THALASSAEMIA IN LIBERIA

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The tribes of central and south-eastern Liberia have been shown to differ strikingly from the tribes of such near-by areas as Sierra Leone and Ghana in the low frequency of the haemoglobin C trait (Neel *et al.*, 1956) and the sickle-cell trait (Livingstone, 1958). Furthermore, 7 out of 904 Liberians, representing all of the tribes of that country, whose haemoglobin was analysed electrophoretically were found to have haemoglobin N (Liberian I haemoglobin; Robinson *et al.*, 1956), a type of haemoglobin reported since then in only two other Africans, one from Ghana and one from Nigeria (Ager and Lehmann, 1958). All but one of these seven individuals were from the Mande-speaking tribes of central Liberia (Loma, Kpelle, Mano, Gio); in these tribes the frequency of individuals possessing haemoglobin N was about 2%. This note records additional unusual haematological observations made by us among some of the tribes of central and south-eastern Liberia.

A number of children with intractable anaemias and massive splenomegaly have been seen in the past several years at the hospital maintained by the Firestone Company at its rubber plantation in south-eastern Liberia. This report is concerned with two of these children who, after treatment for malaria and intestinal parasites, underwent splenectomies.

The first child (Wle), a 5-year-old boy, exhibited a severe anaemia with the characteristics of thalassaemia major. Blood films obtained in March and July, 1958, revealed striking leptocytosis, anisocytosis, microcytosis, poikilocytosis, and normoblastaemia (Fig. 1). While the interpretation of this blood picture is complicated by the fact that it was obtained after splenectomy, the morphology

is nevertheless essentially that of thalassaemia. One of us (W. W. Z.) has repeatedly seen the marked anisocytosis and the appearance of greatly macrocytic leptocytes after splenectomy in classical Caucasian thalassaemia major.

The patient's haemoglobin concentration in July, 1958, when the film was obtained, was 4 g./100 ml. At this time alkali denaturation by the Singer method revealed an excess of 35% foetal haemoglobin. Paper electrophoresis revealed only haemoglobins A and F, and this was confirmed by agar electrophoresis. The quantity available to us was insufficient for the determinations of the A₂ component on the starch block. X-ray films of the skull and long bones showed marked evidences of erythroid hyperplasia. Although the blood studies are less extensive than desirable, there seems little doubt of the diagnosis of thalassaemia major. The parents of this child were not available for study.

The second child (Dukwe) has since died, at 6 years of age, but prior to death repeated erythrocyte counts averaged 2,400,000 cells/c.mm., and the haemoglobin levels ranged between 7 and 7.5 g./100 ml. Blood specimens and blood films from the parents, a sibling, three paternal uncles, and two maternal uncles of Dukwe were flown to the United States for examination. In addition, blood films from two younger siblings of Dukwe were also available for

FIG. 1.—Blood film of Wle.

examination. Although the condition of the blood on arrival precluded complete study, the data obtained, summarized in the Table, suffice to establish a number of significant points.

1. The father (Klegyi) has a blood picture characterized by marked leptocytosis, target cells, and ovalocytes, as well as numerous irregularly shaped microcytes (Fig. 2). The sister (Nayi) has an almost identical blood picture (Fig. 3). She has a moderate anaemia, the father at most a mild one (see Table).

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Haematological Studies on the Family of a Child with Apparent Thalassaemia Major

Individual	Relationship to Patient	Hb (g./100 ml.)	A ₂ Hb (%)	Foetal Hb (%)	Film						
					Anisocytosis	Poikilocytosis	Target Cells	Ovalocytes	Microcytosis	Hypochromia	Spherocytosis
Klegyi	Father	11.2	†	42	—	—	—	—	—	—	—
					+++	+++	+++	+	++	+	+
Belloh	Mother	9.5	5.5	<1	—	0	0	—	—	—	—
					±	±	±	±	±	±	0
Nayi	Sister	12.2	†	34.5	+++	+++	+	++	++	0	+
David	Pat. uncle	8.6	—	<1	0	±	0	±	0	0	0
James	"	12.8	5.19	<1	0	±	0	±	0	0	0
Africa	"	14.3	2.76	<1	0	0	0	±	0	0	0
Korseneh	Mat. uncle	13.4	2.81	<1	±	0	0	±	0	±	0
Nyegbo	"	13.8	2.16	<1	0	0	0	0	0	0	0
Daheh	"	9.8	2.67	<1	—	—	—	—	—	—	—
Ghor	Brother	—	—	—	++	++	+++	++	+	++	0
	Sister	—	—	—	++	++	+++	+	+	++	0

† Values of the A₂ component on the starch block are not reported on this individual because the high concentration of foetal haemoglobin precluded adequate separation.

