Homozygous β thalassaemia in Liberia

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Summary. The clinical and haematological findings in 19 Liberians probably homozygous for β thalassaemia are described. The haemoglobin patterns were similar with Hb F levels in the 30-50% range and a raised level of Hb A₂ and, although the clinical severity varied widely, over half the cases were symptomless and even the more severely affected ones showed a milder picture than that found in Mediterranean races. Haemoglobin-synthesis studies carried out on three homozygotes and two heterozygotes indicated a variable degree of globin-chain imbalance. The reasons for the mild course of the disease in Liberians and other African races are discussed; it is likely that the β -thalassaemia genes in these populations are different from those in other racial groups. It is noted that all persons in this study belong to tribes which have a low incidence of the sickle-cell gene.

Thalassaemia syndromes have been described in most racial groups (Weatherall and Clegg, 1972). However, it has been stated that in Africa, whilst thalassaemia occurs in populations bordering the Sahara, it occurs rarely within the 'sickling belt' (Raper, 1970). Nonetheless published data obtained from surveys and other sources show that the syndromes are encountered occasionally in the African Negro (Stijns and Charles, 1956; Vandepitte, 1959; Watson-Williams, 1965; Esan, 1970; Weatherall *et al*, 1971) and there are indications that in parts of West Africa, mainly Northern Ghana (Ringlehann *et al*, 1968), Upper Volta (Rucknagel and Neel, 1961), and more especially Liberia and its environs (Olesen *et al*, 1959; Neel *et al*, 1961; Willcox, 1975), thalassaemia reaches a fairly high frequency. Homozygous β thalassaemia has also been reported occasionally in American Negroes and recent reports indicate that, judged by *in-vitro* haemoglobin synthesis studies, the condition is remarkably heterogeneous, even in the few cases studied in detail (Scott *et al*, 1962; Weatherall, 1964; Friedman *et al*, 1972; Braverman *et al*, 1973).

During five years' experience in two widely-

separated hospitals in Liberia various thalassaemia syndromes including homozygous β thalassaemia have been often encountered. However, because of the widely held, but mistaken, belief that the latter disorder is only to be found amongst people of Mediterranean extraction, and not in a Negro population, many cases must have been missed in the past and indeed are still overlooked, the manifestations of thalassaemia being attributed to some other cause. The purpose of this report is to describe the clinical and haematological features of homozygous β thalassaemia in a group of West African Negroes and to demonstrate the wide variation in clinical severity in cases having a similar haemoglobin pattern.

Materials and methods

The 19 individuals described were either patients at one of the hospitals at Buchanan on the coast of Liberia or at Yekepa in Northern Liberia, or individuals who were discovered during a thalassaemia survey which has been described previously (Willcox, 1975).

Standard manual haematological methods were used throughout (Dacie and Lewis, 1970). Routine haemoglobin electrophoresis and estimation of Hb-A₂ levels were performed using cellulose acetate as a supporting medium (Weatherall *et al*, 1971). Fetal haemoglobin was determined by a modification of the method of Betke (Weatherall and Clegg, 1972); in five cases the technique of Singer *et al* (1951) was used. In some cases haemoglobin analysis was carried out on starch-gel electrophoresis in a Tris-EDTA-borate buffer system, pH

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8.5, as described by Weatherall and Clegg (1972). The relative rates of α -, β -, and γ -chain production in reticulocytes were determined by short-term *in-vitro* incubations with ^3H leucine as described by Weatherall *et al* (1969).

Results

Family S.

Clinical findings. L.S., a 24-year-old male Mano, was admitted to hospital for observation with a respiratory infection. He had no abnormal physical signs; in particular there were no skeletal deformities and his spleen was not enlarged. On routine haematological examination he was found to be moderately anaemic with a blood film showing the morphological features of thalassaemia. On checking his past medical records it was found that he had a history of 'dark urine' and 'yellow eyes' with haemoglobin levels between 9.0 and 11.0 g/dl. Liver function tests performed a year before admission showed a moderately raised bilirubin with slightly increased transaminases and turbidities. Urinary

urobilinogen was markedly increased. He was discharged after 3 days in hospital.

