MEDICAL PRACTICE

Occasional Survey

Thalassaemia in the British

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British Medical Journal, 1973, 3, 150-155

Summary

Different forms of thalassaemia or related disorders were found in 116 people of apparently pure British stock. Among them were one family with a child homozygous for β -thalassaemia and eight heterozygous relatives, 16 families with 83 persons heterozygous for β -thalassaemia, two families with three persons with Hb H disease and three heterozygous for α -thalassaemia 1, one family with a child apparently homozygous for the "silent β -thalassaemia gene," one family with six members heterozygous for a form of β -thalassaemia intermedia, and three families with 11 members heterozygous for different types of hereditary persistence of fetal haemoglobin. The clinical, haematological, and haemoglobin biosynthetic findings in these persons were similar to those of patients with thalassaemia from other racial groups. The heterozygous state for β -thalassaemia is overlooked in British patients, particularly during pregnancy, because it is not considered in the differential diagnosis of refractory anaemia. In many cases this leads to much unnecessary investigation and potentially harmful treatment.

There seem to be several varieties of hereditary persistence of fetal haemoglobin production among British people. These conditions, while not causing anaemia, may cause difficulties during examination of maternal blood for fetal cells and may, if inherited with a β -thalassaemia gene, produce an unusually high level of Hb F in a person heterozygous for β -thalassaemia.

Introduction

The thalassaemia syndromes are a group of genetic disorders of haemoglobin synthesis characterized by a reduced rate of production of one or more of the globin chains of haemoglobin.¹ They are common in the Mediterranean region, the Middle East, India and Pakistan, and throughout South-east Asia. Thalassaemia has been sporadically reported in families of British descent,²⁻⁶ but these syndromes are thought to occur rarely in North European populations. In the past five years we have seen 116 people of apparently pure British stock with different forms of thalassaemia or related disorders. Because of the varied clinical manifestations and lack of recognition that these disorders may occur in the British, some of these patients had had innumerable investigations and years of unnecessary and possibly harmful treatment before the correct diagnosis was finally established.

We review here the clinical, haematological, and haemoglobin biosynthetic findings in these patients to try to define further a clinical picture which should alert doctors to the diagnosis of thalassaemia in British people.

Patients and Methods

The 116 patients were referred either because of a refractory anaemia or an unusual blood picture found on routine examination or for the confirmation of a suspected diagnosis of thalassaemia. Detailed family studies showed no relatives of Mediterranean, African, or Oriental origin. The group was made up of 16 families containing 83 individuals heterozygous for β -thalassaemia, one family with a child homozygous for β -thalassaemia and eight heterozygous relatives, one family with six members with a form of β -thalassaemia intermedia, two families containing three persons with Hb H thalassaemia, one family with a member apparently homozygous for the "silent" β -thalassaemia gene, and three families with 11 members with disorders similar

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to β -thalassaemia or hereditary persistence of fetal haemoglobin. Clinical data on two of these families have been presented elsewhere,^{7,8} and they have been restudied in detail for the present report.

To obtain a group of normal individuals for standardization of the haematological and haemoglobin analytical methods blood samples were taken from 50 men and 90 women among healthy laboratory staff, medical students, and nurses. The normal siblings and other unaffected family members acted as controls in assessing the findings in the thalassaemic patients.

Haematological methods, including serum iron and total iron binding capacity estimations and non-incubated and incubated red cell osmotic fragilities, followed standard techniques.⁹ All haemoglobin samples were analysed by starch gel electrophoresis, and Hb A₂ levels were estimated by quantitative cellulose acetate electrophoresis.¹ Fetal haemoglobin was estimated by an alkali denaturation method¹⁰ and its intracellular distribution determined by the acid elution technique.¹¹ The relative rates of α -chain and β -chain production were determined by ¹⁴C-amino-acid incorporation in reticulocyte or bone marrow preparations under previously described conditions.¹² After incubation the cells were lysed, total protein was precipitated by the acid acetone method, the α -chains and β -chains were separated,¹³ and the total radioactivity incorporated into each chain was determined. The latter will be reported as the α/β -chain ratio. In some experiments the α -chain pool size was determined by Sephadex gel filtration.¹⁴

