A Case of Red Cell Aplasia in a Negro Child

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Up to 1964 128 cases of congenital red cell aplasia had been reported (Table). All these were in Caucasian children and this was thought to be of genetic significance (Diamond, Allen, and Magill, 1961). Since then Khatua (1964) has described an 18-month-old Indian girl with red cell aplasia, whose chest radiograph showed an enlarged thymus gland, and who responded to steroids, while Shapiro, White, Diseker, and Bentley (1964) reported the condition in a negro girl with absent left kidney and ureter, who did not respond to steroids and who died at 4 months of age with pneumonia.

The present report of pure red cell aplasia is of interest, as it is possibly the result of administering phenylbutazone to the mother in the later months of pregnancy, and is only the second case to be reported in a negro child.

Case Report

A female negro child of Jamaican parents, aged 3 months, was admitted to the Belgrave Hospital on January 20, 1964, with extreme pallor. Four weeks before admission she had diarrhoea which was treated for one week with oral streptomycin. There was no history of bleeding or jaundice, and no family history of anaemia.

This was the mother's sixth pregnancy. At the 33rd week she had a painful elbow and was given phenylbutazone 200 mg. three times a day for 7 days. Delivery was normal at term, following artificial rupture of the membranes. The baby's birth weight was 8 lb. 10 oz. (3,920 g.). She was breast fed for 10 weeks.

On admission she weighed 9 lb. 4 oz. (4,205 g.) and had no abnormal facial characteristics. The spleen and liver were not enlarged and no lymph nodes were palpable. The heart was enlarged, with a haemic systolic murmur at the left sternal border.

Investigations. Hb 2.0 g./100 ml. (14%): 30% Hb-A, 70% Hb-F (at age 14 months Hb-F 5% only): haematocrit 7%, MCHC 34%, reticulocytes 0.2%. WBCs 8,200/c.mm. (47% neutrophils, 45% lymphocytes, 8% metamyelocytes). Ample platelets. Blood group A Rh positive. Sickling test negative. Direct

Coombs test negative. Red cell osmotic fragility normal. Serum iron 275 µg./100 ml. with fully saturated iron-binding capacity. Serum erythropoietin was raised (Dr. R. Sephton Smith). Mother's blood group A Rh + ve; sickling test negative.

Bone-marrow examination showed normal megakaryocytes and granulocyte precursors, but complete absence of red cell precursors. There were numerous macrophages containing iron-free granules.

The plasma electrolytes were normal, blood urea 69 mg./100 ml. (42 mg. 3 days later, 20-30 mg./100 ml. subsequently), total proteins 5.7 g./100 ml. with mild reduction in albumin and α₂-globulin (normal one month later), Wassermann reaction negative. A tryptophan loading test (70 mg. tryptophan/kg.) produced 1.2 micromoles of xanthurenic acid (normal 0.8-4.6) and 1.4 micromoles of anthranilic acid (normal up to 4.0) per kg. body weight in 7 hours.

TABLE
Reported Cases of Congenital Red Cell Aplasia

Reference	No. of Cases	Remarks
Hughes (1961)	70	Estimated total number to 1960
	8	Own cases
Diamond <i>et al.</i> (1961) ..	26	Reviewed their experience over 25 years with 30 cases, 4 of which were included in above total
Bernard, Seligmann, Chassigneux, and Dresch (1962)	14	Including 2 pairs of brothers and sisters
Förare (1963)	2	Sibs of same father and different mothers
Jaso and Hurtado (1963)	2	
Smith (1962)	1	
Lorenzo y de Ibarreta, Bidegain, Barahona, and Garofalo (1961) ..	1	Premature with cleft palate, congenital heart disease, and hepatosplenomegaly
Schorr, Cohen, Schwarz, and Wallerstein (1962)	1	A boy who, at 2 months, was given a 2-week course of chloramphenicol, but whose subsequent course suggested a congenital origin
Gordon and Varadi (1962)	1	Described as 'periodic erythroblastopenia'
Maurus and Fonteyne (1963)	1	
Karstoft (1964)	1	
Total	128	

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FIG.—Haemoglobin and reticulocyte levels related to prednisolone and to infective episodes. The first dose of prednisolone was 50 mg. daily. Blood transfusion, intramuscular iron, and folic acid were also given.

Urine contained no bile pigments, a trace of protein, a few pus cells, and was sterile. Intravenous pyelogram was normal. Skeletal radiography was normal, and chest radiography showed a general enlargement of the heart outline, but no evidence of thymic enlargement.

