a negro, it had a mobility

similar to the present example, and was not associated with disease. Robinson *et al.* (1956) found a haemoglobin in Liberia (Liberia I) that is identical with haemoglobin J, and in both these descriptions the abnormal fraction in A-J individuals accounted for about 60% of the total haemoglobin. Huisman *et al.* (1957) reported the finding of haemoglobin J in an Indonesian, in whom it formed only 35% of the haemoglobin.

Through the kindness of Dr. H. Lehmann and Dr. T. H. J. Huisman the present haemoglobin has been compared with haemoglobins H, I, J, K, and found to correspond with haemoglobin J in its mobility at pH 8.6. Thus the presence of the gene for haemoglobin J in the Indian mainland is established, and this gene (like that for haemoglobin S) appears to have a rather wide variability of expression in heterozygotes, producing in different individuals from about 20% to 60% of the total haemoglobin.

Summary

A haemoglobin variant, with greater mobility than haemoglobin A at pH 8.6, was discovered in an Indian woman in Uganda. It was unassociated with any abnormality in the blood. Its properties are recorded, and correspond with those of haemoglobin J.

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Medical Memorandum

Acute Myeloblastic Leukaemia following Chloramphenicol Treatment

Various blood dyscrasias, ranging from slight granulocytopenia to agranulocytosis and aplastic anaemia, following administration of chloramphenicol have been reported during the last few years, but no case of acute leukaemia has yet been published. A case has recently been seen where acute myeloblastic leukaemia was discovered following agranulocytosis and hypoplasia of bone marrow after a single course of chloramphenicol.

CASE REPORT

A man aged 63 was first seen in September, 1953, with a history of sudden attacks of amnesia over the last year. No very definite abnormality was found on physical examination; a peripheral blood film showed a normal picture with haemoglobin 94%. Wassermann reaction negative. He had no symptoms when seen in January, 1954, but was admitted to this hospital in August, 1954, with further attacks of amnesia, frontal headaches, and momentary aphasia. Examination revealed slight nominal dysphasia, right homonymous hemianopia, slight papilloedema of right disk, and accentuated right-sided tendon jerks. A skull radiograph was normal, but the cerebrospinal fluid was xanthochromic, under enhanced pressure, and contained increased protein and excess globulin. Blood count on August 27: Hb 74%; R.B.C. 4,060,000 per c.mm.; C.I. 0.92; W.B.C. 6,800 per c.mm.; polymorphs 62%; lymphocytes 37%; monocytes 1%. A left carotid angiogram

showed a moderate-sized angiomatous malformation in the temporo-parietal region with pineal shift to the right.

He was admitted to the Manchester Royal Infirmary in October, 1954, for removal of the angioma. On October 14 his haemoglobin was 72%. Operation was on October 22, and the same evening a post-operative clot was removed and blood loss was replaced with 6 pints (3.4 litres) of blood. Chloramphenicol, 500 mg. six-hourly, was started by mouth. Four days later the haemoglobin was 48%. Blood examination on the 29th showed W.B.C. 1,110 per c.mm. (polymorphs 38%, lymphocytes 52%), and on this day chloramphenicol was stopped. A few pints of packed cells was transfused, and on his discharge on November 28 the haemoglobin was 72%.

He was readmitted on February 14, 1955, as he was becoming increasingly pale and listless. There was no enlargement of liver, spleen, or lymph nodes. A soft systolic murmur was present at the apex. Blood pressure 160/90 mm. Hg. Blood count: Hb 40%; R.B.C. 2,600,000 per c.mm.; C.I. 0.98; W.B.C. 850 per c.mm. (polymorphs 17%, monocytes 1%, lymphocytes 81%); platelets 147,000 per c.mm.

He was given a transfusion of 4 pints (2.3 litres) of packed cells on admission, followed by a course of treatment with penicillin, sodium pentose nucleotides, and pyridoxine hydrochloride. Blood examination after transfusion showed: Hb 54%; R.B.C. 2,630,000 per c.mm.; C.I. 1.02; W.B.C. 1,100 per c.mm. (polymorphs 18%, lymphocytes 82%). A further 4 pints (2.3 litres) of packed cells was transfused four days later, and 500 mg. of iron given intravenously; but on February 28 the leucocyte count fell to 600 per c.mm., with 28% polymorphs; sternal marrow puncture showed markedly decreased cellularity and very scanty precursor cells, the appearances being of severe hypoplasia of bone marrow. Packed cells, again 4 pints (2.3 litres), were transfused on March 1, and the blood picture on the 7th was: Hb 85%; R.B.C. 4,060,000 per c.mm.; C.I. 1.04; W.B.C. 1,800 per c.mm. (polymorphs 55%, lymphocytes 45%); platelets 199,000 per c.mm. On March 9 he suddenly became comatose and lumbar puncture revealed blood-stained fluid. After remaining in coma for a few days he gradually improved, C.S.F. on April 1 being clear with normal cells and chemistry. The blood picture during the rest of March remained steady with Hb 75% and W.B.C. 1,500 per c.mm. (polymorphs 42%).