Results

HOMOZYGOUS β -THALASSAEMIA

Clinical Features.—The patient who was homozygous for β -thalassaemia was a 16-year-old girl who had been first investigated when aged 5 because of persistent jaundice and anaemia, and a diagnosis of thalassaemia major was made.⁷ She had never had any blood transfusions or iron therapy. Over the years she had developed skin pigmentation, increasing hepatosplenomegaly, and cardiomegaly. She showed delayed puberty and retarded growth and had a pre-diabetic glucose tolerance curve. Her bone marrow contained excessive iron; a liver biopsy was refused. Her multiple endocrine deficiency state was assumed to be secondary to iron overload.

Haematological Studies.—Recent haematological studies gave the following results: Hb 8.3 g/100 ml; R.B.C. $3.2 \times 10^6/\text{mm}^3$; M.C.H. 25.9 pg; M.C.H.C. 34.9%; M.C.V. 75 μl ; reticulocytes 3.5%. Haemoglobin electrophoresis showed a complete absence of Hb A; the haemoglobin consisted entirely of Hb F and Hb A₂; the Hb A₂ value was 1.1%.

Family Study.—Neither parent was anaemic but the M.C.H. values in each were decreased, being 21.0 pg in the father and 22.5 pg in the mother. Their red cells were hypochromic, varying in shape and size, and with moderate numbers of target cells and rare basophilic stippling. The father had a slightly raised Hb F of 1.1% and a Hb A₂ level of 5.5%; the mother had a more pronounced rise in Hb F of 4.4% and a Hb A₂ level of 5.2%. A paternal grandmother, three paternal aunts, one paternal uncle, and a brother also had β -thalassaemia minor with clinical and haematological findings similar to the parents.

Haemoglobin Synthesis.—Reticulocytes from the proband were incubated for 60 minutes with ¹⁴C-leucine and the distribution of radioactivity in the globin chains of "total globin" was determined (fig. 1). The ratio of production of α -chains to non- α -chains was 3.8:1. This experiment also confirmed that the proband was not synthesizing any β -

chains of Hb A, and therefore she was homozygous for the β^0 type of β -thalassaemia.¹

HETEROZYGOUS β -THALASSAEMIA

Clinical Features.—There were 83 patients heterozygous for β -thalassaemia from 16 families. Their ages ranged from 10 to 83 years. Four of the 16 probands were aged over 50. Nine of the 16 probands presented with refractory hypochromic anaemia, five with refractory anaemia during pregnancy, and two for routine haematological examination. Of

FIG. 1—Haemoglobin synthesis in reticulocytes of British β -thalassaemia homozygote. Reticulocytes were incubated with ¹⁴C-leucine for one hour and the globin chains separated as indicated in the text. Continuous line indicates optical density 280 nm and broken line the incorporated radioactivity. Total absence of β -chain synthesis is indicated by lack of second radioactive peak after γ -chains of Hb F.

the 67 affected relatives 35 were symptom free and had never been investigated or treated for anaemia, though only five had normal haemoglobin levels. The remaining 32 had been anaemic at various times, and in many cases this had provoked numerous investigations and long periods of treatment. A representative pedigree is shown in fig. 2. The only abnormal physical sign in these 83 patients was slight pallor. In particular, the spleen was not palpable and there was no clinical or radiological evidence of skeletal changes. None gave a history of leg ulceration and no ulcer scars were seen.

FIG. 2—Representative family pedigree showing 11 British β -thalassaemia heterozygotes. Probands, II 10, and her sisters II 3, II 5, and II 7 all had severe refractory anaemia of pregnancy, and her niece III 4 had received iron throughout childhood for refractory hypochromic anaemia.

