Vitamin E deficiency: A previously unrecognized cause of hemolytic anemia in the premature infant

The late anemia of some premature infants has been found to be due to hemolysis at six to ten weeks. This anemia is correctable by administration of vitamin E. The vitamin E deficiency is probably induced by low vitamin E stores at birth, and dietary insufficiency, or by factors in the diet causing increased use of vitamin E.

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OVER 40 YEARS AGO Evans and Bishop[1] noted that a fat-soluble substance, now known as vitamin E or tocopherol, was necessary for reproduction in the rat. Although it is recognized that deficiency of vitamin E has various pathologic effects in animals, its role in human nutrition remains undefined.

Vitamin E deficiency has been observed in humans as a consequence of prolonged malabsorption in cases of steatorrhea.[2] In these patients the deficiency is associated with an increased susceptibility of the erythrocytes to in vitro hemolysis in dilute solutions of hydrogen peroxide. In some deficient patients, creatinuria,[3] ceroid deposition[4] in smooth muscle, and focal necrosis of striated muscle[5] have been observed. Vitamin E deficiency has also been suggested to be a causative factor in the anemia of kwashiorkor.[6]

Newborn infants generally have low serum tocopherol levels.[7] Premature infants fed artificial milk diets have low serum tocopherol levels for several months.[8] The low vitamin E serum levels of premature infants have not been associated with any recognized pathologic process until now, even though evidence of disease states has been sought.[9]

While examining the blood of premature infants aged 6 to 10 weeks we noted that some of the infants had a strikingly high number of reticulocytes in the presence of a falling or just stable hemoglobin concentration. The red blood cells were distorted and often fragmented. Since the concentration

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of vitamin E was being determined in other experiments, vitamin E serum levels were obtained in these infants and were found to be low. The in vitro red cell hydrogen peroxide hemolysis test was also markedly positive. Following administration of vitamin E, the reticulocyte count dropped, red cell morphology improved, and the concentration of hemoglobin rose.

After identifying this state in a number of infants, further studies were conducted which showed that this previously unrecognized hemolytic anemia, which develops frequently in infants of low birth weight, could be prevented or markedly improved by the administration of vitamin E.

SUBJECTS, MATERIALS, AND METHODS

All infants described in this report were in the premature nurseries of either the Philadelphia General Hospital or the Hospital of the University of Pennsylvania. They were divided into two groups: (1) 11 infants in whom a hemolytic anemia in association with vitamin E deficiency was recognized and treated, and (2) 25 infants studied prospectively. It was planned to supplement the diets of 10 infants in the second group and to use 15 of them as control infants. It was subsequently discovered, however, that there were varying amounts of vitamin E in one of the formulas and that more infants had received an adequate intake of vitamin E than had been planned; in the final analysis, only 12 infants were considered to be deficient in vitamin E.

Infants were fed either Similac with Iron* (Lot Nos. 48, 97, or 116), Alacta,† or S-26.‡ All infants received vitamin A, C, and D supplements from the first day of life. Infants fed Alacta received supplemental iron as Fer-in-sol,§ to supply 15 mg. of elemental iron per day, starting at one month of age. The 11 infants who were treated with vitamin E received 200 to 800 mg. (270 to 1,090 I.U.) of *d*-alpha tocopherol‖ by mouth over a period of 1 to 4 days.

The infants whose diets were supplemented with vitamin E received vitamin E as Aqua-Sol E,¶ 15.7 mg. a day, or *d*-alpha tocopherol, 9 mg. a day, suspended in 0.6 ml. of Tween 80 beginning on the third day of life. Control infants received Tween 80 without tocopherol.

For most infants in Group 1, weekly

*Similac with Iron, Ross Laboratories, Columbus, Ohio.

†Alacta, Mead-Johnson Laboratories, Evansville, Ind.

‡S-26, Wyeth Laboratories, Radnor, Pa.

§Fer-in-sol, Mead-Johnson Laboratories, Evansville, Ind.

‖Supplied as *d*-alpha tocopheryl acetate N.F., potency 1.36 I.U. per milligram, by the Distillation Products Industries, Rochester, N. Y., through the courtesy of Dr. Stanley Ames.

