most consistent with the original diagnosis of homozygous beta thalassemia.

The benign clinical course of this patient is not atypical for homozygous beta thalassemia in the black subject. In contrast to white subjects, most blacks with homozygous beta thalassemia have a mild form of the disease, need few or no transfusions, and live into and beyond the fourth decade. Recent studies of the synthesis of beta and alpha globin chains in peripheral blood reticulocytes of subjects with thalassemia have suggested that the defect in beta thalassemia trait is milder in blacks than in whites, in that the mean beta/alpha globin chain synthesis rate is higher in blacks.[4,5] However, the studies in subjects homozygous for beta thalassemia have not yet shown a difference between blacks and whites in the beta/alpha ratio in either peripheral blood reticulocytes or bone marrow cells.[4,5] Thus, the molecular basis for the puzzling difference in clinical severity of homozygous beta thalassemia in blacks as compared to whites remains a mystery.

SUMMARY

A 54-year-old woman, perhaps the oldest living American black with homozygous beta thalassemia, has had a relatively benign clinical course since her case was first reported two decades ago. Despite progressive splenomegaly, she has remained active without blood transfusions. This case emphasizes the mildness of homozygous beta thalassemia in black subjects.

References

1. Norris JE, Hanson HH, Loeffler RK: Mediterranean anemia in an adult Negro. *Arch Intern Med* 98:356-364, 1956
2. Crouch ER Jr, Maurer HM, Valdes OS: Probable homozygous beta thalassemia in a Negro child. *Am J Dis Child* 120:356-359, 1970
3. Braverman AS, McCurdy PR, Manos O, et al: Homozygous beta thalassemia in American blacks: the problem of mild thalassemia. *J Lab Clin Med* 81:857-866, 1973
4. Friedman S, Oski FA, Schwartz E: Bone marrow and peripheral blood globin synthesis in an American black family with beta thalassemia. *Blood* 39:785-793, 1972
5. Friedman S, Hamilton RW, Schwartz E: Beta thalassemia in the American Negro. *J Clin Invest* 52:1453-1459, 1973
6. Shepard MK, Weatherall DJ, Conley CL: Semi-quantitative estimation of the distribution of fetal hemoglobin in red cell populations. *Bull Johns Hopkins Hosp* 110:293-310, 1962
7. Jacob HS: Hypersplenism: mechanisms and management. *Br J Haematol* 27:1-5, 1974
8. Motulsky AG: Frequency of sickling disorders in US blacks. *N Engl J Med* 288:31-33, 1973
9. Conley CL, Weatherall DJ, Richardson SN, et al: Hereditary persistence of fetal hemoglobin: a study of 79 affected persons in 15 Negro families in Baltimore. *Blood* 21:261-281, 1963
10. Huisman THJ, Schroeder WA, Charáche S, et al: Hereditary persistence of fetal hemoglobin. heterogeneity of fetal hemoglobin in homozygotes and in conjunction with beta thalassemia. *N Engl J Med* 285:711-716, 1971
11. Zelkowitz L, Torres C, Bhoopalam N, et al: Double heterozygous beta-delta thalassemia in Negroes. *Arch Intern Med* 129:975-979, 1972
12. Stamatoyannopoulos G, Fessas P, Papayannopoulou T: F-thalassemia: a study of thirty-one families with simple heterozygotes and combinations of F-thalassemia with A_2-thalassemia. *Am J Med* 47:194-208, 1969

Vitamin E-Dependent Anemia in a Premature Infant

KENNETH C. HENDERSON, MD,† Macon, Ga, and EVAN TORCH, BA, BS,‡ Augusta, Ga

The physiologic role of vitamin E remains in doubt, but its best established biochemical action is that of an antioxidant. By combining with free radicals, vitamin E seems to prevent the chain of reactions called "lipid peroxidation." By this mechanism, oxidative damage to lipid membranes, including the red cells and the membranes of other intracellular organelles, may be prevented. This hypothesis provides a good explanation for the hemolytic aspects of the anemia in vitamin E deficiency and for the sensitivity of the erythrocytes to peroxides, hyperbaric oxygen, iron, and natural destructive elements of cell membranes.[1]