Haematological findings. The haematological findings were: Hb 11.6 g/dl, RBC $5.8 \times 10^{12}/\text{l}$, MCH 20 pg, MCHC 30.5 g/dl, MCV 65 fl, reticulocytes 11.6%. Blood film showed marked hypochromia with aniso-poikilocytosis, marked polychromasia, some target cells, and a few circulating normoblasts. Haemolysis was not complete at 0.2% NaCl in the osmotic fragility test. Haemoglobin analysis revealed a Hb-F value of 44.5% and a Hb A₂ of 4.6%. The Hb F was heterogeneously distributed among the red cells.

Family study. The family pedigree is shown in Fig. 1 and the haematological data in Table I. The mother had died 10 years previously giving birth to twin boys. The proband had eight living sibs including non-identical twins. An elder sister, said to be an albino, had died several years earlier. It will be seen that six sibs have the pattern of homozygous β thalassaemia. The Hb-F levels ranged from 29–57% and in each case it was distributed heterogeneously among the red cells. None of these persons showed any disability from their disorder and their previous medical histories were normal except that one female sib had been moderately anaemic during each pregnancy but after delivery the haemoglobin level had risen to between 10 and 12 g/dl. It was not possible to obtain any reliable information about the mother except that she was probably anaemic. It seems very likely that she was a thalassaemia homozygote. If she had been

FIG. 1. Pedigree of family S.

TABLE I
ROUTINE HAEMATOLOGY AND HAEMOGLOBIN ANALYSIS IN FAMILIES

Pedigree No.	Age	Hb (g/dl)	RBC ($\times 10^{12}/\text{l}$)	MCH (pg)	MCV (fl)	MCHC (g/dl)	RBC Morphology*	Hb A ₂ (%)	Hb F (%)
I.1	A	13.3	5.2	25.6	82.7	30.9	(+)	5.0	0.9
I.3	A	10.7	3.8	28.1	92.1	30.5	Normal	2.2	0.7
II.2	A	15.2	5.3	28.7	87.0	33.0	Normal	2.7	0.7
II.3	30	12.3	5.4	22.7	68.5	33.2	++	4.4	48.2
II.4	28	14.1	6.0	23.5	75.0	31.3	(+)	3.8	0.9
II.6	26	14.0	6.0	23.3	73.3	31.8	++	5.2	46.1
II.8	22	11.6	5.2	22.3	73.1	30.5	++	5.8	29.0
II.9	19	12.9	5.5	23.4	74.5	31.4	(+)	3.9	1.0
II.10	17	10.8	3.9	27.6	87.1	31.8	++	3.1	57.5
II.11	10	11.2	5.5	20.3	69.0	29.5	++	3.6	46.0
II.12	10	12.8	6.1	20.9	63.9	32.8	+	6.0	42.0
II.13	9	10.7	3.9	27.4	79.4	34.5	Normal	2.6	0.6
II.14	7	11.5	4.2	27.4	90.4	30.3	(+)	6.0	0.6
II.15	6	10.6	4.0	26.5	85.0	31.1	Normal	2.9	0.6
III.1	13	12.0	4.5	26.7	88.9	30.0	(+)	4.0	2.9
III.2	8	11.3	5.0	22.6	74.0	30.5	(+)	4.7	2.3
III.3	7	11.6	4.7	24.6	82.9	29.7	(+)	4.0	2.9
III.4	5	11.4	5.2	21.9	69.2	31.7	(+)	4.4	1.2
III.5	20/12	11.4	5.5	20.7	60.0	34.5	(+)	4.6	3.3

* RBC morphology (+) indicates slight abnormalities, + and ++ more severe abnormalities.

