

Interaction of β -thalassaemia and Hereditary Persistence of Foetal Haemoglobin*

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Hereditary persistence of foetal haemoglobin (HPFH) is a term used to describe an inherited high level of Hb-F which is present throughout life and is not associated with anaemia. In that respect and by showing interaction with the S and C variants of adult haemoglobin, it resembles β -thalassaemia, and at one time it was described as 'non-microcythaemic thalassaemia'. There are, however, 3 fundamental differences from β -thalassaemia: (1) absence of any haematological and clinical abnormality (Edington and Lehmann, 1955 a, b), (2) presence of foetal haemoglobin in all red cells rather than in separate clones (Bradley, Brawner, and Conley, 1961), and (3) in contrast to β -thalassaemia, Hb-A₂ is never raised in the heterozygote, and in the one homozygote described so far by Wheeler and Krevans (1961) HbA₂ was as completely absent as Hb-A.

Whereas β -thalassaemia may be considered as a specific defect in the gene controlling the formation of the β -chain, HPFH is thought to be due to a failure of switching on the β -chain production necessary for the transition from foetal haemoglobin ($\alpha_2\gamma_2$) to adult haemoglobin ($\alpha_2\beta_2$). The gene for the β -chain would be affected therefore only indirectly by a failure at the controller locus. The fact that Hb-A₂ ($\alpha_2\delta_2$) as well as Hb-A ($\alpha_2\beta_2$) are missing in the homozygote for the HPFH has been interpreted as indicating that the genes for the β and the δ chains are close neighbours on the chromosome and are 'switched on' by the same operon, which seems to be absent in HPFH (Wheeler and Krevans, 1961; Neel, 1961; Motulsky, 1963; Ceppellini, 1963).

The simple heterozygote for HPFH has now been widely seen, and in a recent review, Conley, Weatherall, Richardson, Shepard, and Charache (1963) quote references to 110 persons so affected including 64 seen by them at The Johns Hopkins Hospital in Baltimore. To these can be added 13 more reported since by Sukumaran, Randelia,

Sanghvi, and Merchant (1961), Brumpton, de Traversé, and Coquelet (1961), Barkhan and Adinolfi (1962), and Thompson and Lehmann (1962). Unpublished observations have also been made in Nigeria by G. M. Edington and E. J. Watson-Williams. In addition to this large number of persons with the phenotype A + F, Conley *et al.* (1963) refer to 20 with the phenotype S + F and 9 with the phenotype C + F; again 1 each has been seen additionally by Thompson and Lehmann (1962). Though the haemoglobin composition of the blood as a whole is the same as in homozygous sickle-cell anaemia, namely some 80-90% Hb-S with the rest Hb-F and a trace of Hb-A₂, those subjects with a combination of sickling and HPFH are clinically well. The presence of foetal haemoglobin in *all* red cells counteracts the sickling tendency (Bradley *et al.* 1961; Mitchener, Thompson, and Huisman, 1961). Conley *et al.* (1963) have pointed out that in the light of present-day knowledge some of the cases described as S + F or C + F are more likely to be instances of sickle-cell thalassaemia or Hb-C thalassaemia. The Hb-F level was too low in some, and Hb-A was present in others; also some were clinically affected.

Double heterozygosity for β -thalassaemia and HPFH has so far been described in 5 families. Kraus, Koch, and Burckett (1961) and Wheeler and Krevans (1961) saw it in American Negroes, Sukumaran *et al.* (1961) saw it in an Indian Christian family; Fessas (1962) reported it from Greece, where he also observed the combination of HPFH with α -thalassaemia, and Barkhan and Adinolfi (1962) described it in a family of mixed Indian and Portuguese origin. The affected individuals were on the whole well, but there was a mild haemolytic disorder, presumably due to thalassaemia.

We have seen again a family showing interaction between β -thalassaemia and HPFH, and it is of interest in view of the previous reports from India (Sukumaran *et al.*, 1961) and from a part-Indian family (Barkhan and Adinolfi, 1962) that this family is of pure Indian stock.

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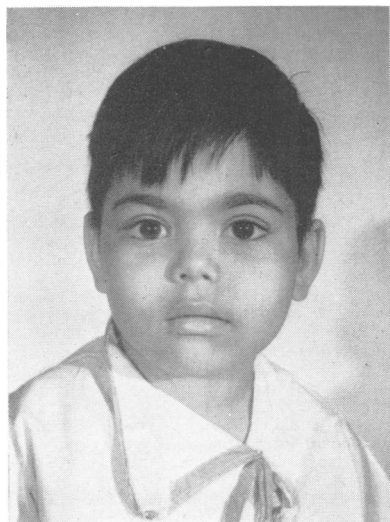


FIG. 1. The patient.

