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MEGALOBLASTIC ANEMIA COMPLICATING THALASSEMIA*

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Megaloblastic erythropoiesis is known to occur in patients with chronic hemolytic anaemia. It has been described in association with sickle cell anemia (Oliner and Heller 1959), thalassaemia (Robinson and Watson 1963), congenital spherocytosis (Delamore *et al.* 1961), and acquired hemolytic anemia (Forshaw and Harwood 1963). In a survey of the literature up to 1962, Robinson and Watson (1963) recorded 16 cases and added one of their own. The youngest patient in their review was 1½ years old, and there appears to be a paucity of reports in the younger age groups.

The object of this communication is to report two cases of megaloblastic anemia complicating thalassaemia in infants.

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Methods and Material

Hematological techniques employed have been described in an earlier communication (Nagaratnam *et al.* 1958). Paper electrophoresis of hemoglobin was carried out at pH 8.6. The alkali denaturation technique of Singer *et al.* (1951) was used for estimating fetal hemoglobin. Brilliant cresyl blue vital staining was used to demonstrate intra-erythrocytic inclusions. Marrow smears were stained with Leishman's stain.

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Report of Cases

Case 1. A female infant, aged 9 months, was admitted with a history of pallor and difficulty in breathing of 6 months' duration. The child was breast-fed. There was no history of frequent respiratory tract infections or diarrhoea. The milestones were delayed. On examination, the child was well-nourished and breathless at rest. Other than the extreme pallor, the skin was normal. There was no discoloration, ulceration, or edema. The hair was normal in colour and the conjunctivae were not icteric. There were jerky movements of both eyes and rolling movements of the head. The lymph glands were not palpable. The heart and lungs were normal. The liver was palpable 3 cms. below the costal margin. The spleen was not palpable.

Investigations. Hemoglobin was 2. 3 G.%, P.C.V. 8%, R.B.C. count 790,000 per c.mm., M.C.H.C. 29%,

M.C.V. 100 cμ and reticulocytes 4%. A peripheral smear showed marked oval macrocytes and anisopoikilocytosis. No nucleated or target cells were seen. No intra-erythrocytic inclusions were seen and tests for sickling were negative. The marrow was cellular and erythropoiesis was megaloblastic in type (Fig. 1). No abnormality was seen in the white cell series. Paper electrophoresis revealed no abnormal hemoglobin. Alkali-resistant hemoglobin was 17.5%.

A diagnosis of megaloblastic anemia complicating thalassaemia was made. The child was treated with blood transfusions and folic acid orally, which increased the hemoglobin to about 10 G%.

Hemoglobin analysis of the father's blood showed hemoglobin with a mobility similar to A and E types. Alkali-resistant hemoglobin was 1.3%, and tests for sickling were negative. The mother's blood revealed no abnormal hemoglobin, the alkali-resistant hemoglobin was 1.08% and tests for sickling were negative.

Case 2. An 8-month-old female was admitted with a history of fever and pallor of two weeks' duration. On examination she was pale. The lymph glands were not palpable. The heart and lungs revealed no abnormality. The abdomen was soft The liver was 5 cms. and the spleen 3 cms. below the costal margin.

Investigations. Hemoglobin was 3.7 G.%, P.C.V. 12.5%, R.B.C. count 1.19 millions, M.C.V. 104.2 cμ, M.C.H.C. 29%, W.B.C. 35,400 per c.mm. inclusive of nucleated red cells. polymorphs 19%, lymphocytes 80%, eosinophils 1%, reticulocytes 8%. Peripheral blood smear examination showed anisopoikilocytosis, marked macrocytosis, a large number of nucleated red cells and a few target cells; neutropenia with an increase in lymphocytes which showed no abnormality. The marrow was cellular and erythropoiesis was megaloblastic in type. X-ray of the skull showed no abnormality; that of the forearm and hands showed a generalised rarefaction. There was evidence of healing rickets at the lower end of the radius and ulna. Filter paper electrophoresis showed no abnormal hemoglobin and alkali resistant hemoglobin was 14% which was high for the age. Tests for sickling were negative. Intra-erythrocytic inclusions were seen.

A diagnosis of megaloblastic anemia complicating thalassaemia was made. She was treated with blood transfusions and folic acid for about 6 weeks. She was last seen 2 months after her first admission, when her hemoglobin was 9.8 G%. We were informed 3 weeks later that she had died at home after a brief illness lasting 2-3 days.

Family study. Hemoglobin analysis revealed no abnormal hemoglobin in the father and his alkali resistant hemoglobin was 5.2%. The mother showed no abnormal hemoglobin on electrophoresis; her alkali resistant hemoglobin was 0.825% and tests for sickling were negative.