TABLE II
HAEMOGLOBIN SYNTHESIS DATA ON FAMILY MEMBERS

Family	Family Member	Diagnosis	α Chain (total cpm)	$\beta + \gamma$ Chain (total cpm)	β Chain (total cpm)	α/β	$\alpha/\beta + \gamma$
S	Propositus	β -Thalassaemia homozygote	6200	2333	—	—	2.6
	Sister	β -Thalassaemia homozygote	7088	2772	—	—	2.5
		β -Thalassaemia homozygote	6210	4290	—	—	1.4
J	Propositus	β -Thalassaemia homozygote	7670	4620	—	—	1.6
	Father	β -Thalassaemia heterozygote	4120	—	4080	1.0	—
	Mother	β -Thalassaemia heterozygote	1994	—	1488	1.3	—

FIG. 2. Globin-chain synthesis in the peripheral blood of L.S. The cells were incubated for 1 hour with 50 μ Ci of 3 H leucine and 'total cell globin' prepared (see Methods). The column was washed until all non-absorbed material was eluted and a salt gradient started at the position marked by the arrow. The elution profile of the γ , β , and α chains together with the incorporated radioactivity is shown.

heterozygous for β thalassaemia the probability of there being seven homozygous children would have been less than 1 in 500.

Haemoglobin synthesis. The relative rates of synthesis of α , β , and γ chains in the peripheral blood of L.S. and one of his homozygous sibs were determined by 3 H leucine incorporation studies. The results are summarized in Table II and Fig. 2. The ratio of $\alpha/\beta + \gamma$ radioactivity in two separate determinations on the cells of the propositus was 2.66 and 2.55 while that of a homozygous sib was 1.45.

Family J

Clinical findings. M.J., an 8-year-old girl, was found to have the haematological picture of homozygous β thalassaemia during a school survey. According to her well-baby and school-health re-

cords she had never been sick apart from occasional cough and fever, and worm infestations. She had no abnormal physical signs and her spleen was not enlarged.

Haematological findings. Hb 12.3 g/dl, RBC $6.3 \times 10^{12}/l$, MCH 19.5 pg, MCHC 33.2 g/dl, MCV 58.7 fl, reticulocytes 3.5%. The blood film showed a hypochromic microcytic picture with anisocytosis, poikilocytosis, polychromasia, and target cells. In an osmotic fragility study haemolysis was not complete at 0.2% NaCl. The Hb A₂ was 5.9% and Hb F 43.6% with a heterogeneous distribution among the red cells.

Family study. M.J.'s father was Grebo and her mother Kru; there was a younger sister. The parents and sister all had β -thalassaemia trait. They were not anaemic but the MCH values were slightly reduced being 25 pg in the father, 23 pg in the mother, and 22 pg in the sister. The red cells of each showed slight morphological abnormalities. The father had an Hb-A₂ level of 5.9% and an Hb F of 2.8%; the mother's values were Hb A₂ 4.5% and Hb F 2.5% and the sister's Hb A₂ 5.2% and Hb F 4.5%. A second wife and her two elder children were normal. The younger child aged 8 months, had an Hb level of 10.8 g/dl and an MCH of 22 pg with a hypochromic, microcytic blood picture showing some target cells. The Hb-F level was 12.8% but the Hb A₂ was 2.4%. It was thought this could possibly have been β -thalassaemia trait with associated iron deficiency causing a reduction of the Hb A₂ level to the normal range.

Haemoglobin synthesis. Haemoglobin synthesis studies were carried out on the propositus and both parents (Table II). The $\alpha/\beta + \gamma$ 3 H-leucine incorporation ratio in the cells of the propositus was 1.66. Despite the findings of heterozygous β thalassaemia in both parents, the α/β incorporation ratios were 1.00 in the father and 1.34 in the mother.