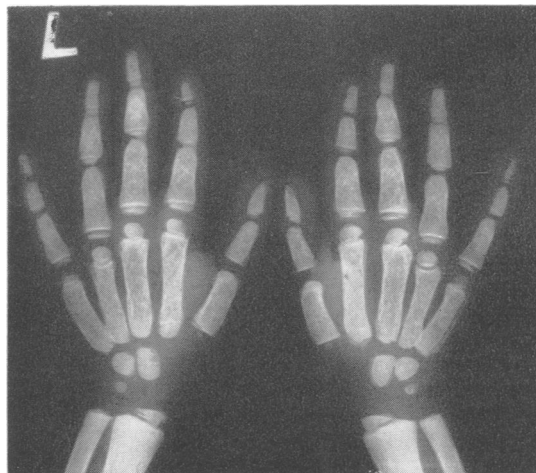


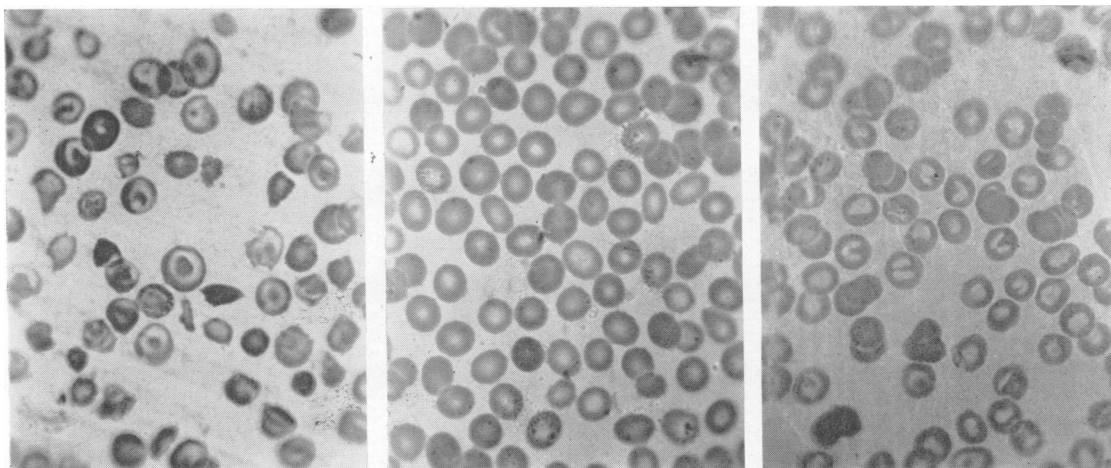
FIG. 3. Radiograph of patient's hand.

Case Report

The propositus (R.V.), a 5½-year-old boy, was admitted with a history of anaemia from birth; iron therapy had failed to produce an improvement. He had the characteristic facies of thalassaemia major (Fig. 1). His liver and spleen were enlarged (4 cm.) and firm. Haematological (Fig. 2 and Table I) and radiological findings (Fig. 3) were compatible with a diagnosis of thalassaemia major. A family study however (Fig. 4 and Table I) showed that the father did not have thalassaemia but was a typical case of HPPFH, but that the mother had β -thalassaemia minor. Administration of

TABLE I

	Father	Mother	Propositus (R.V.)	Brother
Red cells (mill./c.mm.)	5.3	4.6	3.5	5.0
Hb (g./100 ml.)	15.0	11.2	8.5	14.2
PCV (%)	45	42	32	43
MCV (c. μ)	84.9	91.3	91.4	86.0
MCH (μ g.)	28.3	24.4	24.3	28.4
MCHC (%)	33	27	25	33
Reticulocytes (%)			4	
Osmotic fragility	0.48-0.32	0.32-0.28	0.45-0.10	0.44-0.36
Abnormal Hb	Nil	Nil	Nil	Nil
Hb-F (%)	20	3	66	Nil
Hb-A ₂	Not raised	Raised	Not raised	Not raised
Distribution of Hb-F	In all cells	Unequal	In all cells	—

FIG. 2. Blood films of (a) propositus, (b) father, (c) mother. (Leishman, $\times 1,150$.)

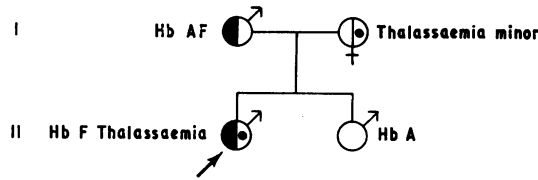


FIG. 4. Pedigree of family.

folic acid, 20 mg. daily by mouth (Luhby and Cooperman 1961), raised the patient's haemoglobin level from 8.5 to 10.9 g./100 ml. The brother of the patient was also examined and was found to be haematologically and otherwise normal. Blood smears from both parents and both children were stained for foetal haemoglobin (Fig. 5) according to Kleihauer and Betke (1960): Hb-F was demonstrated in all cells of the father, and in all cells of the propositus; there was an unequal distribution in the cell population of the mother, and none was seen in the smear of the younger brother.

Summary

Another example is presented of the interaction of β -thalassaemia and persistence of high foetal haemoglobin. Of the families reported previously 2 were of American Negro origin, 1 was Greek, 1 was Indian, and 1 was of mixed Indian and Portuguese stock. It is of interest that this new example comes again from India. The anaemia of the double heterozygote was more severe than in the previously described cases, but it responded to some extent to folic acid therapy.

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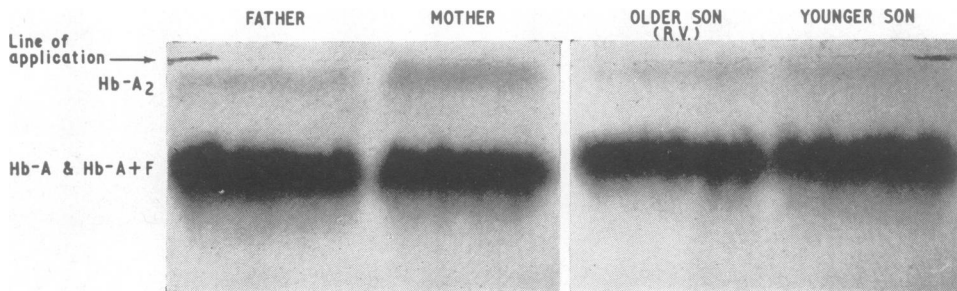


FIG. 5. Electrophoresis of haemoglobin-TRIS buffer pH 8.9. The Hb-A₂ fraction is raised only in the mother, and in the propositus it is, if anything, low. Mixtures of Hb-A and Hb-F do not separate by this technique (Craddock-Watson, Fenton, and Lehmann, 1959).

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