The second popular hypothesis regarding the need for vitamin E points to a more specific metabolic function. Advocates of this viewpoint maintain that efforts to establish the occurrence of lipid peroxidation or cell wall destruction have not been successful in vivo. There is evidence that vitamin E may be a structural component of biologic membranes and that it affects induction and repression of certain enzyme systems.[2] Pertinent to the role in erythropoiesis are observations suggesting a requirement for vitamin E in heme biosynthesis.[3]

†From the Department of Pediatrics, Medical College of Georgia, and the Intensive Care Nurseries, Medical Center of Central Georgia, Macon, Ga.

‡Fourth year medical student, Medical College of Georgia, Augusta, Ga. Reprint requests to Medical Center of Central Georgia, 777 Hemlock St, Macon, Ga 31208 (Dr. Henderson).

We report an instance of persistent anemia in a premature infant which responded to vitamin E therapy.

CASE REPORT

This male infant weighed 992 gm (2 lb 3 oz) at birth after an estimated gestation of 32 weeks. The mother was 21 years old. She had received dexamethasone (Decadron), 4 mg given intramuscularly, on three consecutive days before delivery. The infant was in good condition at birth and received oxygen therapy for 12 hours for a mild respiratory distress syndrome. Feeding was begun after 24 hours. At 20 days of age the baby was begun on a regimen of multivitamins A, D, C and 0.3 ml of ferrous sulfate (Fer-In-Sol) twice a day. Two days later the infant's hemoglobin level was 10.1 gm/100 ml, and the reticulocyte count was 0.9%. Over the next three days the infant passed loose stools, and feeding of a nonlactose formula was begun. The mother gave a family history of milk intolerance. By the 38th day the infant was gaining 20 to 30 gm a day and was taking 35 ml of formula every three hours by nipple. The hemoglobulin level was 9.6 gm/100 ml, and the reticulocyte count was 1.7% at that time. On the 50th hospital day the baby had pitting edema of the lower extremities. A blood count revealed a hemoglobin level of 7.6 gm/100 ml, hematocrit value of 22.6%, and a reticulocyte count of 19%. The red blood cell morphology showed slight anisocytosis with moderate polychro-

masia and an occasional schistocyte. The infant's level of free vitamin E in the serum was 2.8μg/ml (normal, 5μg to 20μg/ml).

On the 51st day the infant gained 90 grams and the scrotum grew large and tight. Vitamin E was given in an oral dose of 25 units daily. The infant continued to receive formula containing vitamin E, and he began to receive regular lactose feedings before discharge.

Three days after the addition of 25 units of vitamin E daily the reticulocyte count had dropped to 14% and the hematocrit value had risen to 26%. On the 55th day the edema was substantially reduced.

The iron supplement remained constant during vitamin E therapy. The weight gain during treatment with vitamin E averaged 30 gm/day for four days and averaged about 20 gm over the next four days despite a decrease in peripheral edema.

On the 63rd day, 12 days after starting vitamin E therapy, the vitamin E level in the serum was 15μg/ml. The hemoglobin level was 9.4 gm/100 ml, hematocrit value was 28.5%, and reticulocyte count was 5.4%.

DISCUSSION

Oski and Barness,[4] in 1967, reported a group of premature infants 6 to 10 weeks of age who were anemic with a falling hemoglobin concentration in spite of strikingly high reticulocyte counts. The red blood cells were distorted and often fragmented. The serum concentration of vitamin E was found to be low. The in vitro red cell hydrogen peroxide hemolysis test was also markedly positive. After administration of vitamin E, the reticulocyte count dropped, red cell morphology improved, and the concentration of hemoglobin rose. The anemia ranged from approximately 6 to 9 gm% and could not be reversed by administration of iron, vitamin B_{12}, or folic acid. The bizarre red cell morphology and persistent reticulocytosis in the presence of a falling hemoglobin level suggested a hemolytic process. The administration of vitamin E returned reticulocyte and hemoglobin levels to normal and erased, in large part, the abnormal forms from the blood picture. Other pertinent findings in their study included the fact that an increase in the quantity of unsaturated fatty acids in the diet increased the need for vitamin E. They also suggested that iron, routinely administered to preterm infants, antagonized absorption of vitamin E, as did administration of vitamin C.