¶Aqua-Sol E, U.S. Vitamin Corporation, New York, N. Y.

Table I. Eleven infants treated with *d*-alpha tocopherol*

Birth weight (grams)	*Age at treatment (days)*	*Diet*	*Total dose vitamin E (mg.)*	*Maximum response (days)*	*Pretreatmen*		
					Hemoglobin (Gm /100 ml.)	*Reticulocyte count (%)*	*H_2O_2 hemolysis (%)*
1,100	73	S-26	200	7	7.0	9.0	77
1,280	40	Alacta	500	12	5.4	15.6	88
1,380	65	Alacta	600	7	9.5	7.8	58
1,400	48	Similac	600	13	8.5	4.0	71
1,450	51	Similac	800	11	7.4	6.4	62
1,500	70	Similac	400	10	7.6	8.2	93
1,500	77	Similac	400	10	8.0	4.6	90
1,520	49	Alacta	750	7	8.1	9.4	87
1,560	47	Alacta	400	13	7.8	8.3	99
1,780	61	Alacta	250	10	8.0	8.4	—
1,920	43	Similac	425	10	6.2	8.0	75
Mean 1,480 ± 205 ± S.D.	57.0			10	7.6 ± 1.1	8.2 ± 2.9	80 ± 14

*Normal serum tocopherol (50 adults): 0.65 to 1.40 mg./100 ml. (mean 0.94 mg./100 ml.) hydrogen peroxide hemolysis te

hematologic data were obtained prior to therapy and daily after initiation of treatment. In all infants in Group 2, hemoglobin, hematocrit, red blood cell count, reticulocyte count, and peripheral blood film inspections were determined each week. Hydrogen peroxide hemolysis tests and serum tocopherol assays were performed at biweekly intervals. All infants were tested for glucose-6-phosphate dehydrogenase deficiency and hemoglobinopathies.

The infants described in Group 1, the "treatment group," remained in the hospital until response to vitamin E therapy had been evaluated. Infants in Group 2, the "prevention group," remained in the nursery for a minimum of 42 days and were not discharged until they had reached weights of 2,200 to 2,500 grams.

Hemoglobin, microhematocrit, red blood cell count, reticulocyte count, and sickle cell preparations were performed by standard techniques.[10] Heinz body stains and red cell osmotic fragilities were performed by the methods described by Dacie and Lewis,[11] and glucose-6-phosphate dehydrogenase assays by the method of Zinkham, Lenhard, and Childs.[12]

Serum tocopherol was determined by a slight modification of the method of Quaife, Scrimshaw, and Lowry[13]; 0.4 ml. of serum was employed and all other reagents were proportionately increased. Red cell hydrogen peroxide hemolysis tests were done in duplicate by the method of Rose and György.[14]

The pyknocytes were estimated on each infant by counting 1,000 erythrocytes in a peripheral blood film when the infants were 6 weeks of age.

In two infants autologous red cell survival studies were performed employing chromium[51] as described by Read and associates.[15]

RESULTS

Treatment group. The 11 anemic infants who had a low serum tocopherol level and/or a markedly positive hydrogen peroxide hemolysis test were treated with *d*-alpha tocopherol.

In Table I some of the clinical data and the hematologic responses in these infants are summarized. All were Negro, and 10 were females. There were 2 sets of twins. Birth weights ranged from 1,100 to 1,920 grams, with a mean of 1,480 grams. Five infants had been fed Similac with Iron, five Alacta, and one S-26. Age at the time of diagnosis and treatment ranged from 44 to 77 days with a mean of 57 days. Hemoglobin prior to treatment ranged from 5.4 to 9.5

