

and because of the large numbers of tablets the patient was having to take. Furthermore, very frequent estimations of his electrolyte levels were required.

Since it had been demonstrated by Lee *et al.* (1964) that the tumour itself was the source of production of a substance having anti-diuretic-hormone activity, we felt that a direct attempt to suppress this with antimetabolic agents might prove a more effective measure. The patient was therefore given a single dose of 40 mg. of nitrogen mustard (his weight at this time being 80 kg.; the dosage of the drug was 0.5 mg./kg.) and 10 days later the 9 $\alpha$ -fluorohydrocortisone was withdrawn. Thereafter, serum sodium and potassium levels remained within normal limits; serum osmolarity rose and urine osmolarity fell. For the first week after withdrawal of 9 $\alpha$ -fluorohydrocortisone urine sodium loss increased again, but one month later had fallen to less than half its level before treatment. Over a follow-up period of three months the patient remained in normal electrolyte balance; no potassium or sodium supplements were required, and he complained only of a persistent cough.

#### COMMENT

Direct attack on the tumour with antimetabolic agents or perhaps x rays therefore seems to offer a more satisfactory treatment for the hyponatraemic state associated with carcinoma of the bronchus. Among those who have previously reported cases only Schwartz *et al.* (1960) have followed up the effect of such treatment on the electrolyte state. Over a period of five days they also found some improvement in the abnormality, although over this short period the serum sodium level did

not rise. Most other patients have been treated with various sodium-retaining steroids with limited success.

The mechanism of production of the water and electrolyte abnormalities remains uncertain. There seems no doubt that the tumour in most cases produces an anti-diuretic hormone. Ross (1963) suggested that the reduced aldosterone production which had been demonstrated might be secondary to expansion of the plasma volume induced by inappropriate anti-diuretic hormone production. In the present case the reduction in the daily loss of urinary sodium which resulted from suppression of the tumour activity offers some support for the view that the primary and perhaps the only basic abnormality is the excessive production of anti-diuretic hormone by the tumour.

We are grateful to Dr. A. Brown for permission to study the patient under his care.

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## Case of Intrauterine Death Due to $\alpha$ -Thalassaemia

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Neonatal death in which an abnormal haemoglobin formed the major component of the foetal blood was first reported by Lie-Injo Luan Eng and Jo Bwan Hie (1960). The abnormal haemoglobin was "fast-moving" and is now known to be identical with haemoglobin Bart's (Lie-Injo Luan Eng *et al.*, 1962). The clinical picture closely resembled erythroblastosis foetalis, but there was no evidence of blood-group incompatibility between mother and infant. Both parents in the cases recorded were examined when available and showed haematological abnormalities resembling those found in  $\alpha$ -thalassaemia trait. Further cases in the Chinese race have been published since (Banwell and Strickland, 1964). We wish to record a case in a Greek Cypriot family living in East London, which would seem to be the first case reported in a non-Chinese family. The rarity of such cases is presumably due to the fact that the incidence of the gene for  $\alpha$ -thalassaemia is so relatively low outside S.E. Asia. According to Fessas (personal communication) the  $\alpha$ -thalassaemia gene is probably more common in Cyprus than on the Greek mainland, and it is therefore not surprising that the first case should have been seen in a Greek Cypriot family.

#### CASE REPORT

A Greek Cypriot married woman aged 28 was first seen in July 1964. She had had two previous pregnancies. The first, in 1962, while she was still in Cyprus, had ended at 36 weeks with the spontaneous delivery of a stillborn child. The parents had no information regarding the cause of death. The second pregnancy, in 1963, resulted in the birth of a healthy male child who is alive and well. She was seen regularly at the German Hospital from 12 weeks onwards of her third pregnancy. She was a fit woman with an

initial haemoglobin of 70% (10.2 g.). Her blood group was B rhesus-positive and there were no abnormal antibodies or haemolysins in her serum. Pregnancy was uncomplicated until at 35 weeks no foetal heart could be heard. Five days later labour began spontaneously, and a stillborn foetus was delivered in hospital on 22 December 1964. The foetus was female, weighed 4 lb. 12 oz. (2,150 g.) and had a swollen abdomen. The placenta was thick and "fleshy."