Two transfusions of 150 ml. each raised the haemoglobin to 60% in 8 days (Fig.). Bone-marrow biopsy again showed absence of erythropoiesis. Prednisolone was started on February 16, 1964. One week later reticulocytes appeared in the peripheral blood, and rose to a peak of 22% in 12 days. Hb rose to 75% in 18 days, and fell gradually thereafter. There was also a noticeable rise in platelets up to 1 million/c.mm. Bone-marrow biopsy 2 weeks after starting steroids showed a regenerating cellular marrow with very active macronormoblastic erythropoiesis (L : E ratio 1 : 2). Macrocytes appeared in the peripheral blood. This was thought to be due to a relative deficiency of folic acid, but FIGLU test was normal (less than 2 mg./hour of formiminoglutamic acid excreted after an oral dose of 4 g. histidine). Two weeks after stopping steroids Hb had fallen to 52% and reticulocytes to 0.5%. The bone-marrow was poorly cellular with normal granulocytopoiesis and thrombocytopoiesis, but only a few intermediate and late normoblasts were seen. The serum iron had fallen to 40 μ g./100 ml; with a total iron-binding capacity of 400 μ g./100 ml. Oral iron was therefore given.

Hb and reticulocytes were estimated twice weekly thereafter. There were two peaks of reticulocytosis from 0 to 16.5% in 4 days and from 0 to 10% in 6 days, associated with upper respiratory tract infections at ages 7 and 9 months, and from 1 to 20% in 5 days accompanying a staphylococcal pneumonia at 17 months (Fig.). As no steroids were being given at these times, they were possibly due to endogenous steroid output accompanying the stress of infection. Two prolonged courses of prednisolone in September 1964 and January 1965 also resulted in good haematological response (Fig.). Bone-marrow biopsies at the time of each peak showed active regeneration of erythropoiesis, and in the intervals showed absence of erythropoiesis.

Discussion

Because of associated congenital anomalies in a few cases, a familial incidence in others, and a high urinary excretion of tryptophan intermediary metabolites in many, it is thought that congenital red cell aplasia is a hereditary metabolic defect in erythroid differentiation from stem cells. There were no congenital malformations in our case, nor a familial incidence, and tryptophan urinary metabolites were not increased.

We are not aware of any case of congenital red

cell aplasia attributable to the administration of drugs to the mother. Of 30 cases reported by Diamond *et al.* (1961), 2 of the mothers had been receiving drugs, one stilboestrol and the other thyroid, throughout pregnancy. The mother of one of the eight cases described by Hughes (1961) received chlorothiazide and reserpine. Chlorothiazide can cause thrombocytopenia (Nordqvist, Cramér, and Björntorp, 1959), but Lucey (1961) does not report blood dyscrasias following reserpine or stilboestrol.

The red cell aplasia in our case was possibly due to the administration of phenylbutazone to the mother 7 weeks before delivery. It has been shown that phenylbutazone crosses the placental barrier and appears in the foetal blood in one-tenth to one-half the concentration in the maternal blood (Leuxner and Pulver, 1956; Strobel and Leuxner, 1957).

Among the various blood dyscrasias following phenylbutazone therapy, isolated depression of erythropoiesis is rare (McCarthy and Chalmers, 1964). Swineford, Curry, and Cumbia (1958) reported a 54-year-old woman who developed pure red cell aplasia after taking 200-400 mg. of the drug daily for 10 months for rheumatoid arthritis. She responded promptly to a short course of prednisone. Of 83 reports of red cell aplasia without pancytopenia collected at the drug registry of the American Medical Association during the 10-year period from 1953 to 1963, 3 cases in adults were attributed to phenylbutazone. Two of them recovered; the outcome of the third is not known (Norman De Nosaquo, 1964, personal communication).

In the 30 days of complete areticulocytosis (August 20 to September 20, 1964) in our patient, Hb fell by 2.9 g./100 ml., i.e. at the rate of 0.1 g./100 ml. daily, a figure in agreement with the fall of 0.093-0.108 g./100 ml. per day found by Diamond *et al.* (1961) in their cases. Thus if we presume that a uniform previous fall of 0.1 g./100 ml. per day had occurred before admission at 90 days of age, the cord blood would have been 11 g./100 ml., a low figure which raises the possibility that the aplasia existed before birth. There is some reason, therefore, to question the advisability of giving this drug during pregnancy.

Summary

A case of congenital red cell aplasia, the second to be reported in a negro child, is described. Reticulocytosis and rise in haemoglobin concentration followed courses of steroid or episodes of respiratory infection. The role of phenylbutazone administered to the mother 7 weeks before delivery is discussed.

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