		Post treatment				
Red cell count (10^6/mm.^{3})	*Serum tocopherol (mg./100 ml.)*	*Hemoglobin (Gm. %)*	*Reticulocyte (%)*	*H_2O_2 hemolysis (%)*	*Red cell count (10^6/mm ^{3})*	*Serum tocopherol (mg./100 ml.)*
—	—	10.0	6.6	23	—	—
—	—	8.3	6.4	1	—	—
2.96	0.29	10.7	3.2	0	3.82	1.03
3.10	0.38	10.9	2.1	16	3.98	1.20
3.00	0.35	9.5	4.0	3	3.15	1.31
2.98	0.41	10.3	2.9	5	3.82	1.04
3.34	0.09	10.2	1.9	0	3.80	1.01
2.97	0.00	9.7	4.0	25	3.50	0.85
2.92	0.36	9.8	4.1	8	3.54	0.81
—	0.25	10.2	3.4	—	—	0.78
2.67	0.14	8.6	4.6	0	3.03	0.56
2.99 ± .19	.25 ± .15	9.8 ± .8	3.9 ± 1.5	8 ± 10	3.58 ± .34	.95 ± .23

Less than 4 per cent.

Gm./100 ml. with a mean of 7.6 Gm. Reticulocyte counts ranged from 4.0 to 15.6 per cent with a mean of 8.2 per cent. Following treatment with *d*-alpha tocopherol, the serum tocopherol level rose to normal levels, and in vitro hemolysis in the presence of hydrogen peroxide decreased. During an average interval of 10 days from the start of *d*-alpha tocopherol therapy the mean hemoglobin rose from 7.6 to 9.8 Gm./100 ml. and the mean reticulocyte count fell from 8.2 to 3.9 per cent. The rise in hemoglobin and the fall in the reticulocyte count are both statistically significant.

Other causes of hemolysis were excluded. All patients had normal-for-age hemoglobin electrophoresis patterns. Five infants had normal incubated and unincubated red blood cell osmotic fragilities. No patient had clinically evident jaundice between 4 and 10 weeks of age and in no patient was significant splenomegaly present.

Prevention group. Of 29 infants in the prospective study, 25 were available for statistical comparison. One infant died, one was discharged before reaching 6 weeks of age, one was found to have glucose-6-phosphate dehydrogenase deficiency, and one had alpha-thalassemia trait.

The diets of these 25 infants are listed in Table II. Ten received Similac with a vitamin E supplement, six received Similac

Table II. Comparison of the hematologic status of "vitamin E–sufficient and –deficient" premature infants

Birth weight (grams)	*Diet**	*Serum tocopherol (mg./100 ml.)*	*H_2O_2 hemolysis (%)*	*Lowest hemoglobin (Gm./100 ml.)*	*Highest reticulocyte count (%)*	*Red cell count at time of peak reticulocytosis (10^6/mm.^{3})*
E "sufficient"						
930	Similac-ASE	0.76	29	8.6	3.1	2.90
1,020	Similac-ASE	0.97	0	8.6	2.7	2.81
1,060	Similac-ASE	0.97	—	7.8	3.9	2.60
1,130	Similac-E	—	7	8.6	2.8	2.73
1,280	Similac-E	0.90	24	11.0	2.1	3.93
1,320	Similac-E	1.30	0	11.4	3.5	3.65
1,340	Similac	0.78	11	10.3	2.9	3.01
1,380	Similac-E	1.55	6	8.6	1.9	2.80
1,400	Similac	1.05	3	8.5	3.8	2.74
1,400	Similac-E	0.79	8	8.2	4.1	2.40
1,430	Similac-ASE	—	4	9.0	2.9	3.07
1,450	Similac	1.12	—	9.6	3.2	2.90
1,470	Similac-E	0.82	7	9.6	2.7	2.86
Mean 1,278 ± 180		1.00 ± .25	9 ± 9	9.2 ± 1.3	3.1 ± .7	2.95 ± .42
E "deficient"						
900	S-26	—	51	7.2	10.0	2.80
940	Similac	—	84	7.4	8.1	2.40
1,000	Alacta	0.15	100	6.3	12.4	2.20
1,060	Alacta	0.24	59	10.4	7.1	3.40
1,100	Alacta	0.09	—	6.2	5.6	1.80
1,130	Alacta	—	81	9.0	7.6	4.00
1,240	Alacta	0.31	38	7.7	5.6	2.50
1,270	Similac	0.15	75	5.0	3.0	1.79
1,300	Alacta	0.32	66	8.5	6.6	—
1,300	S-26	0.38	38	7.5	5.1	2.40
1,400	S-26	—	48	9.4	4.5	2.90
1,470	Similac	0.16	89	8.4	4.7	2 62
Mean 1,176 ± 182		.22 ± .10	66 ± 21	7.7 ± 1.5	6.7 ± 2.5	2.62 ± .21

*ASE, Aqua-Sol E, 15.7 mg. per day.

