

# Congenital (Erythroid) Hypoplastic Anaemia: Modified Expression in Males

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Intractable anaemia beginning soon after birth or in the first few months of life, and due to a hypoplastic state of the bone-marrow, is rare. As case reports have accumulated, it has become clear that this rather broad description includes a variety of syndromes. One of these, first described briefly by Josephs (1938) and Diamond and Blackfan (1938), has come to be recognized as a clearly-defined entity under the title of 'congenital (erythroid) hypoplastic anaemia'. The criteria for its recognition were laid down very clearly by Josephs: aplasia affecting the red cells only, the presence of the disease from birth, and the absence of fluctuation in the severity of the anaemia.

Having reviewed the literature and 30 cases of their own, Diamond, Allen, and Magill (1961) and Allen and Diamond (1961) gave a full description of the clinical and pathological features of the disease. They noted its lack of response to any form of treatment except steroids, and that though some remission might occur after life had been prolonged by repeated transfusions, the complications of multiple transfusions very often led to death. They also found that the incidence was the same in boys as in girls, but that boys were more likely to survive. In their own 28 families there were 5 pairs of affected sibs, but they were unable to decide whether the disease was inherited, though they thought that 'five families showing more than one affected child attest to the familial (though not necessarily genetic) nature of the disease. Further study of the intriguing probability of a genetic role is needed.' A significant contribution to this last question was made by Förare (1963). He observed the characteristic disease in two children borne by different mothers to the same father, plainly suggesting that it was carried by a single 'dominant' gene. The family to be described below closely parallels that of Förare, and may explain why a dominant gene, which when fully expressed is lethal in infancy, should have

survived in the population before the days of effective treatment.

### The Family

A girl (the index case, III.5 in Fig. 1) was born in 1953 at full term, weighing 2410 g. She had become noticeably pale by the age of 1 month, and at the age of 2 months she was first seen, and admitted to hospital. Hb was then 4.0 g./100 ml.; there was no ABO or rhesus incompatibility. Transfusion raised the Hb to 14.2 g./100 ml., but 3 months later she was readmitted with the Hb again 4.0 g./100 ml. A tibial marrow aspirate at that time showed that all marrow elements were normal except for an almost complete absence of erythrocyte precursors. At the age of 9 months, after ineffective treatment with various haematinics, including liver extract and riboflavine, and two further transfusions, she was treated with cortisone; and for the first time reticulocytes appeared in her blood, while during 2 months of this treatment her Hb rose from 8.3 to 10.4 g./100 ml. When she was aged 18 months, and after further steroid treatment, a few erythroid precursors were found in the marrow, and at the age of 32 months these had increased. After several unsuccessful attempts to dispense with steroids, the treatment was finally terminated when the child was 5 years old. In the succeeding 10 years her Hb level has remained around 12 g./100 ml., and she has been able to live normally and to pass through a normal menarche. Her height, however, has remained below the third centile.

A younger sister (III.6) born in 1956 is not affected. A brother (III.7) died at the age of 3 days from intestinal obstruction thought to be due to meconium

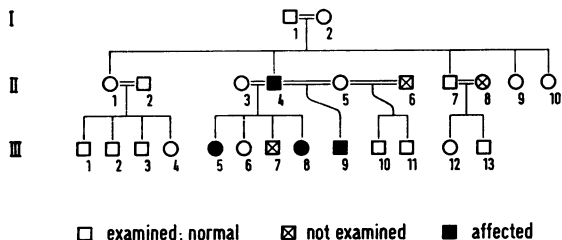


FIG. 1.—Family tree.

ileus; his Hb level at a time when he was probably dehydrated was 132%. At necropsy no evidence of mucoviscidosis or anaemia was found.

Another sister (III.8) was born at full term in 1961, weighing 2466 g. She was brought to hospital at the age of 7 weeks, when her Hb was found to be 4 g./100 ml. The marrow, normal in other respects, contained only three recognizable normoblasts per 1000 cells, though there were many small lymphocyte-like cells or 'haematogones'. A transfusion of packed cells raised the Hb to 16.6 g./100 ml., but a week later the marrow was unchanged. Reticulocytes, counted daily for 10 days, never rose above 0.03%, and Hb fell steadily to 8.6 g./100 ml. When the child was 14 weeks old, treatment with prednisolone was started and there was a prompt reticulocyte response, reaching 16.4% three weeks later. The marrow now showed disappearance of the 'haematogones' and their replacement by normoblasts. In the following few years many attempts to reduce or abolish steroid therapy were made without success, the Hb level falling with each attempt, and the marrow reverting to a state of severe erythroid hypoplasia, as shown on two occasions at the ages of 3 and 5 years. However, steroid therapy was stopped when the child was 6½ years old, and in the ensuing year Hb has been stable at about 8 g./100 ml. During full steroid therapy the red cells appeared normal, but without treatment they show considerable anisocytosis with some oval cells and some macrocytes.

