HAEMOGLOBIN 'BARTS'— A RARE ABNORMALITY IN THE NEWBORN

BY

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The study of qualitative abnormalities in haemoglobin is of fairly recent date. Two normally occurring haemoglobin variants have, however, been known for a long time: adult haemoglobin (Hb A) and foetal haemoglobin (Hb F) (Körber, 1866). They can be distinguished by alkaline denaturation, a test which has become routine practice in neonatal paediatrics (Singer, Chernoff and Singer, 1951).

About 10 years ago sickle cell anaemia was found to be due to an abnormal haemoglobin, now known as Hb S, which differs chemically from normal and is distinguished by its low solubility in the reduced state (Pauling, Itano, Singer and Wells, 1949). This decreased solubility implies a tendency to 'crystallization' (more correctly: conversion to semisolid gel) within the erythrocyte and is the cause of its sickle shape.

In the years that followed a great number of abnormal haemoglobin variants were detected, mainly among non-European people. Some of these are of great clinical significance, others are chiefly of genetic and anthropological interest. These variants were designated by the letters of the alphabet more or less in chronological order of detection.

By 1958 progress in this field had gathered so much speed, that confusion in nomenclature was likely to arise. Also, it could be foreseen that the letters of the alphabet would not suffice for all haemoglobin variants. So, when Ager and Lehmann (1958) detected a hitherto unknown abnormal haemoglobin, they named the new variant after the hospital in which the investigation had been carried out: Haemoglobin 'Barts'. This pigment was present with both Hb F and Hb A in the blood of an infant of mixed West Indian ancestry. Subsequently, about 30 infants with haemoglobin 'Barts' have been detected (Lehmann, 1959) in Mediterranean and non-European countries. This article records the second case observed in Great Britain.

Case Report

The infant's mother, I.B., aged 37 years, is a West Indian woman of negro stock. Before coming to England in 1956, she had five children born in Jamaica, of whom three are still alive. She had been married twice, the first husband, a 'white man', being the father of the first child only. The four other children had a Jamaican father.

The second of these five children died at the age of 9 days; the cause of death is not known. The fifth child was born prematurely and died when 3 days old. She does not know of any blood disease among her children, or any other members of her family.

In this country I.B. contracted a third marriage, also to a West Indian. His skin is of the same dark colour as that of I.B., but his features are not typically African and suggest the possibility of some Asian ancestry.

I.B. conceived in 1958, the date of expected delivery being June 14, 1959. The pregnancy progressed normally until 26 weeks when she had an episode of abdominal pain and vaginal bleeding. Further episodes of ante partum haemorrhage followed, necessitating admission to hospital. There, the placenta was found to be low lying, but was not considered to be praevia.

Surgical induction at 38 weeks was followed on May 27 by normal delivery of a female infant, weighing 7 lb. (3,170 g.) and measuring 20 in. (50 cm.). Her condition was only fair and in spite of the dark pigmentation the theatre sister noticed her pallor and commented on it.

Cord blood examination was carried out by the regional blood transfusion laboratory under the direction of Dr. W. Weiner, and gave the following results: blood group A, rhesus negative, direct Coombs test negative, bilirubin 0.6 mg./100 ml.

The next day the baby's capillary haemoglobin was estimated to be 94% (13.9 g.). This relatively low value was thought to be due, possibly, to transplacental blood loss. No physical abnormality was found and progress seemed to be satisfactory.

When the baby was 6 days old marked pallor and lethargy were noticed. The spleen was enlarged, but not the liver. There was no evidence of any haemorrhagic diathesis. In view of the baby's parentage it was regarded as essential to exclude sickle cell anaemia and to carry out further investigation.

Laboratory Investigation. Blood examinations were limited by the difficulty of venepuncture and had to be spread over a relatively long period.

The haemoglobin level fell from 10.8 g. (73%) on June 1, at the age of 6 days, to 8.6 g. (58%) on June 12.