TABLE III
ROUTINE HAEMATOLOGY AND HAEMOGLOBIN ANALYSIS IN FAMILY W

Relationship to propositus	Age	Hb (g/dl)	RBC ($\times 10^{12}/l$)	MCH (pg)	MCV (fl)	MCHC (g/dl)	RBC Morphology*	Hb A ₂ (%)	Hb F (%)
Husband	A	14.6	5.1	28.6	84.3	33.9	Normal	3.0	0.7
Son	9	11.2	4.5	24.9	82.2	30.3	+	5.6	0.7
Son	8	11.6	5.0	23.2	74.0	31.3	+	6.2	2.4
Daughter	6	10.6	4.9	21.6	67.3	32.1	+	5.7	1.5
Son	5	12.2	5.2	23.2	66.6	34.8	+	6.3	2.6
Daughter	7/12	10.8	4.5	24.0	68.8	34.8	+	3.9	5.0
Daughter	7/12	11.4	4.4	25.9	70.4	36.7	+	3.9	6.5

* RBC morphology: + indicates moderate abnormalities with microcytosis, aniso-poikilocytosis, and some target cells.

Family W

Clinical findings. R.W., a 26-year-old Kru woman, delivered twins in hospital. She was found to be anaemic with a blood picture suggestive of thalassaemia. She showed no abnormal physical signs and her spleen was not enlarged. Apart from anaemia in previous pregnancies she had been well. Following discharge regular checks were made and 1 year after delivery she was well with a haemoglobin remaining at about 11 g/dl.

Haematological findings. Immediately after delivery the Hb was 7.9 g/dl and a blood film showed marked red-cell abnormalities with circulating normoblasts. The Hb A₂ was 6.5% and the Hb F 40%. One month after discharge the Hb was 10.8 g/dl, RBC $5.0 \times 10^{12}/l$, MCH 21.6 pg, MCHC 25.1 g/dl, MCV 69.7 fl, and reticulocytes 7.8%. The blood film still showed marked abnormalities with target cells but this time no normoblasts were seen. The Hb-A₂ level was 5.2% and the Hb F was 41.3%; the latter was heterogeneously distributed among the red cells.

Family study. R.W. was married and had six living children. One child had died from bronchopneumonia at the age of 18 months and another was stillborn. The husband was normal and all the children had β -thalassaemia trait (Table III). The twin girls were investigated when they were 7 months old.

Family E

Clinical findings. J.E. was a Bassa male aged 8 years. He was admitted to Yekepa hospital with severe anaemia, icterus, and gross splenic enlargement (Fig. 3). It was not known how long he had been ill. Radiology of the skull and hands showed mild changes, consistent with thalassaemia intermedia. He was transfused and a splenectomy performed. Post-operatively he developed malaria. The histological report on the spleen from Karo-

FIG. 3. Case J.E., aged 8 years.

linska Hospital, Stockholm stated that the appearances were consistent with thalassaemia major.

Haematological findings. Hb 5.2 g/dl, RBC $3.2 \times 10^{12}/l$, MCH 16.2 pg, MCHC 24.5 g/dl, MCV 67.5 fl, reticulocytes 8.0%. The blood film showed morphological changes of the type seen in thalassaemia, with many circulating normoblasts. Osmotic fragility was decreased, haemolysis not being complete at 0.2% NaCl, and the bone marrow showed normoblastic hyperplasia with positive iron staining. The Hb A₂ level was 5.1% and the Hb F

32.2%; the latter was heterogeneously distributed among the red cells.

Family study. The father was dead. The mother, paternal uncle, and elder brother all had β -thalassaemia trait. None were anaemic but the MCH values were low, being 22.8 pg in the mother and 24.6 pg in both males. The mother showed moderate morphological changes of the red cells, and the other two slight changes only. The mother had an Hb A₂ of 5.9% and Hb F 1.4%, the uncle Hb A₂ 4.6% and Hb F 1.1%, and the brother Hb A₂ 4.3% and Hb F 4.1%.