2. Both the father and the sister show a very marked elevation in the proportion of the haemoglobin, which is foetal in type.

3. The mother (Belloh) has an elevation in the A_2 component of her haemoglobin, a possible indication of thalassaemia minor. However, the accompanying cytological abnormalities are minimal.

4. A brother of the father exhibits suggestive morphological abnormalities of the erythrocytes in the absence of an elevated A_2 . Another brother, however, has an elevated A_2 component, though only minimal cytological abnormalities, resembling in this respect the mother.

Comment

Elevated foetal haemoglobin fractions in individuals who are *haematologically normal* have been encountered independently in Ghana by Edington and Lehmann (1955) and in Liberia by ourselves (Neel *et al.*, 1956; Zuelzer, 1958, 1959). Family studies have revealed that this characteristic is inherited as a dominant trait (Jacob and Raper, 1958; Went and MacIver, 1958). In our present family studies, the elevation in the proportion of foetal haemoglobin is accompanied by very significant cytological abnormalities. Unfortunately, in the presence of increased amounts of foetal haemoglobin the technique for A_2 determination becomes unreliable, and

FIG. 2.—Blood film of Klegyi, father of Dukwe.

FIG. 3.—Blood film of Nayi, sister of Dukwe.

we are thus unable to make an unequivocal statement concerning the A_2 proportions in these two individuals. However, the fact that one of the father's brothers had an elevated A_2 makes it highly probable that, independent of a gene for high F, Dukwe's father also possesses a second gene which may either be thalassaemia itself or, in any event, resemble thalassaemia in that it leads to an abnormally high A_2 component.

Discussion

At the moment there appear to be several alternative interpretations of the unusual findings in the two remarkable individuals Klegyi and Nayi. One would be that the haematological abnormalities are all manifestations of the gene responsible for the high foetal component. In this case these individuals would be the first presumed heterozygotes for this gene in whom there are marked haematological abnormalities. The second possibility is that the haematological manifestations are the expression of a single thalassaemia or thalassaemia-like gene. We have already referred above to the third and, to us, the most likely interpretation—namely, that the individuals in question are heterozygous both for the thalassaemia (or high A_2) gene and for the "high F haemoglobin" gene. They therefore appear to represent a new clinical haematological entity. The mother appears to have thalassaemia minor, unless one wishes to assume that a second non-thalassaemic gene can produce elevated A_2 as discussed above.

The son, Dukwe, who first brought the family to our attention, may be presumed to have inherited the thalassaemia gene from both parents—whether he also inherited the high foetal gene from his father it is impossible to say. An alternative interpretation concerning this son is that he owed his disease to the combination of a single thalassaemia gene inherited from his mother and a single "high foetal plus erythrocyte abnormalities" gene inherited from his father. In this case he would represent a new subtype of thalassaemia major, a situation corresponding to the recognition of genetic subtypes of sickle-cell disease (cf. Neel, 1952).

Subsequent to the recognition of these two children, an effort has been made to derive a *minimum* estimate of the frequency of thalassaemia minor in this part of Liberia. During a period of two months a total of 98 haemoglobin specimens from Liberia have been subjected to paper electrophoresis. The results on 21 of these were thought to be suggestive of the presence of increased amounts of A_2 , and these specimens were subjected to starch block electrophoresis. In 11 out of these 21 cases the presence of an increased amount of A_2 was confirmed. The minimal frequency of this characteristic, here taken as a probable indication of thalassaemia minor, is 11%. If there occur in Liberia other significant causes of an increased A_2 component, then this is of course an overestimate. On the other hand, inasmuch as the presence of an increased amount of A_2 often cannot be suspected on the basis of paper electrophoresis, the true frequency of thalassaemia minor (or high A_2) may well be even higher than these rather surprising results would indicate.

Despite a great deal of haematological research in Africa south of the Sahara, thalassaemia major has been encountered on only one previous occasion (Vandepitte, 1959), and may be assumed to be quite rare (Jacob and Raper, 1958). The presence of thalassaemia minor in the Belgian Congo has been the subject of a recent paper,

but the data do not permit a frequency estimation (Stijns and Charles, 1956). At the moment it would appear legitimate to infer that, in addition to the haematological characteristics mentioned earlier, at least some of the tribes of south-eastern Liberia are also distinguished by a relatively high frequency of the thalassaemia gene or a gene behaving much like thalassaemia. In a number of haematological respects, then, they manifest a closer affinity to certain of the peoples of North Africa than to the tribes who now surround them, tribes some of whose ancestors apparently have migrated westwards from the vicinity of Nigeria in relatively recent times (Livingstone, 1957).