A full blood count on June 16 yielded the following results: Hb 9.3 g. (63%); R.B.C. 3,580,000; W.B.C. 9,700; P.C.V. 31.5 ml.; M.C.V. 88 μ ; M.C.H.C. 30.5%.

Reticulocyte counts varied between 0.2% and 3%.

A stained blood film on June 3 revealed numerous target cells and a small number of microspherocytes; this finding was repeatedly confirmed on subsequent examinations (Fig. 1).

Sickle cells were not found in sealed wet blood film preparations, either with or without reducing agent. No inclusion bodies were seen in the red cells after 'cold incubation' with cresyl violet solution.

Haptoglobin was present in the serum. The serum iron on August 7, was 0.059 mg./100 ml.

Haemoglobin electrophoresis was carried out by Dr. H. Lehmann who demonstrated the presence of Hb 'Barts' as well as Hb A and Hb F (Fig. 2). This was confirmed on subsequent examinations.

INVESTIGATION OF THE MOTHER. A full blood count was done on June 8, with the following results: Hb. 12.0 g. (81%); R.B.C. 4,390,000; W.B.C. 5,000; P.C.V. 43 ml.; M.C.V. 98 μ ; M.C.H.C. 28%.

FIG. 1.

FIG. 2.

A

F
A

Bart's

FIG. 1.—Composite picture of a blood film having numerous target cells and occasional microspherocytes.

FIG. 2.—A normal (AA) compared with Baby B. Note 'fast' Hb in baby.

FIG. 3.—Father (AS), Mother (AA).

The stained film showed moderate regenerative activity consistent with recovery from a mild anaemia of pregnancy. No sickle cells were found. The serum iron level was 0.092 mg./100 ml.

Haemoglobin electrophoresis revealed Hb A only (Fig. 3).

INVESTIGATION OF THE FATHER. Full blood count revealed Hb 14.0 g. (95%); R.B.C. 5,700,000; W.B.C. 7,000; P.C.V. 46 ml.; M.C.V. 81 μ ; M.C.H.C. 30%.

Reticulocytes 2%. Sickle cells were found to be present after incubation with sodium bisulphite, in very large numbers.

Serum iron level 0.141 mg./100 ml.

Haemoglobin electrophoresis clearly demonstrated the presence of Hb S, as well as Hb A. The father was, therefore, confirmed as a heterozygous carrier of the sickle cell trait (Fig. 3).

Further progress. Baby B. was in reasonably good health when discharged from hospital on June 21. The haemoglobin level was then 9.0 g. (61%). The infant was seen repeatedly in out-patients and found to make satisfactory progress, but the haemoglobin level was dropping and on August 11 was as low as 7.1 g. (48%). Anti-anaemic treatment, including iron, folic acid and ascorbic acid was given. At the age of 15 weeks the total haemoglobin was 8.6 g. (58%) and haemoglobin 'Barts' was no longer demonstrable.

The infant was last seen on September 22; she was then nearly 4 months old and in good general health. The haemoglobin had risen to 9.8 g. (66%), but the blood picture was still hypochromic and microcytic. Target cells were still present and the osmotic resistance of the red cells was raised. Haemoglobin 'Barts' was absent from the electrophoretogram, but Hb F was still present, accounting for 6.8% of total haemoglobin.

Discussion

Anaemia in the new-born period can have many causes including prematurity, infection, maternal deficiency states, blood loss and haemolysis. In the present case, a contributory action of maternal deficiency anaemia and foetal blood loss cannot

be excluded. The presence of large numbers of target cells is, however, strongly suggestive of a primary abnormality of the red blood cells whilst a small number of microspherocytes may be consistent with the haemolytic character of the process.

This anaemia was present from birth: the haemoglobin reading of 94% on the first day of life is definitely low. Moreover, pallor was noticed at birth.