*Investigation.*—Blood from the infant was obtained post mortem and was more than one week old when received in this laboratory; regrettably, no reliable haematology was possible. Electrophoresis of the haemoglobin showed a very high proportion of an abnormal "fast" haemoglobin which had the characteristics of haemoglobin

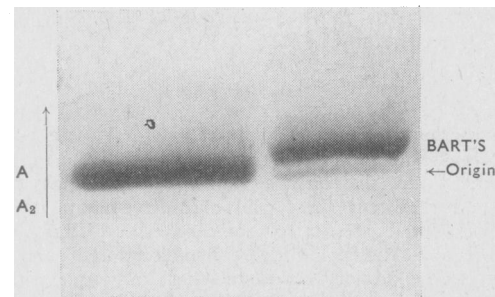


FIG. 1.—Electrophoresis of haemoglobin from stillborn baby on cellulose acetate paper in Tris buffer pH 8.9. Normal control on left.

Bart's on cellulose acetate paper, in barbiturate buffer pH 8.6, Tris buffer pH 8.9 (Fig. 1), and phosphate buffer pH 6.5. Alkali-resistant haemoglobin was 52% of the total haemoglobin by Singer's one-minute denaturation test. An approximate Singer's test on the fast haemoglobin after elution from cellulose acetate gave rather more than 50% alkali resistance, which would account for the figure of 52%.

The proportion of haemoglobin Bart's present, detected by elution of a stained cellulose acetate strip, was 92% of the total haemoglobin, with the minor component moving parallel with haemoglobin A. Foetal haemoglobin was not detected. A trace of haemoglobin

H may have been present, but it was not possible to confirm this by search for inclusion bodies in the red cells.

The presence of haemoglobin Bart's as the major component and the absence of foetal haemoglobin was kindly confirmed by Dr. Lehmann.

Haematological and electrophoretic studies, including tests for H inclusions, were undertaken on both parents, the one sibling, and the father's sister. The results are given in the Table. All four members of the family examined have in common a high red-cell count, a low M.C.H., poikilocytosis, and abnormal fragility, and in the mother it was possible to demonstrate typical H inclusions (Fig. 2).

Table of Results

	Hb (%)	R.B.C. (mill.)	P.C.V. (%)	M.C.H. ( $\mu$ g.)	M.C.H.C. (%)	M.C.V. (c. #)	Poikilocytes	Fragility in Saline†	H Inclusions‡	Serum Fe $\mu$ g./100 ml.	Electrophoresis
Mother	72	4.5	36	24	29	80	+	Decreased	+	84	Normal
Father	94	6.4	45	21	30	70	+	"	N.D.	83	"
Aunt*	82	5.8	41	21	29	69	++	"	"	"	"
Sibling	76	6.1	38	18	29	62	+	"	"	"	"

N.D. = Not detected.

\* Father's sister.

† Fragility screening test: 50 c.mm. of blood is added to 5 ml. of 0.4% buffered saline and allowed to stand for 45 minutes at room temperature. Normally the majority of red cells haemolyse, giving a clear or slightly opaque solution, but in thalassaemia and other haemoglobinopathies the cells are less fragile and the solution remains cloudy, often with a distinct sediment of intact cells.

‡ H inclusions were investigated by the method of Lehmann (1961).

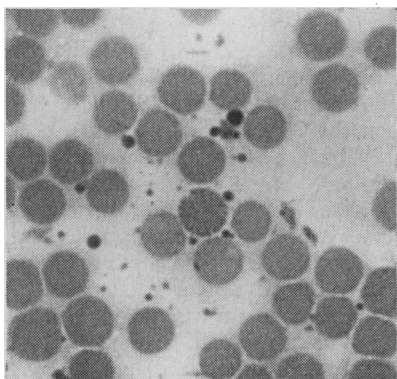


FIG. 2.—Red cell containing H inclusions from peripheral blood of mother. ( $\times 100$  objective  $\times 6$  eyepiece.)