A stepbrother (III.9) of the affected girls, having the same father but a different mother, was born in April 1968; his birthweight was 2863 g. and period of gestation probably 38 weeks. He had been jaundiced for a few days after birth, and subsequently he had minor difficulties with feeding. Previous experience had warned the parents, and they brought the child for examination when he was 10 weeks old, not being satisfied with his progress. Hb was then 9.3 g./100 ml., but, significantly, his red cells were leptocytic as in a neonate, and no haemoglobin was eluted from them in the acid elution test. At the age of 12 weeks his bone-marrow, though normal in respect of granulocytes and megakaryocytes, showed only 3% of normoblasts; these were normal in appearance, but there were also many (19%) 'haematogones', as in his older sister. No treatment was given, but he was closely watched. At the age of 3½ months his Hb had fallen to 7.8 g. but at 5 months it had risen to 10 g./100 ml. This level was maintained without treatment, and at the age of 1 year Hb was 10.4 g./100 ml. However, as in the two girls, there were still some macrocytes in the blood film.

Other relevant observations on the affected children were as follows.

*Urine chromatography* was performed twice on III.5 (each time at the end of a relapse and before treatment had been begun again), and once on III.9, at the age of 12 weeks. No abnormal amino acids and no abnormal metabolites were found on any occasion.

*Chromosomes* of the blood lymphocytes of III.8 were normal.

*Haemoglobin electrophoresis* of III.8 and her father was normal. In particular, there was no excess of Hb A2. *Maturation of erythropoiesis* with age was studied especially in III.8, by the method of acid elution. At the age of 7 weeks this child's blood contained neither adult nor intermediate erythrocytes, a state of affairs corresponding to that in a fetus of about 32 weeks' gestation (Fraser and Raper, 1962); aplasia must therefore have supervened at that age or earlier. Under steroid therapy adult cells appeared, but fetal cells have never completely disappeared, varying from about 1% during remission to 20% during relapse after steroid withdrawal. The older sister still showed scanty fetal cells at age 12½.

In the case of the affected boy, no adult red cells were to be seen when he was aged 10 weeks, but they appeared while the haemoglobin was falling, and numbered 50% at age 12 weeks, 75% at 7 months, and over 90% at age 1 year. In him therefore the process of fetal-to-adult 'switch-over' began late, proceeded slowly though by natural means, and was far from complete after one year.

#### Family Investigations

The surviving sib of the three affected children (III.6) was normal clinically and haematologically, and showed no fetal erythrocytes. So were the two mothers involved (II.3 and 5). The two children borne by II.5 to another father were also normal.

The father (II.4) was apparently healthy, and so far as he knew his infancy had been normal. At the age of 45 his Hb was 14.6 g./100 ml., and he showed 1% of reticulocytes. But a stained film, which was orthochromic, showed a minor degree of poikilocytosis and anisocytosis, occasional cells above normal size, and very occasional polychromatic cells (Fig. 2). There was no apparent cause for these appearances (at a normal Hb level), which were exactly the same as those seen in the affected girls during full remission. A further resemblance to his daughters was the presence of occasional fetal cells (Fig. 3); these numbered about 1 per 500 erythrocytes, and their presence was undoubtedly significant in a healthy male who was not a carrier of thalassaemia. Taken together, these blood findings could be regarded as the expression of the abnormal gene in this parent.

The paternal grandparents of the patients, and three aunts, one uncle, and six cousins were examined. Hb levels and blood films were normal in all these persons, except for minor iron deficiency signs in a few of them. In particular, none of these paternal relations showed any fetal erythrocytes in the blood; this makes it most unlikely that the father carried the benign family trait of arrested 'switch-over' from fetal to adult erythropoiesis (Raper, 1963). It was disappointing not to find some evidence of transmission through the grandfather; however, he was 72 years old.