Family K

Clinical findings. N.K. was a small Mano girl, said to be 6 years old but appearing rather more.* She was admitted with anaemia, icterus, and a grossly enlarged spleen; the liver was also enlarged. Skull radiology showed slight widening of the diploë but without a fully-developed 'hair-on-end' appearance. She was treated with folic acid and chloroquin in spite of a negative malaria smear. The spleen reduced in size slightly and she was discharged after a stay in hospital of about 2 months. Hb was then 8.5 g/dl. No follow up studies were possible.

Haematological findings. Hb 7.4 g/dl, RBC $3.54 \times 10^{12}/l$, MCH 20.9 pg, MCHC 29.6 g/dl, MCV 70 fl, reticulocytes 22%. The blood film showed marked red-cell abnormalities with circulating normoblasts. Osmotic fragility was reduced, haemolysis is not being complete at 0.2% NaCl. The iliac-crest marrow showed normoblastic hyperplasia with excess iron. The Hb A₂ was 6.4% and Hb-F 27.8%; the latter was distributed heterogeneously among the red cells.

Family study. Both parents were investigated. Neither was anaemic but both had the pattern of thalassaemia trait with low MCH values, slight morphological abnormalities of the erythrocytes, and Hb-A₂ levels of 4.6% and 7.0%, and Hb-F levels of 1.7% and 1.8%, respectively.

Family G

Clinical findings. D.G., a Gio girl of 6 or 7 years, was admitted with malaria and was treated with chloroquine and folic acid.

Haematological findings. Hb 7.2 g/dl, RBC $4.0 \times 10^{12}/l$, MCH 18 pg, MCHC 28 g/dl, MCV 62 fl, reticulocytes 12%. The blood film showed marked

erythrocyte abnormalities with circulating normoblasts. Iliac-crest marrow showed normoblastic hyperplasia with increased iron. Haemolysis was just complete at 0.2% NaCl in the osmotic fragility test. The Hb-A₂ level was 5.1% and the Hb F 42.5% with a heterogeneous distribution.

Family study. Both parents and two sibs were living but it was only possible to investigate the mother. Her blood showed the pattern of β -thalassaemia trait with a low MCH, slight morphological changes of the erythrocytes, and a Hb A₂ level of 5.0% and an Hb F of 1.1%.

Family N

Clinical findings. T.N., a female Bassa child of about 5 years of age, was referred to the laboratory from a workers' polyclinic because of anaemia and splenomegaly. Only a few preliminary investigations were made and the child was not brought back to the clinic.

Haematological findings. Hb 5.4 g/dl, MCHC 28 g/dl. Blood film showed a hypochromic picture with marked red-cell abnormalities and some circulating normoblasts. A smear for malarial parasites was negative. Haemoglobin analysis showed an Hb A₂ of 3.8% and an Hb F of 44.6%.

Family studies. Blood samples were taken from the mother and a younger brother, at the same time as the patient. Both were moderately anaemic. The mother had the pattern of S thalassaemia with Hb S 52.3%, Hb F 20.1%, and Hb A₂ 3.5%. The brother had sickle-cell trait.

Case S.L.

Clinical findings. S.L. was a 10-year-old girl from the Bassa tribe. She was admitted to Buchanan hospital with a 7-year history of anaemia, icterus and a massively enlarged spleen. She was not transfused and after diagnosis was treated with folic acid. She was discharged after about a month in hospital and was not seen again. Although the parents were contacted no family studies were possible.

Haematological findings. Hb 6.6 g/dl, MCHC 30 g/dl, reticulocytes 13.8%. The blood film showed a hypochromic microcytic picture with marked aniso-poikilocytosis, polychromasia, basophilic stippling, and many circulating normoblasts. Osmotic fragility curves showed an increased resistance; haemolysis was not complete at 0.2% NaCl. The bone marrow showed normoblastic hyperplasia. The Hb A₂ was 6.2% and Hb F 30.7%.

* In many cases it was impossible to obtain accurate date-of-birth data.