The characteristic properties of haemoglobin 'Barts' were summarized by Lehmann and his colleagues (Ager, Hunt, Kohler and Lehmann, 1959). Here we draw attention to only some of its peculiarities:

(1) Both in the process of electrophoresis and of chromatography 'Barts' is one of the fastest moving haemoglobin variants so far known. Its position relative to other haemoglobins varies with the particular method used and with the pH of the buffering medium.

(2) Spectroscopically, 'Barts' is closely similar to foetal haemoglobin and shows the tryptophan band, which is characteristic of Hb F.

(3) Hb 'Barts' is less resistant to alkali denaturation than Hb F, but more so than Hb A.

(4) Hb 'Barts' tends to disappear, with progressing age, from the infant's blood much in the same way as 'normal' foetal haemoglobin does.

An apparent exception to this last-mentioned rule was recently discovered in a child whose 'Barts' had persisted beyond infancy. This child was found to be homozygous for thalassaemia (Choremis, Zannos-Mariolea, Ager and Lehmann, 1959).

Heredity. As haemoglobin 'Barts' is associated with infancy, there is no hope of finding any evidence of it in the parental electrophoretogram. Genetic investigations, which play so great a part in the study of other haemoglobinopathies, have so far failed to yield any positive results. This does not imply that we shall necessarily have to wait until those few infants with 'Barts', who are known at present, reach the reproductive age. Genetic information may be forthcoming from observation of their younger siblings. Where, in addition to true sibs, half-brothers and half-sisters are available for investigation, the possibilities of study are wider. In the present case history, I.B. with her three sets of

families almost fulfilled conditions designed for laboratory experiments and our regret of not being able to investigate her previous children is so much greater. We shall, of course, try to keep her under observation in any future pregnancies.

The finding of a heterozygous sickle cell trait in the father is an interesting observation, but in the light of our present knowledge this fact is unconnected with the infant's haemoglobinopathy.

Summary

Haemoglobin 'Barts' was found in the blood of an anaemic West Indian newborn girl. No evidence of this abnormal haemoglobin variant was found in either parent, but the father was heterozygous for Hb S. By the age of 15 weeks 'Barts' could no longer be demonstrated in the infant's electrophoretogram. This is the second case found in this country.

This paper could not have been written without the generous help given by Dr. Hermann Lehmann, who not only carried out the crucial diagnostic tests, but also

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REFERENCES

- Ager, J. A. M., Hunt, J. A., Kohler, H. G. and Lehmann, H. (1959). Haemoglobin 'Bart's'. Seventh European Congress of Haematology, London, Abstract 320.
- and Lehmann, H. (1958). Observations on some 'fast' haemoglobins: K, J, N and 'Bart's'. *Brit. med. J.*, 1, 929.
- Choremis, C., Zannos-Mariolea, L., Ager, J. A. M. and Lehmann, H. (1959). Persistence of haemoglobin 'Bart's' beyond infancy in a child with thalassaemia. *Ibid.*, 2, 348.
- Körber, E. von. (1866). Inaug. Dissertation, University of Dorpat. Quoted by Singer *et al.* (1951).
- Lehmann, H. (1959). Personal communication.
- Pauling, L., Itano, H. A., Singer, S. J. and Wells, I. C. (1949). Sickle cell anemia, a molecular disease. *Science*, 110, 543.
- Singer, K., Chernoff, A. I. and Singer, L. (1951). Studies in abnormal hemoglobins. I. Their demonstration in sickle cell anemia and other hematologic disorders by means of alkali denaturation. *Blood*, 6, 413.
- Surveys of haemoglobinopathies not referred to in text*
- Abnormal Haemoglobins*. Symposium organized by the C.I.O.M.S. (Council for International Organizations of Medical Sciences), held in Istanbul, 1957. Edited by J. H. P. Jonxis and J. F. Delafresnaye. (1959). Blackwell, Oxford.
- Beaven, G. H. and Gratzner, W. B. (1959). A critical review of human haemoglobin variants. *J. clin. Path.*, 12, 101.