Haematological Findings.—The data for haemoglobin and red cell indices for the 83 β -thalassaemia heterozygotes and control subjects are summarized in table I. The mean

TABLE 1—Summary of Haematological Findings in the 83 British β -thalassaemia Heterozygotes. Figures in Parentheses are the Mean $\pm$ One Standard Deviation

	Sex	Hb (g/100 ml)	R.B.C. ($\times 10^6/\text{mm}^3$)	M.C.H. (pg)	M.C.V. (%)	M.C.H.C. (%)	Serum Iron ($\mu\text{g}/100\text{ ml}$)	T.I.B.C. ($\mu\text{g}/100\text{ ml}$)	Saturation (%)	Hb A ₂ (%)	Hb F (%)
β -thalassaemia	M.	8.7-14.7 (11.8 $\pm$ 1.5)	4.6-6.6 (5.6 $\pm$ 0.6)	18.6-25.6 (21.5 $\pm$ 1.3)	63.1-77.1 (70.5 $\pm$ 4.2)	19.0-33.0 (31.3 $\pm$ 1.1)	70-225 (117 $\pm$ 40)	220-405 (309 $\pm$ 49)	19-61 (38 $\pm$ 14)	3.8-6.2 (4.9 $\pm$ 0.5)	0.5-9.4 (1.8 $\pm$ 0.7)
	F.	8.4-12.5 (10.8 $\pm$ 0.9)	4.3-6.7 (5.1 $\pm$ 0.5)	18.8-25.1 (21.8 $\pm$ 1.4)	63.0-82.1 (70.3 $\pm$ 4.8)	24.2-36.1 (31.0 $\pm$ 1.9)	60-198 (114 $\pm$ 38)	180-465 (315 $\pm$ 64)	19-100 (36 $\pm$ 15)		
Normal	M.	11.6-17.1 (14.4 $\pm$ 1.3)	4.1-5.5 (5.0 $\pm$ 0.5)	26.4-37.7 (31.6 $\pm$ 2.1)	85.1-96.0 (90.6 $\pm$ 4.6)	30.8-35.0 (33.0 $\pm$ 1.4)	70-156 (113 $\pm$ 33)	300-429 (357 $\pm$ 45)	23-46 (31 $\pm$ 9.0)	1.5-3.2 (2.4 $\pm$ 0.5)	0.1-0.9 (0.4 $\pm$ 0.1)
	F.	11.7-15.0 (13.4 $\pm$ 0.9)	3.2-4.8 (4.4 $\pm$ 0.4)	25.4-36.8 (31.3 $\pm$ 2.3)	75.4-102.0 (92.6 $\pm$ 8.0)	29.5-36.0 (33.1 $\pm$ 1.4)	60-112 (79 $\pm$ 22)	305-366 (341 $\pm$ 22)	17-33 (23 $\pm$ 7.0)		

haemoglobin values for the male and female heterozygotes (11.8 and 10.8 g/100 ml respectively) were significantly lower than those of the male and female control populations (14.4 and 13.4 g/100 ml respectively) ($P < 0.02$). The M.C.H. and M.C.V. values in both male and female heterozygotes were significantly reduced ($P < 0.002$) (table I, fig. 3). The overlap of M.C.H.C. values between the thalassaemic and control populations was considerable. All the thalassaemia heterozygotes showed abnormalities of their red cells, including hypochromia, variation in the shape and size, and a variable amount of basophilic stippling. No individual was encountered who had evidence of β -thalassaemia as judged by a raised Hb A₂ level but a completely normal haematological picture. Comparison of the fragility of non-incuba-

FIG. 3—Comparison of mean cell haemoglobin values between the β -thalassaemia and normal control populations.

ted and incubated red cells of seven of the propositi with those of 20 control subjects showed a reduced mean cell fragility (M.C.F.) in the non-incubated sample in only three cases, but after incubation all the thalassaemia samples showed a notable reduction in M.C.F. The values were as follows; non-incubated range for M.C.F. 0.270-0.420 (controls 0.390-0.450); incubated range 0.185-0.295 (controls 0.460-0.560).