Case E.N.

Clinical findings. E.N., a 13-year-old Grebo girl was first admitted to Yekepa hospital in 1968. She had splenomegaly and anaemia with a Hb of 7.3 g/dl. Her blood film showed marked abnormalities with many circulating normoblasts. She was transfused with 3 units of blood and discharged shortly after; the Hb was then 8.5 g/dl. She was readmitted in 1969 with a Hb of 6.0 g/dl. After transfusion splenectomy was performed. The histological report from Sweden was 'haemolytic anaemia of unknown aetiology'. Her Hb level at discharge was 9.6 g/dl. She was admitted again 18 months later with abdominal pain and developed deep jaundice 24 hours after admission. The jaundice improved gradually and she was discharged 3 weeks later. During the last period in hospital she was investigated more thoroughly and found to have the laboratory findings of thalassaemia major. Radiology of skull and long bones showed changes consistent with this diagnosis. No family studies were made and the patient was not seen again after discharge.

Haematological findings. The results at her last admission were: Hb 8.0 g/dl, MCHC 31 g/dl, reticulocytes, 10%; the blood film showed a hypochromic microcytic picture with marked anisocytosis, poikilocytosis, polychromasia, basophilic stippling, and large numbers of circulating normoblasts. A malaria smear was negative. The bone marrow showed normoblastic hyperplasia. The Hb A₂ was 5.0% and Hb F 40%.

Case M.B., a 15-year-old male, was admitted to Yekepa hospital with anaemia, icterus, and massive splenomegaly. His tribe was not recorded but he was probably Bassa. After laboratory investigation he was transfused with 4 units of blood and discharged a month later; the Hb level was then 9.4 g/dl. No family studies were possible.

Haematological results. Hb 5.2 g/dl. Blood film showed marked red-cell abnormalities with target cells and circulating normoblasts. The Hb A₂ was 5.7% and Hb F 37%.

Case G.S.T.

Clinical findings. G.S.T., a multiparous Bassa woman of between 40 and 50 years of age, was admitted to Yekeba hospital with severe anaemia and hepatosplenomegaly. She was also found to have an aortic aneurysm. Radiology of the skull, carried out because of the blood findings, demonstrated some widening of the diploë without a 'hair-on-end' appearance. Following laboratory investiga-

tion she was transfused with 2 units of blood and discharged after about a month in hospital. Her Hb at that time was 7.5 g/dl. No family studies were possible.

Haematological results. The Hb was 4.4 g/dl; reticulocytes 8.3%. The blood film showed a hypochromic microcytic picture with marked anisopoikilocytosis, polychromasia and basophilic stippling. Circulating normoblasts were present. A malaria smear was negative. The sternal marrow showed normoblastic hyperplasia and contained excessive iron. Osmotic fragility was decreased, haemolysis was not complete at 0.2% NaCl. Hb A₂ level was 5.9% and Hb F 87%, both estimations being made before the transfusion.

Case A.M.

Clinical findings. A.M., a 15-year-old Bassa male, was admitted to Yekepa hospital with pneumonia, anaemia, and malaria. He complained of pains in the long bones. He was icteric and showed moderate splenomegaly. He was discharged after treatment for malaria and pneumonia. No family studies were made and the patient was not seen again.

Haematological findings. Hb 6.4 g/dl, reticulocytes 10%. Blood film showed hypochromia with marked aniso-poikilocytosis, target cells, polychromasia and basophilic stippling. Circulating normoblasts were present. The Hb A₂ was 7.5% and Hb F 37.4%.

Case D.P.P.

Clinical findings. D.P.P., a 20-year-old male Grebo, was admitted to Yekepa hospital for investigation of anaemia, icterus, and splenomegaly. Skull and bone radiology showed appearances consistent with thalassaemia major. Family studies were not possible as relatives all lived in South East Liberia. The patient stated that he had a younger brother who had been in a Liberian Government Hospital for severe anaemia but no further details were known.