E, *d*-alpha tocopherol acetate in Tween 80, 9 mg. per day (12.2 I.U.).

alone, six Alacta alone, and three S-26 alone.

It was found during the course of this study that the tocopherol content of the Similac varied considerably from lot to lot and therefore the effect of supplementation was complicated by the vitamin E content of this formula. The tocopherol content of the S-26 remained constant (Table III). Of the 25 infants, 13 proved to be vitamin E "sufficient" and 12 vitamin E deficient. Vitamin E "sufficiency" is arbitrarily defined as a serum tocopherol value of greater than 0.50 mg./100 ml.[7] and an in vitro hydrogen peroxide hemolysis test of less than 30 per cent.

The hematologic data in these 2 groups of infants are listed in Table II. The initial hemoglobin levels not shown in the table, were similar for the 2 groups. The mean hemoglobin level during the first week of life was 17.9 Gm. per cent for the "sufficient" group and was 18.6 Gm. per cent for the deficient group. The lowest observed hemoglobin in each infant in either treatment group is recorded along with the highest reticulocyte count observed during the period of 42 to 56 days of life. The mean hemoglobin value was significantly higher, 9.2 ± 1.3 Gm./100 ml. in the infants receiving supplemental vitamin E than it was in those in the deficient group in whom the mean hemoglobin was 7.7 ± 1.5 Gm./100 ml. The reticulocyte count, both relative and absolute, was significantly lower in the vitamin E–sufficient group. The mean reticulocyte count for this group was 3.1 ± 0.6 per cent contrasted with a mean reticulocyte count of 6.7 ± 2.6 per cent in the vitamin E–deficient infants. The mean number of pyknocytes in the sufficient infants was 1.7 per cent (range 0.3 to 2.7 per cent) and in the deficient infants it was 6.6 per cent (range 1.8 to 23.9 per cent).

Table III. A comparison of the tocopherol content of several lots of Similac* and of S-26†

Food	*Alpha tocopherol (mg./reconstituted quart)*	*Alpha tocopherol (mg./Gm. of fat)*
Similac Lot No.		
48	4.0	0.131
97	0.73	0.024
116	0.98	0.031
S-26 Lot No.		
B-9-S	4.4	0.128
A-4-U	5.1	0.153
A-2-V	5.2	0.163

*Determined by David Herting, Distillation Products Industries, Rochester, N. Y.

†Determined by Wisconsin Alumni Research Foundation.

The hematologic data for these 12 vitamin E–deficient infants are statistically comparable with those of the deficient infants in Table I. For purposes of statistical comparison the 23 vitamin E–deficient infants are contrasted with the 13 vitamin E–sufficient infants in Table IV. The sufficient group had a significantly higher mean hemoglobin, 9.2 ± 1.3 versus 7.7 ± 1.3, ($p < 0.01$) and a significantly lower mean reticulocyte count, 3.1 ± 0.7 versus 7.4 ± 2.8, ($p < 0.001$). Although the two groups were similar in birth weight, race, and age when studied, they differed significantly with respect to hemoglobin concentration and reticulocyte count on the basis of their vitamin E status.