Discussion

Megaloblastic erythropoiesis may occur as a complication of hemolytic states. This has been attributed to a relative folic acid deficiency caused by marrow hyperplasia, but the precipitating factor may be some dietary deficiency or infection. Cha-

narin *et al*. (1959) found that the increased need for folic acid was due to an absorption defect. Chatterjea (1959) found megaloblastic marrow in six cases with HbE-thalassaemia and thalassaemia. Bannerjee *et al* (1957) estimated vitamin B_{12} levels and folic acid levels in 27 cases and found that the total vitamin B_{12} levels were distinctly low in 4 and folic acid levels in 3. Chatterjea (1959) attributed the deficiency involving B_{12} and/or folic acid to the associated deficiency that may exist in a general population of a similar socioeconomic status. Aplastic crises occur in thalassaemia. Fessas (1959) found definite megaloblastic transformation of erythropoiesis and myelopoiesis in one case and a less pronounced one in another during such a crisis, responding to folic acid.

Increased fetal hemoglobin levels can occur with megaloblastic marrow, but they are never so high as in the cases described. The resemblance of primitive embryonic nucleated red cells to megaloblasts suggested the presence of Hb F in pernicious anemia, using the alkali denaturation test (Iverson and Larsen 1956). In ten cases of untreated pernicious anemia, Beaven *et al.* (1960) found that Hb F was present in 6, in a proportion ranging from a 'trace' to 2%. They further studied 7 cases of megaloblastic anemia due to folic acid deficiency of varied etiology including those associated with pregnancy and anti-convulsant therapy. Hb F was detected at 'trace' level in only one of them where there has also been associated iron deficiency. They recorded a case of megaloblastic anemia following total gastrectomy and splenectomy done for peptic ulcer in whom the pre-treatment level of Hb F was 9 per cent. They have discussed the normal course of disappearance of Hb F in infancy, and their work indicates that increased levels of Hb F may not only result as abnormal persistance from infancy but alternatively from reactivation of the specific process for its formation. Megaloblastic anaemia of infancy is not uncommon in this country (Nagaratnam *et al.* 1968) and thalassemia occurs in the general population (Nagaratnam *et al.* 1958, Nagaratnam and Sukumaran 1967).

Again, the possibility of hereditary persistence of high foetal haemoglobin associated with megaloblastic anemia has to be ruled out. Intracellular distribution of fetal hemoglobin determined by the acid elution method shows a characteristic pattern in this condition, thus differing from β-thalassaemia carriers. One or both parents should show a high foetal hemoglobin. The parents of both infants did not show raised levels of fetal hemoglobin, though the father of Case 2 had a fetal hemoglobin, of the order of 5.2%. This however, is too low for this condition. These together wth the family study, indicate that they are cases of thalassaemia complicated by megaloblastic anemia.

Summary

Two cases of thalassaemia complicated by megaloblastic erythropoiesis are described as occurring in infants aged 9 and 8 months. This association together with the causes of megaloblastosis in chronic hemolytic states have been discussed. Abnormal persistence of fetal hemoglobin occurs

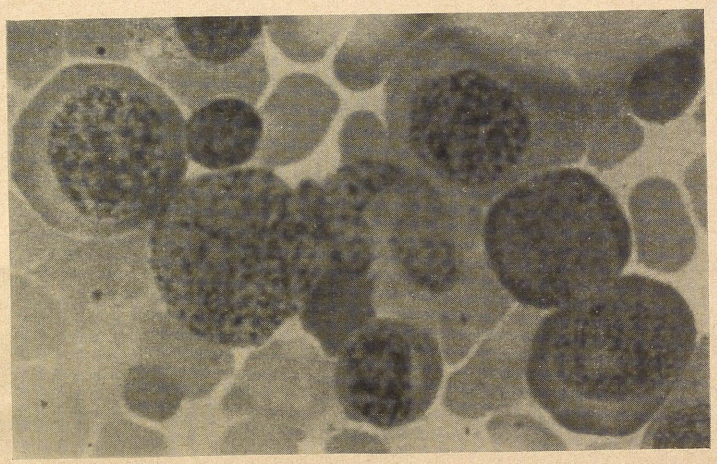

Fig. 1.—Megaloblasts in various stages of maturation.
(H and E × 100).

in genetically determined hemoglobinopathies and in thalassaemia. Increased Hb F levels can also occur in megaloblastic anemias of varied aetiology but they are not so high as in the cases described. In hereditary persistence of fetal hemoglobin the levels are much higher in the heterozygous states.

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