Haemoglobin Analysis.—The Hb A₂ values ranged from 3.8 to 6.2% (mean 4.9%) compared with the control population's range of from 1.5 to 3.2% (mean 2.5%). In absolute terms these patients had an increase in Hb A₂ production with a mean value of 1.06 pg per cell, as derived from the M.C.H. value. The level of Hb A₂ was not altered significantly during pregnancy. The Hb F values ranged from 0.46 to 9.46% (mean 1.8%). In the controls the Hb F values ranged from 0.15 to 0.9%. Raised Hb F levels were found in 65 out of the 83 heterozygotes. This proportion is higher than that usually quoted for β -thalassaemia heterozygotes, but the increase in Hb F was very small in most cases and this observation probably reflects the high sensitivity of the method used for Hb F determination.¹⁰

Iron Status.—Serum iron and total iron binding capacity (T.I.B.C.) estimations for heterozygous β -thalassaemia were carried out on 53 of the patients (33 female and 20 male) and 20 of their normal siblings (table I). The difference in the serum iron levels, T.I.B.C., or percentage saturation between males and females in the thalassaemic group was not significant, though serum iron levels were significantly lower in the female than in the male control populations. Twenty-three of the female and three of the male heterozygotes gave a history of repeated courses of iron therapy lasting from a few months up to 20 years. Five females and four males had iron binding saturations of 50% or more. One 68-year-old woman who had received iron intermittently for 15 years had a totally saturated iron binding capacity and clinical evidence of iron overload. There was a significant correlation between age and percentage saturation in the females ($r = 0.371$, $P < 0.05$) but not in the males. Two iron deficient β -thalassaemia heterozygotes were seen, both under 10 years old. The marrow iron stores were increased in all patients with increased saturation of their total iron binding capacities but in only one were standard liver function tests abnormal. Liver biopsies were not carried out.

Haemoglobin Synthesis.—The relative rates of α -chain and β -chain production were determined in the bone marrow or peripheral blood, or both, of five of the β -thalassaemia heterozygotes. In each case an excess of α -chains was produced and a pool of free α -chain was shown in the marrow and blood by gel filtration experiments. The α/β -chain production ratio in the reticulocytes ranged from 1.8/1 to 2.2/1 (normal range 0.85-1.08), while in the bone marrow there was slightly less chain imbalance. In the marrow, however, there was a relatively large pool of α -chains and imbalanced chain production was observed at all stages of erythroid maturation. These findings are almost identical with those reported from this laboratory for β -thalassaemia heterozygotes from other racial groups.¹⁴

Complications and Special Clinical Problems.—The commonest complication was a worsening of the anaemia during pregnancy. A history of anaemia in one or more pregnancies was obtained from five of the propositi and 15 of their relatives. The haemoglobin values of a group of β -thalassaemia heterozygotes estimated during and after pregnancy, together with the percentage change in haemoglobin levels, are summarized in table II. Coexistent iron or folate deficiency was excluded in all but two cases by studies of serum iron levels, bone marrow iron content, and serum and red cell folate levels. Folate deficiency may have been a contributory cause in cases 5 and 7. In the remainder there was no response to iron or large doses of intramuscular folate. Blood transfusions in successive pregnancies were required in case 7 to maintain a satisfactory haemoglobin level. Globin chain synthesis was studied during and after pregnancy in one case; no change in the α/β -chain ratio was seen.

Diagnostic Errors.—Inquiries showed that 14 of the propositi and 32 of the 67 affected members of their families received a variety of diagnostic labels before their condition had been diagnosed correctly. These included iron deficiency anaemia, megaloblastic anaemia, sideroblastic anaemia, leuk-

TABLE II—Effect of Pregnancy on Haemoglobin level in British β -thalassaemia Heterozygotes

Case No.	Hb Level Before Pregnancy (g/100 ml)	Hb Level During Pregnancy (g/100 ml)	Drop in Hb Level (%)	Postpartum Hb (g/100 ml)
1	10.6	9.5 (12 weeks)	10.4	10.5
2	11.3	10.3 (20 weeks)	8.9	11.6
		10.2 (36 weeks)	9.7	
3	11.6	9.5 (34 weeks)	18.1	11.5
4	12.3	9.3 (16 weeks)	24.4	12.4
	11.2	8.5 (22 weeks)	24.1	11.3
5		7.0 (33 weeks)	37.5	
	11.2	10.0 (20 weeks)	10.7	11.4
	10.0	7.5 (20 weeks)	25.0	9.5
6		8.5 (term)	15.0	
	9.5	8.3 (12 weeks)	12.6	9.5
7	10.5	4.5 (33 weeks)	57.2	10.5
	10.5	6.0 (20 weeks)	42.9	10.5
Mean	10.9	8.4	22.8	10.9