DISCUSSION

Infants of low birth weight frequently develop anemia at 6 to 10 weeks of age with hemoglobin levels of 6 to 9 Gm./100 ml. This anemia cannot be prevented by iron

Table IV. A comparison of the hematologic values for vitamin E–deficient and –sufficient infants

Value	*E sufficient, 13 infants*	*E deficient, 23 infants*	*p*
Hemoglobin (Gm.%)	9.2 ± 1.3	7.7 ± 1.3	< 0.01
Reticulocytes (%)	3.1 ± 0.7	7.4 ± 2.8	< 0.001

or vitamin B_{12} administration[16] and rarely responds to folic acid therapy.[17] The anemia has been attributed to marrow erythroid production insufficient to keep pace with the rapidly expanding blood volume.[18] Many of the infants manifest marked marrow erythroid activity and peripheral reticulocytosis. The rate of weight gain with its attendant increase in blood volume does not seem sufficient to account for the observed anemia if the erythrocytes which are produced in increased numbers survive normally. Wolff and Goodfellow[16] documented this persistent reticulocytosis in small premature infants during the study of the effects of iron supplementation. Their figures for hemoglobin levels and reticulocyte counts are graphically illustrated in Fig. 1. On Fig. 2 are superimposed the responses of the 11 infants in the present study to vitamin E therapy. Although the initial hemoglobin levels for this group are in the usual range for this age, the response to treatment is greater than that expected to occur spontaneously during this period of life.

The difference in hemoglobin and reticulocyte count between the vitamin E–sufficient and vitamin E–deficient infants further supports the proposal that tocopherol plays a role necessary for these infants of low birth weight. Although the anemia cannot be invariably corrected, the hemolytic component is eliminated or markedly suppressed.

Nature of the anemia. The anemia in these infants was characterized morphologically by the presence of a small number of spherocytes, variable numbers of irregularly contracted, spiculated red cells, red cell fragments, anisocytosis, and polychromasia (Fig. 3). These abnormal forms could first be recognized in increased numbers at approximately 1 month of age and were generally maximal at 6 to 10 weeks of age.

The bizarre red cell morphology and the persistent reticulocytosis in the presence of a falling or just stable hemoglobin level suggested that a hemolytic process was present. This was confirmed by the demonstration of a shortened autologous chromium[51] red cell survival in the two infants so tested.

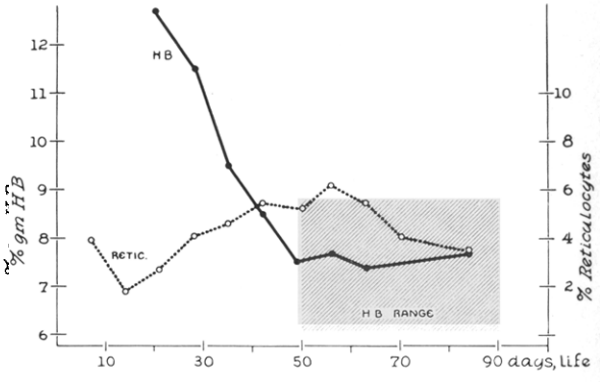

Fig. 1. The mean hemoglobin, hemoglobin range, and mean reticulocyte count for 10 small premature infants (< 1,200 grams) during the first 90 days of life. A persistent reticulocytosis is evident associated with a falling or just stable hemoglobin. (From Wolff, J. A., and Goodfellow, A. M.: Pediatrics 16: 753, 1955.)

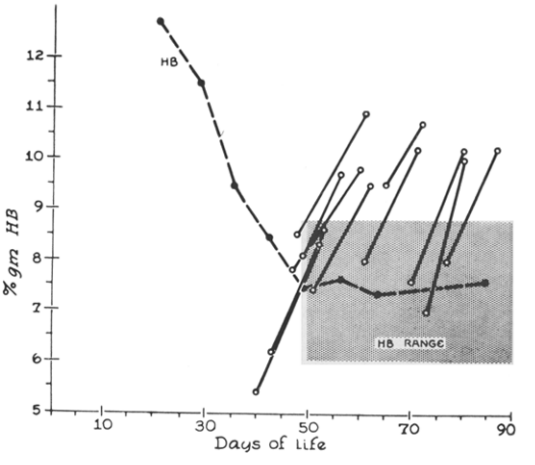

Fig. 2. Increases in hemoglobin levels of the 11 infants treated with vitamin E are superimposed on the normal range for the age.[16] It should be noted that an increase in the level of hemoglobin does not generally occur spontaneously or so rapidly at this age in infants of low birth weight.