Haematological studies. Hb 7.0 g/dl, RBC $3.7 \times 10^{12}/l$, MCH 18.9 pg, MCHC 32 g/dl, MCV 60 fl, reticulocytes, 10%. Blood film showed marked red-cell abnormalities (Fig. 4) including target cells and there were some circulating normoblasts. Osmotic fragility was decreased, haemolysis not being complete at 0.2% NaCl. Sternal marrow showed normoblastic hyperplasia with excess iron. The Hb A₂ was 6.3% and the Hb F 42.1%; the

FIG. 4. Case D.P.P., blood film. (May-Grünwald Giemsa, $\times 250$.)

FIG. 5. Case D.P.P., acid-elution preparation of blood film. ($\times 250$.)

latter was heterogeneously distributed among the red cells (Fig. 5).

Discussion

We have described the clinical and haematological findings together with the haemoglobin constitution in 19 individuals apparently homozygous for β thalassaemia. Because this group contains, as far as we know, the largest number of Negro β -thalassaemia homozygotes yet to be reported, and because of the remarkable clinical heterogeneity shown by these patients, it is particularly important to decide whether they all represent genuine β -thalassaemia homozygotes. The clinical and haematological findings were those of thalassaemia minor or intermedia. In every case there was an elevated level of Hb F with values ranging between 28% and 87% for the entire group. Furthermore the Hb-A₂ level was elevated in all cases. Family studies, where complete, showed typical heterozygous β thalassaemia with elevated levels of Hb A₂, and in some cases of Hb F, in both parents, sibs, or children of the apparent homozygotes. There was no evidence

suggestive of $\delta\beta$ thalassaemia or hereditary persistence of fetal haemoglobin in any of these families.

Although there was a broad spectrum of clinical disability in this group the disease is obviously milder than that found in other racial groups. Thus the seven affected homozygotes in family S had no clinical abnormalities and those in families J and W showed no more disability than do β -thalassaemia heterozygotes in other racial groups. Even in those who were more severely affected the presenting age ranged from 6 to 20 years which is certainly much later than for β -thalassaemia homozygotes in other racial groups. Furthermore, in at least two of the cases who came to splenectomy malaria may have contributed to the splenomegaly. The radiological changes in the bones, although definite, were not nearly as severe as those seen in β -thalassaemia homozygotes in other racial groups. This last observation suggests that the degree of ineffective erythropoiesis and the expansion of the erythroid mass is considerably less in this group of Negro homozygotes than is usually observed in homozygous β thalassaemia.

Why then does the homozygous state for β thalassaemia in Liberia result in a milder clinical picture than that observed in Mediterranean races? There are two main possibilities. One is that there are other genes segregating in these families which reduce the severity of expression of the β -thalassaemia gene. It is now well established that the presence of an α -thalassaemia gene in individuals homozygous or heterozygous for β thalassaemia reduces the degree of globin-chain imbalance and hence the degree of ineffective erythropoiesis (Kan and Nathan, 1970; Knox-Macaulay *et al*, 1973). Although we do not have biosynthetic data on many family members in this study, even on genetic evidence it seems unlikely that this is the explanation. Thus in family S where there are seven mildly-affected homozygotes each would have had to have inherited an α -thalassaemia gene as well as the two β -thalassaemia genes and this seems an unlikely event. Since there are no obvious environmental factors which might ameliorate the action of the β -thalassaemia genes in this population we are left with the second possibility, i.e. that β -thalassaemia genes in this Negro population are different from those in other populations.