aemia, malabsorption syndromes, recurrent blood loss, rheumatic fever, lead poisoning, and polycythaemia. They had also received a wide range of treatments for their anaemia, including folic acid and vitamin B₁₂ injections, pyridoxine, liver extracts, gluten-free diet, corticosteroids, and in one case an appendectomy. One patient underwent a hysterectomy for what was thought to be refractory iron deficiency anaemia secondary to menorrhagia. She had increased iron stores in the bone marrow and an increased saturation of her total iron binding capacity; she had received oral iron therapy over a 20-year period. In another patient repeated intramuscular iron injections had resulted in persistent buttock pain for which physiotherapy was required. One patient had received repeated iron injections, one of which resulted in a stiff, painful hip which required an osteotomy. Evidence of increased iron stores was present in about 15% of the group.

β -THALASSAEMIA INTERMEDIA

A disorder with the clinical features of β -thalassaemia intermedia was traced through two generations of an Irish family. Detailed haematological and biosynthetic studies indicated that it was a distinct and probably newly-recognized form of β -thalassaemia.

Clinical and Haematological Features.—The propositus was a 51-year-old man from Dublin who had been jaundiced all his life. An enlarged spleen was found on routine clinical examination. He had recently undergone cholecystectomy for pigment stones. A recent blood picture was as follows: Hb 8.9 g/100 ml; M.C.H. 27 pg; M.C.V. 80 μ l; M.C.H.C. 30%; reticulocytes 3.0%. The blood film showed only slight hypochromia but marked variation in the size and shape of the red cells with moderate basophilic stippling. Bone marrow showed pronounced erythroid hyperplasia with inclusion bodies in the normoblasts. ⁵⁹Fe studies indicated much ineffective erythropoiesis. An identical clinical and haematological picture was seen in two sisters of the propositus, both of whom had undergone splenectomy and cholecystectomy. Three other family members were similarly affected.

Haemoglobin Analysis.—All the affected members of the family had raised Hb A₂ levels in the 4.5% range and slightly raised Hb F levels in the 1% range. No unstable haemoglobins were found.

Haemoglobin Synthesis.—Studies of α -chain and β -chain production in the bone marrow and peripheral blood of the propositus and the peripheral blood of one of his sisters showed a chain imbalance similar to that seen in the β -thalassaemia heterozygotes. The α/β -chain production ratios ranged from 1.5 to 2.3:1. We concluded that this condition represented a distinct form of β -thalassaemia, possibly due to excessive α -chain production or to a primary defect in cell division with secondary globin chain imbalance.¹⁵

HAEMOGLOBIN H DISEASE

Three persons with Hb H disease were found among the members of two British families.

Clinical Features.—The propositus in the first family was a 17-year-old boy who presented with generalized joint pains and malaise. He was found to be moderately anaemic and after prolonged investigation, during which he was thought to have rheumatic fever or a collagen vascular disorder, the diagnosis of Hb H disease was finally established.⁸ The condition was also found in a 19-year-old brother who had no clinical disability. Both brothers had enlarged spleens palpable 2-3 cm below the costal margin. Because of continued anaemia and ill health the propositus underwent splenectomy in 1967. He was well for a year after the operation, though his platelet count gradually increased. He then had repeated episodes of superficial thrombophlebitis. Extensive investigation and treatment with a variety of anticoagulants and other agents had no effect on this process and he died in 1968 of massive pulmonary embolic disease. His affected sibling remains well. The propositus in the second family was a 70-year-old woman with a lifelong history of intermittent anaemia for which she had had many courses of oral and parenteral iron. When first seen in 1968 she was pale; the spleen was palpable 6 cm below the left costal margin. Her haemoglobin level was then 9.6 g/100 ml and her blood film showed marked hypochromia with variation in shape and size of the red cells, which also showed basophilic stippling. Incubation of the red cells with brilliant cresyl blue showed numerous inclusion bodies. There was pronounced erythroid hyperplasia of the bone marrow with a gross increase in iron. There was no evidence of erythroleukaemia at the time of study or on subsequent follow-up investigation.