#### Discussion

For infants with the fully developed syndrome of congenital hypoplastic anaemia, the chance of

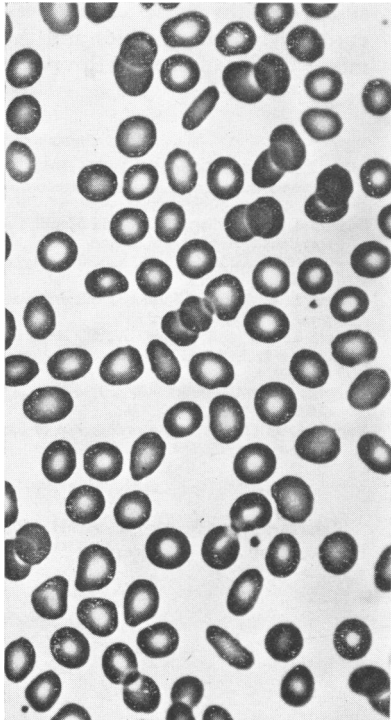


FIG. 2.—Blood film of II.4 (Romanowsky.  $\times 670$ .)

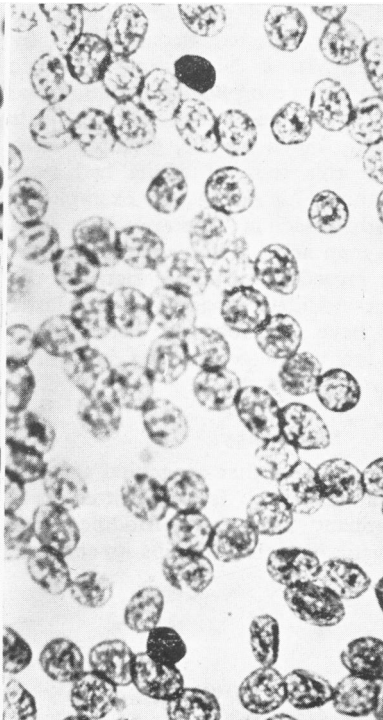


FIG. 3.—Blood film of II.4. (Acid elution, eosin stain, blue filter.  $\times 670$ .)

survival in the past was remote. Until Gasser introduced the use of steroids for this disease in 1951, the only means of prolonging life was by blood transfusion, frequently repeated; and many children died from the complications or sequelae of this. It seems certain that very few indeed of the children in whom the disease had been recognized survived to reproductive age.

When the disease began to be reported in sibs, it would have been natural to assume that it was carried by a 'recessive' gene, lethal in the homozygous form in affected children, and unexpressed in their heterozygous parents; but this idea was never clearly formulated. However, Förare's case disposed of this possibility, and also of any suggestion that even so rare a disease was regularly caused by spontaneous mutation. In his family the father was healthy, but clearly carried an abnormal gene, presumably in the heterozygous state. The same applies to our family, and in both cases it is hardly credible that the affected children could have been other than heterozygotes for the gene.

If this is so, it poses the question of why some heterozygotes survive to adult life, and others

succumb in childhood. The expression of the gene must be profoundly modified in certain persons. To explain this, one clue is available; in both families in which transmission is explicit, it is the male parent who carries the gene without ill effect. In our family it is further noteworthy that of the three affected children the male child was the least affected, and up to the present is surviving without treatment. Indeed, his anaemia might have escaped diagnosis, and even serious notice, but for the clue provided by the grave illness of his sisters. Still more might a similar anaemia in the father have been disregarded in the 1920's. Thus it seems likely that the gene has undergone sex modification in this family, and this is in agreement with the fact, already noticed, that in general boys are less severely affected than girls, and have a better chance of survival. We postulate, therefore, that the most important element in the survival of the gene for this disease is a modification of its effects in the male; and that its survival in the population before the days of effective treatment was due to its transmission by very mildly affected males.

In addition to this, we consider that our observa-

tions on the father's blood provide a means of detecting very mildly affected heterozygotes by direct examination. In a healthy non-anaemic adult, the combination of morphologically abnormal red cells and scanty but easily detected fetal cells denotes disordered, but adequate, erythropoiesis, and suggests that this state of affairs had been present from birth. This occurs, for example, in compensated  $\beta$ -thalassaemia minor, which was absent from this man and his immediate relations. In his case, we regard these minor signs as the expression of sex-modified congenital hypoplastic anaemia. They have probably not been looked for before, but are worth considering in similar families.

### Summary

A family study confirms that congenital anaemia of 'Diamond-Blackfan' type is transmitted as a Mendelian dominant character. Modified expression of the gene in males explains its survival,

and a healthy male carrier was shown to have erythrocyte abnormalities and the persistence of a minor degree of fetal erythropoiesis.

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