An unusually mild form of thalassaemia major was reported in two children from Liberia by Olesen *et al* (1959) and these cases appear to be similar to the more severely affected individuals in the present series. Although Olesen *et al* (1959) thought that the patients might be heterozygous for β thalassaemia and hereditary persistence of fetal haemoglobin this now seems unlikely. Mild homozygous β thalassaemia has been well documented in American Negroes (Scott *et al*, 1962; Weatherall, 1964; Crouch *et al*, 1970 [who reviewed 10 similar cases found in the literature]; Friedman *et al*, 1972; Braverman *et al*, 1973). Although, like the present series, these cases have shown considerable variability of clinical disability, there is no doubt that the condition is milder than is seen in Mediterranean races; indeed many cases were asymptomatic and have never required transfusion. The haemoglobin patterns in these reports are remarkably similar to those observed in the Liberian cases. Thus in most cases the Hb F level has ranged between 30 and 50% and there has practically always been an elevated level of Hb A₂. The latter finding is different from that observed in non-Negro patients with homozygous β thalassaemia in which the Hb A₂ level may be subnormal or normal and is only rarely elevated (reviewed by Weatherall and Clegg, 1972). Thus this is a form of β thalassaemia⁺ with a rather constant level of Hb F, an

elevated level of Hb A₂, and a variable but relatively mild clinical expression. Whether this is a different type of thalassaemia mutation to Mediterranean β thalassaemia, or whether it is the same mutation modified by other genetic factors in the Negro, remains to be ascertained.

β Thalassaemia^o occurs occasionally in Negroes (Weatherall, 1964) but the homozygous state has only been observed occasionally (Ringelmann and Rudwick, 1972). This produces the clinical picture of classical Cooley's anaemia. It was not observed in the present study. There may well be another form of β thalassaemia in Africans in which Hb-A synthesis occurs at about 5% of the total haemoglobin (Weatherall, 1964). This may have been observed in case G.S.T. in the present series although detailed follow-up studies were not possible.

The haemoglobin synthesis findings in the present study are rather similar to those reported previously for Negro β -thalassaemia homozygotes (Hamilton and Schwartz, 1970; Friedman *et al*, 1972; Braverman *et al*, 1973). There was a moderate degree of globin-chain imbalance in the homozygotes although less than that usually observed in the severely affected non-Negro cases (Weatherall *et al*, 1965). Of the two heterozygotes studied in the present study, one showed balanced synthesis similar to that reported by Hamilton and Schwartz (1970), while the other showed slight chain imbalance at the lower range of that seen in non-Negro β -thalassaemia heterozygotes (Knox-Macaulay *et al*, 1973).

All evidence indicates therefore that homozygous β thalassaemia with a variety of clinical pictures is fairly common in Liberia and probably the neighbouring parts of Guinea and Ivory Coast. It is important that the clinician be aware of this or the condition will continue to go unrecognized together with other syndromes that can be expected when thalassaemia is present in the same population as structural haemoglobin variants. Furthermore, the diagnosis may be complicated because of other diseases causing splenomegaly, icterus and anaemia, which may be found together with thalassaemia in the same patient. The most common of these in Liberia is chronic malaria. If a thalassaemia homozygote is found to have a positive malaria smear the manifestations may be attributed to malaria only and thalassaemia remain undiagnosed. Routine haemoglobin analysis with Hb A₂ and F estimations would of course disclose β thalassaemia, but these investigations are beyond the scope of most hospital laboratories in Liberia at the moment. A simple screening test for β thalassaemia is required. Because of the remarkable homogeneity of the haemoglobin patterns in the homozygotes an alkali-

denaturation technique for estimating Hb F would be a very simple preliminary investigation in such cases.

The significance of the fact that a large number of cases of β thalassaemia come from Northern Liberia is uncertain; it may be reflection of the greater interest shown in the problem in Yekepa during 1972–73. There is evidence however for a tribal distribution of β thalassaemia, the majority of cases diagnosed being from the Kru linguistic group of tribes ie, Bassa, Kru, Grebo, etc. The other two tribes represented in this report speak a Mande tongue. It is interesting that these two, the Mano and Gio, together with the Kru group, are the tribes with the lowest sickling rates in Liberia (Livingstone, 1958). The significance of this observation is discussed elsewhere (Willcox, 1975).

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