Haemoglobin Analysis.—Haemoglobin electrophoresis on starch gel (pH 8.5 and 7.0) showed a pattern typical of Hb H disease in all three patients. The level of Hb H ranged from 6 to 15% and traces of Hb Barts were present in each case.

Haemoglobin Synthesis.— α/β chain production ratios of 0.30, 0.42, and 0.50 respectively were found in the three patients. These are in the same range as those observed in patients with Hb H disease from other racial groups.¹⁶

Family Studies.—The father and paternal grandmother of the two male siblings showed haematological and haemoglobin synthetic evidence of the α -thalassaemia-1 trait. Similar findings were observed in one of the two sons of the 70-year-old woman in the second family.

OTHER THALASSAEMIA-LIKE STATES

One family was studied in which the propositus, a 19-year-old man, presented with intermittent jaundice for many years. He was an underdeveloped youth with pallor, mild icterus, splenomegaly. Laboratory findings were: Hb 12.2 g/100 ml, reticulocytes 2%, serum bilirubin 3.2 mg/100 ml (conjugated 0.6 mg/100 ml). The blood film showed marked variation in the shape and size of the red cells with hypochromia, marked basophilic stippling, and polychromasia. The red cell osmotic fragility was notably decreased. There was pronounced erythroid hyperplasia in the bone marrow with abundant free iron but no ring sideroblasts. Serum iron was 170 μ g/100 ml; the whole-blood lead level was normal. Haemoglobin analysis showed Hb F 10.2% and Hb A₂ 3.1%. The blood picture and the Hb A₂ and F levels in both parents were normal. Thus the clinical and haematological findings were those of thalassaemia intermedia, while the youth's parents were apparently normal. These findings are very similar to those described¹⁷ for the "silent" β -thalassaemia gene. The family would not allow further studies to be made to measure the α/β -chain production ratios.

HEREDITARY PERSISTENCE OF Hb F

Several surveys have shown that a few apparently normal North European adults, probably about 1% of the population, have raised levels of Hb F in the 1-3% range.^{18,20} This condition has been called the "Swiss type" of hereditary persistence of fetal haemoglobin. We have carried out detailed studies of two such families. In one (fig. 4), the propositus, a 32-year-old woman, was found to have a raised level of Hb F during routine screening for transplacental haemorrhage. She was followed up over several years, when the level of Hb F ranged from 3.48 to 3.64%. Levels of Hb F of 1.77% and 1.26% respectively were found in her two daughters. None of these persons had any detectable haematological abnormalities and the α/β -chain production ratio in the reticulocytes of the propositus is unity.

We have seen a similar example of a genetically determined increase in fetal haemoglobin in association with β -thalassaemia (fig. 4). In this family the 83-year-old propositus had typical β -thalassaemia trait with 5.5% Hb A₂ and 3.8% Hb F. Her husband was dead. Her 43-year-old son had a similar blood picture with 4.9% Hb A₂ and 11.1% Hb F—a much higher level of fetal haemoglobin than was encountered in the other 83 β -thalassaemia heterozygotes in this study. One of his sons had typical β -thalassaemia trait, while a 4-year-old daughter, with a completely normal blood picture and red cell indices, had 8.6% Hb F. Thus it seemed that genes for both β -thalassaemia and persistent Hb F were present in this family; the findings in the fourth generation explained the unusually high level of Hb F in the son of the propositus, who was presumably heterozygous for both genes.

FIG. 4—Families showing hereditary persistence of small amounts of Hb F. In Family A this gene existed together with that for β -thalassaemia, while in Family B it existed alone. Essential Hb F and A₂ figures are shown next to individual family members. (For interpretation and haematological and haemoglobin synthetic studies see text.)