He was fairly well, getting up and about, and cheerful though often irrational, till April 2, when an abscess developed in the right gluteal region and streptomycin treatment was added; the abscess opened spontaneously and discharged for a few days before healing. The blood count on April 4 was: Hb 68%; R.B.C. 2,910,000 per c.mm.; W.B.C. 1,700 per c.mm. (polymorphs 34%, lymphocytes 65%, monocytes 1%); but as the leucocyte count fell to 600 per c.mm. on the 19th 2 pints (1.1 litres) of packed cells was transfused. Average blood count during the following month was: Hb 45%; R.B.C. 2,100,000 per c.mm.; W.B.C. 2,000 per c.mm. (polymorphs 20%, lymphocytes 78%). He complained of abdominal pain, but examination of urine and by barium meal showed no abnormality, and liver function tests gave normal results.

Two pints (1.1 litres) of blood was transfused on May 10. Another abscess developed in the right buttock a week later; a further course of streptomycin and penicillin was given without effect, and the abscess was incised with removal of a small amount of thick pus containing a moderate number of leucocytes and numerous Gram-positive cocci in clusters, and from which coagulase-positive *Staphylococcus aureus* was grown. It gradually healed.

On May 26 raised circular pinkish nodules developed on the chest and back. Liver and spleen were not palpable and there were no enlarged lymph nodes. Peripheral blood count: Hb 41%; R.B.C. 1,840,000 per c.mm.; C.I. 1.12; W.B.C. 13,000 per c.mm. (immature cells, type not definitely identified, 33%; monocytes 41%, lymphocytes 11%, metamyelocytes 5%, polymorphs 10%). Sternal marrow puncture showed predominance of primitive blast cells with occasional premyleocytes, myelocytes, metamyelocytes, and

polymorphs. Erythrocyte reaction was normoblastic and cells were poorly presented, only an occasional proerythroblast and intermediate and late normoblast being seen. The picture was one of acute myeloblastic leukaemia; this was confirmed by Dr. J. F. Wilkinson, and 3 pints (1.7 litres) of packed-cell blood transfused. On June 1 a few areas of haemorrhages developed under the skin. For the first time both liver and spleen were palpable, but no lymph nodes. The pinkish skin nodules were more prominent. The patient was slightly febrile and occasionally irrational.

On June 11 he was given 6-mercaptopurine, 50 mg. six-hourly, and this was continued up to the 26th, 3 pints (1.7 litres) of packed cells having been given on the 18th. Blood counts remained as follows: on June 2—Hb 36%, W.B.C. 9,900 per c.mm. (blast cells 81%, unidentified cells 4%); and on June 15—Hb 39%, W.B.C. 12,300 per c.mm., with 81% blast cells. On June 23, following transfusion, the Hb was 56%, but the W.B.C. had fallen to 2,700 per c.mm., probably due to the 6-mercaptopurine; it further fell to 1,200 per c.mm. four days later.

On June 29 the patient suddenly became comatose, starting with a right-sided convulsion, and died two hours later. Permission for necropsy was withheld.

COMMENT

Since 1950 innumerable cases of blood dyscrasia following chloramphenicol administration have been reported in the world literature; these range from transient depression of the bone marrow causing minor granulocytopenia to fatal aplastic anaemia involving erythrocytes, granulocytes, and platelets. Usually they occur after prolonged administration of large doses, but cases are on record in which aplastic anaemia has developed after a single course or after a small precipitating dose at an interval of weeks or months after a sensitizing course. In the present case only one course of chloramphenicol to a total of 12 g. was given, and it seems certain that the patient had not had the drug previously.

No case has hitherto been described of acute leukaemia developing after chloramphenicol treatment. Recently Wilkinson (1955) has drawn attention to the occurrence of acute leukaemia as a sequel to agranulocytosis caused by sulphonamides, and he cited nine cases of acute leukaemia developing after sulphonamide therapy. If acute leukaemia can follow agranulocytosis due to sulphonamides there is no reason why it cannot similarly develop after treatment with chloramphenicol. The hypoplastic bone marrow, in an effort to produce cells, may suddenly pour primitive blast cells into the circulation, giving a picture of leukaemia.

In the present case leukaemia was found after an abscess had developed. Sometimes a leukaemoid reaction of the marrow is seen after an acute fulminating infection, but in the present case the findings in the peripheral blood and marrow, correlated with the clinical findings, left no doubt as to the diagnosis of leukaemia—severe anaemia, thrombocytopenia, granulocytopenia, and a high percentage of blast cells in the peripheral blood and marrow are not seen in any other condition. A sternal marrow biopsy was not carried out before the operation or immediately after it, and the possibility that the process was present before the administration of chloramphenicol cannot be ruled out. The patient died in spite of treatment with the new cytotoxic drug 6-mercaptopurine and repeated blood transfusions. Cortisone was not tried.

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