## DISCUSSION

Heterozygous thalassaemia is a hereditary syndrome characterized by microcytosis and hypochromia of the red cells associated with an increased resistance of the cells in hypotonic saline and usually a normal serum iron, although occasionally alterations in erythrocyte morphology may be entirely absent. The haematological findings in both parents of the stillborn child described in this article are very suggestive of heterozygous thalassaemia.

Much knowledge has been acquired in recent years regarding the structure of the haemoglobin molecule, an understanding of which helps one to appreciate the differences between the various types of thalassaemia. Normal haemoglobins consist of two pairs of polypeptide chains, haemoglobins A,  $A_2$ , and F being represented as  $\alpha_2\beta_2$ ,  $\alpha_2\delta_2$ , and  $\alpha_2\gamma_2$  respectively, and, as can be seen,  $\alpha$ -chains are common to all three. Haemoglobin  $A_2$  comprises less than 3% and haemoglobin F less than 1% of the total haemoglobin in the normal adult, the remaining 96% being haemoglobin A.

Ingram and Stretton (1959) postulated the now generally accepted hypothesis that there are two forms of thalassaemia—one affecting  $\alpha$ -chain synthesis, the other  $\beta$ -chain synthesis.

$\alpha$ -Chain thalassaemia is characterized by an impairment of  $\alpha$ -chain synthesis and therefore affects production of all three haemoglobins A ( $\alpha_2\beta_2$ ),  $A_2$  ( $\alpha_2\delta_2$ ), and F ( $\alpha_2\gamma_2$ ). Diagnosis of  $\alpha$ -thalassaemia trait in the adult can be very difficult (Fessas, 1965), because the balance in the synthesis of the various fractions is kept constant and there is practically no surplus of  $\beta$ - or  $\gamma$ -chains. The only indication of  $\alpha$ -chain deficiency may be the presence of very rare cells containing typical H inclusion bodies due to minute quantities of haemoglobin H ( $\beta_4$ ), and even these are often absent. In the neonatal period diagnosis is simpler because usually, in addition to small amounts of haemoglobin H, there is its foetal counterpart, haemoglobin Bart's, varying from 5 to 25%; this haemoglobin was first described by Ager and Lehmann (1958) and shown to consist of tetramers of  $\gamma$ -chains ( $\gamma_4$ ) (Hunt and Lehmann, 1959).

The better-known  $\beta$ -chain thalassaemia is characterized by an impairment of  $\beta$ -chain synthesis. This form of thalassaemia minor has been classified by Fessas (1965) into types I and II. Type I has an elevated HbA<sub>2</sub> ( $\alpha_2\delta_2$ ) and a variable increase of HbF ( $\alpha_2\gamma_2$ ) varying from normal up to 8%. Type II, without an elevated HbA<sub>2</sub>, is further subdivided into (i) and (ii): the former usually having an elevated HbF 8–16%, the latter having no or only a mild increase on HbF. It may be impossible to distinguish  $\beta$ -thalassaemia trait type II (ii) from  $\alpha$ -thalassaemia trait in the absence of inclusions and family studies.

Homozygous inheritance of the gene for  $\alpha$ -thalassaemia results in  $\alpha$ -chain synthesis being suppressed to such a degree that during foetal life haemoglobin F ( $\alpha_2\gamma_2$ ) is largely replaced by haemoglobin Bart's ( $\gamma_4$ ) and at birth the production of adult haemoglobin A ( $\alpha_2\beta_2$ ) is so small that it is insufficient for survival. This condition as forecast (Ingram and Stretton, 1959) is incompatible with extrauterine survival.

Homozygous inheritance of the gene for  $\beta$ -thalassaemia gives rise to thalassaemia major, which usually presents as a severe haemolytic anaemia of childhood.

The haematological findings in the mother are characteristic of  $\alpha$ -thalassaemia trait, and in the father, father's sister, and sibling they are extremely suggestive of this condition. The infant's blood electrophoretically is typical of homozygous  $\alpha$ -thalassaemia.

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