Increased levels of Hb F ranging from 5.0 to 21.1% were found also in six members of a Sunderland family. There were no haematological abnormalities and the red cell in-

dices and Hb A₂ levels were normal. Full details of haemoglobin synthetic studies will be presented elsewhere. In all these families the Hb F was heterogeneously distributed among the red cells.

Discussion

The thalassaemias are classified into two main varieties, α and β , depending on which of the adult globin chains is produced in reduced amounts. The types of α -thalassaemia of clinical importance are the Hb Barts hydrops syndrome and Hb H disease, while the β -thalassaemias, which produce a variable degree of anaemia, are the homozygous and heterozygous states for the different forms of β and δ β -thalassaemia.¹ The related syndromes of hereditary persistence of fetal haemoglobin are not associated with any clinical disability but may cause diagnostic problems resulting from the presence of variable quantities of fetal haemoglobin in adult life. In the present study we have encountered most of these conditions except the Hb Barts hydrops syndrome in a group of individuals of apparently pure British stock. In no case could any relation of Mediterranean or Oriental background be traced. Thus though the incidence is obviously low, these disorders must be considered in the differential diagnosis of refractory anaemia in British people.

The clinical, haematological, and biosynthetic findings in those homozygous and heterozygous for β -thalassaemia and those with Hb H disease among these British families are identical in every way with those reported from other racial groups.^{12,16} The homozygous β -thalassaemic child produced no β -chains whatever; thus she has the β -thalassaemia¹ variety of β -thalassaemia. This is particularly common in South-east Asia and northern Italy but has been reported in Greeks and Africans, and so this finding provides no definite indication of the origin of the β -thalassaemia gene. Indeed, though most of the β -thalassaemic heterozygotes came from North Wales and Cheshire it has been impossible to trace them back to any particular area. Surveys currently being carried out suggest a relatively high incidence in the mining villages near Sunderland.²¹

By far the commonest form of thalassaemia in British people seems to be heterozygous β -thalassaemia. The group of 83 heterozygotes described here had a significant degree of anaemia and nearly half of their 67 relatives had been investigated on one or more occasions for refractory anaemia. Since the propositi were nearly all referred for anaemia, however, these families may not be a completely representative group. Thus this form of selection of case material may have biased the series in favour of the more severe form of the condition. A better picture of the clinical expression of β -thalassaemia in British people would be obtained by a population survey of healthy young adults. From the data obtained in this and other studies (table III) it is clear that the M.C.H. is the most useful haematological parameter with which to distinguish β -thalassaemia from normal and by using an electronic cell counter it should be relatively easy to screen large populations for β -thalassaemia trait, performing Hb A₂ estimations only on those

TABLE III—Comparison of Haematological and Haemoglobin Analytical Findings between Greek, Thai, and British β -thalassaemia Heterozygotes. Figures in Parentheses are the Mean $\pm$ One Standard Deviation

Race	Sex	No.	Hb (g/100 ml)	R.B.C. ($\times 10^9/\text{mm}^3$)	M.C.H. (pg)	Hb A ₂ (%)	Hb F (%)	Authors
Greek	M.	85	10.4-16.6 (13.9 $\pm$ 1.2)	5.1-7.8 (6.3 $\pm$ 0.4)	18-29 (22.0 $\pm$ 1.9)	3.6-6.6 (5.2 $\pm$ 1.1)	0.9-8.3 (3.1)	Malamos <i>et al.</i> (1962) ²⁷
Thai	M.	104	9.2-15.4 (12.1 $\pm$ 1.4)	4.2-7.9 (5.9 $\pm$ 0.7)	16-34 (20.0 $\pm$ 3)	3.6-7.1 (5.1 $\pm$ 0.6)	0.7-8 (1.5 $\pm$ 1.3)	Pootrakul <i>et al.</i> (1973) ²⁸
	F.	43	8.2-16.0 (10.8 $\pm$ 0.9)	3.3-7.3 (5.2 $\pm$ 0.7)				
British	M.	32	8.7-14.7 (11.8 $\pm$ 1.5)	4.6-6.8 (5.6 $\pm$ 0.6)	19-26 (21.5 $\pm$ 1.3)	3.8-6.2 (4.9 $\pm$ 0.5)	0.5-9.4 (1.8 $\pm$ 0.7)	Present study
	F.	51	8.4-12.5 (10.8 $\pm$ 0.9)	4.3-6.7 (5.1 $\pm$ 0.5)	19-25 (21.8 $\pm$ 1.4)			

with low M.C.H. values. Iron deficiency might produce some false-positive results but there should be few false-negatives.