Among the recognized nutritional requirements which must be met for the premature infant in the first years of life is the increased need for utilizable iron. Although the gestationally immature infant is born with iron stores which approximate those of full-term infants, when measured in terms of milligrams per kilogram of body weight, the premature infant's body mass, and consequently blood volume and hemoglobin mass, normally increase at a far more rapid rate than the full-term infant's during the first year. For this reason, supplementing the premature infant's diet with iron has been recommended.

Melhourn and Gross[5,6] found that the lowest concentration of hemoglobin and the highest reticulocyte counts were seen in infants whose gestational age was less than 36 weeks and who were receiving iron while being deficient in vitamin E. Conversely, infants receiving vitamin E supplement without additional iron maintained the highest hemoglobin concentration throughout the same period. Oral administration of iron was implicated as interfering with intestinal absorption of vitamin E. No matter what the gestational age might be, iron interfered with absorption. They also found evidence that ionized iron increases in vitro and in vivo RBC hemolysis.

Ritchie et al[7] pointed out two more aspects of the vitamin E-deficient hemolytic anemia syndrome in premature infants. This group noted prominent edema as a previously unrecognized initial manifestation. The edema was most evident in the lower extremities and genitalia. The cause of edema may be that the capillary membrane, like that of the erythrocyte, undergoes oxidative damage that permits excessive transudation of fluid. They also presented data to substantiate the claim that the amount of vitamin E requisite to prevent deficiency rises when polyunsaturated fatty acid content of the diet is increased. They also found that infants fed breast milk had normal serum levels of vitamin E, whereas those fed artificial formulas had almost uniformly low serum levels of vitamin E.

SUMMARY

Reported is a case of a premature infant who developed a well documented hemolytic anemia which responded to vitamin E therapy. The infant developed the syndrome while receiving an artificial formula containing iron and vitamin E, plus iron supplementation. The infant had a feeding problem which may have complicated absorption of vitamin E. It is suggested that premature infants who are formula fed should not receive iron supplement until they have doubled their birth weight or have a hemoglobin concentration of less than 10 mg%. Premature infants should receive supplemental vitamin E if they are not breast fed.

References

1. Wintrobe MM, Lee GR, Boggs DR, et al: *Clinical Hematology*. Philadelphia, Lea & Febiger, 7th Ed, 1974, pp 148, 149
2. Lucy JA: Functional and structural agents of biological membranes: a suggested structural role for vitamin E in the control of membrane permeability and stability. *Ann NY Acad Med* 203:4, 1972
3. Murty HS, Cassi PI, Brooks SK, et al: Biosynthesis of heme in the vitamin E deficient rat. *J Biol Chem* 245:5498, 1970
4. Oski FA, Barness LA: Vitamin E deficiency: a previously unrecognized cause of hemolytic anemia in the premature infant. *J Pediatr* 70: 211, 1967
5. Melhourn DK, Gross MA: Vitamin E-dependent anemia in the premature infant. I. Effects of large doses of medicinal iron. *J Pediatr* 79:569-580, 1971
6. Melhourn DK, Gross MA: Vitamin E-dependent anemia in the premature infant. II. Relationships between gestational age and absorption of vitamin E. *J Pediatr* 79:581-588, 1971
7. Ritchie JH, Fish MD, McMasters V, et al: Edema and hemolytic anemia in premature infants. *N Engl J Med* 27:1185, 1969