Summary

This report deals with evidence for the occurrence of thalassaemia in Liberia, and for a gene independent of thalassaemia associated with the production of high concentrations of foetal haemoglobin. This evidence is based on the cases of two children seen at the Firestone Hospital, in south-eastern Liberia, presenting the clinical and haematological features characteristic of thalassaemia major together with significant findings in several members of the family of one of them (Dukwe); and on a preliminary survey of thalassaemia minor in this part of Liberia indicating a minimum frequency of 11%. A new haematological entity is proposed in the case of the father and sister, representing a heterozygous state both for the thalassaemia (or high A_2) gene and for the high F "haemoglobin" gene. The possibility that the disease of the propositus (Dukwe) is the result of a new subtype of thalassaemia major is also considered.

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In presenting the Sixth Annual Report of the National Fund for Poliomyelitis Research, Sir CHARLES DANIEL, the chairman, said, "The total sum raised this year is some £9,000 greater than last year's figure, but the relative cost of raising this amount has also increased slightly. This is due to two main factors. On May 1, 1958, the National Fund announced its special appeal for £500,000. This entailed considerable initial expenditure on advertising. The second cause is a slight but definite hardening that we have detected in the attitude of the public. There is no doubt that, with the more general availability in this country of poliomyelitis vaccine, the emotional appeal connected with poliomyelitis has to a certain extent lessened. This is not to say that there is any feeling that the Fund's usefulness has diminished. Nor is there any suggestion that considerable work does not still remain to be done in the field of poliomyelitis prevention, while, of course, there is no decrease in the problems of poliomyelitis treatment and rehabilitation."

DISTURBANCES OF PIGMENTATION WITH CHLOROQUINE

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The use of antimalarial preparations in the treatment of rheumatoid arthritis originated in an observation by Page (1951) that two patients with coexistent rheumatoid arthritis showed a marked amelioration of joint symptoms while under treatment with mepacrine for chronic discoid lupus erythematosus. This finding was substantiated by later workers (Bagnall, 1957; Fuld and Horwich, 1958). Mepacrine has now been abandoned in favour of chloroquine because the former drug was shown to cause discoloration of the skin and agranulocytosis (Custer, 1946; Bagnall, 1957).

The value of chloroquine in the treatment of rheumatoid arthritis has not yet been fully assessed, and it will take some time before its worth can be accurately determined. A recent report (Fuld and Horwich, 1958) suggests that it is a successful form of therapy with minimal side-effects when used in a dose of 400–600 mg. daily.

In view of this report of the comparative lack of side-effects it is felt that attention should be drawn to the following disturbances of pigmentation which have been observed in three patients treated with chloroquine. Two of the patients have rheumatoid arthritis, and the third suffers from disseminated lupus erythematosus.

Case 1

An unmarried medium brunette aged 22 was seen in November, 1957, and gave a history of pain and swelling in the wrists, hands, knees, and ankles of five months' duration. The appearance of the joints was typical of early acute rheumatoid arthritis. The sedimentation rate was 42 mm. in one hour (Westergren). Initial treatment with aspirin and phenylbutazone did not produce satisfactory improvement, and it was then decided to try chloroquine diphosphate ("avlocor"). This was given in a dose of 250 mg. b.d. for one week and then increased to 250 mg. t.i.d. for a further week. Within the two weeks objective and subjective improvement occurred; the joints were less painful with increased range of movement, and the sedimentation rate fell to normal. Treatment was maintained with 250 mg. b.d. thereafter.

The first indication of toxic reaction presented after seven weeks' treatment, when she complained of "glare" when looking at lights, blurring of vision, and nausea. Ophthalmological examination showed no abnormality. At this time the dose of chloroquine was reduced to 250 mg. daily; her joints remained pain-free and the visual upset subsided. After 11 weeks of treatment it was noticed that her eyebrows and eyelashes had become fairer and the proximal $\frac{1}{4}$ in. (6 mm.) of the scalp hair had become much lighter in colour. When seen again after 20 weeks' therapy there was obvious bleaching of the scalp hair. The eyelashes, eyebrows, and axillary and pubic hair were also bleached. She complained that on exposure to sunlight her