When the data on the 83 British β -thalassaemia heterozygotes are compared with those obtained from other racial groups (table III) clearly, as judged by both haematological and haemoglobin analysis, β -thalassaemia heterozygotes present a remarkably similar clinical picture throughout the world. Such homogeneity suggests that reports of apparent β -thalassaemia heterozygotes with severe anaemia and splenomegaly or the finding of unusually high levels of Hb F or A₂ must be viewed with caution, and that such cases probably represent different genetic disorders or the interaction of other forms of thalassaemia or hereditary persistence of Hb F with β -thalassaemia.

By far the most important clinical problem encountered in the British β -thalassaemia families was anaemia of pregnancy. This has been noticed in other populations.^{22, 23} One woman in the present series required repeated blood transfusion in pregnancy, and several had dangerously low haemoglobin levels. Folic acid deficiency was a possible aetiological factor in only two cases and none were iron deficient. Though women with β -thalassaemia can raise their red cell mass during pregnancy the response is less than normal,²⁴ and this results in a refractory anaemia at about mid-term.

Many of the β -thalassaemia heterozygotes had undergone numerous investigations with considerable psychological trauma, and had received repeated courses of iron and other haematinics. The iron studies suggest that several of the women who had received iron therapy for many years may have had a significant degree of iron overload, and four patients in the series had had local side effects after parenteral iron therapy. These extraordinary medical histories show clearly that thalassaemia is missed in British patients because it is not seriously considered in the differential diagnosis of refractory anaemia.

The clinical and haematological findings which could alert clinicians to the existence of this disorder (tables I and III, fig. 3) include a mild anaemia, a history of repeated anaemias in pregnancy, red cells showing variable hypochromia with a low M.C.H. and M.C.V. and basophilic stippling, a high red cell count, a normal or raised serum iron level with normal or increased iron stores in the marrow, and a raised level of Hb A₂. When diagnosed, the heterozygous patients need a simple explanation together with a card to carry which indicates the diagnosis and includes instructions to their physicians not to prescribe iron unless the iron stores are first assessed. It should be remembered that iron deficiency can occur in β -thalassaemia—indeed, two children with this complication were noted in this series. β -thalassaemia heterozygotes require careful surveillance and full folic acid supplements throughout pregnancy.

The more severe forms of β -thalassaemia and Hb H disease are rare in British people. The diagnosis and management of these disorders has been fully discussed elsewhere.¹ Several forms of hereditary persistence of Hb F synthesis clearly occur in the British population. So far we have not encountered the Negro or Greek forms of this disorder, in which the Hb F is uniformly distributed among the

red cells.^{25, 26} Several families with low levels of Hb F in the 1-3% range without haematological changes or globin chain imbalance have been observed. They seem to represent the "Swiss" type of persistent Hb F production as defined by Marti.¹⁸ At least two families have been found, however, in which higher levels of Hb F are inherited. The relation of this condition to $\delta\beta$ -thalassaemia is under investigation.

Clearly all these conditions must be considered when screening for transplacental haemorrhage or in thalassaemia surveys based on the presence of fetal haemoglobin. Furthermore, the inheritance of one of these genes together with that for β -thalassaemia may produce an unusually high level of Hb F in an apparent β -thalassaemia heterozygote.

H.K.-M. was supported by a Nuffield Foundation Fellowship. D.J.W. and J.B.C. are grateful to the Medical Research Council, the Wellcome Trust, and the Research Committee of the United Liverpool Hospitals for financial support. We wish to thank all the physicians who referred us patients with thalassaemia; in particular we wish to thank Dr. Jillian Mann, of the Children's Hospital, Birmingham, for help with the study of the homozygote patient.

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