Red cell survival half-times of 11 and 15 days were recorded in these infants.

The response to vitamin E therapy also supports the hypothesis that the anemia has a major hemolytic component. Following vitamin E therapy the hemoglobin level rose promptly and the reticulocyte count fell. The clinical course of one treated infant is illustrated in Fig. 4.

The reticulocyte counts did not invariably

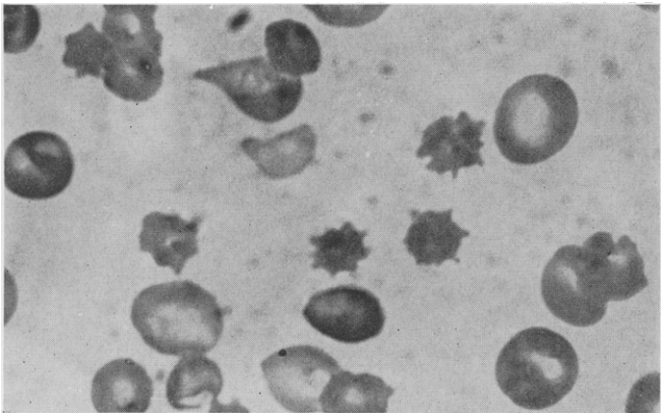

Fig. 3. Peripheral smear from a vitamin E–deficient infant illustrating the large numbers of irregularly contracted erythrocytes. (×1,000.)

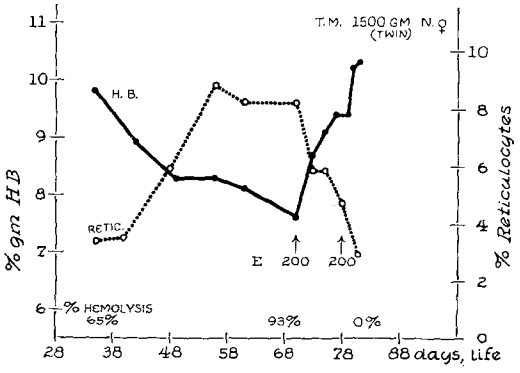

Fig. 4. The clinical course following vitamin E therapy (E 200) in a vitamin E–deficient infant. The prompt rise in the concentration of hemoglobin is associated with a prompt fall in the reticulocyte count.

return to normal following vitamin E therapy, which suggests that other factors also may be contributing to the shortening of red cell life-span in these small infants.

Red cell osmotic fragility, both incubated and unincubated, was normal in five vitamin E–deficient infants.

Bone marrow changes. In three vitamin E–deficient infants in whom bone marrow aspirations were performed, erythroid hyperplasia was observed. No megaloblastic changes were evident. Erythroid precursors frequently were polyploid, and changes in nuclear chromatin patterns could be observed (Fig. 5). These changes consisted of clumping and "homogenization" of the chromatin with deposition of the chromatin at the periphery of the nucleus and the presence of a more pale central area. These changes are similar to those observed in vitamin E–deficient monkeys.[19]

Relation to infantile pyknocytosis. Tuffy, Brown, and Zuelzer[20] described the regular occurrence of distorted and contracted erythrocytes in the blood of newborn infants. Premature infants had more of these forms than did term infants and the numbers of these cells increased during the first few months of life in the premature infant. "Infantile pyknocytosis" was the term applied to an accentuation of this process which was characterized by the presence of a hemolytic anemia. Keimowitz and Desforges[21] have recently presented evidence to suggest that this defect is a result of an abnormality of the cell environment rather than of the red cell itself. They showed a decreased life-span for normal cells transfused into an infant with apparent infantile pyknocytosis.

The cells observed in these infants are indistinguishable from the pyknocytes of Tuffy, Brown, and Zuelzer.[20] Infants with vitamin E deficiency had more of these cells at 6 weeks of age. It is of interest that in patients with acanthocytosis, a hereditary defect in beta lipoprotein synthesis, red cells of similar morphologic appearance are present and such individuals are markedly vitamin E deficient.[22]

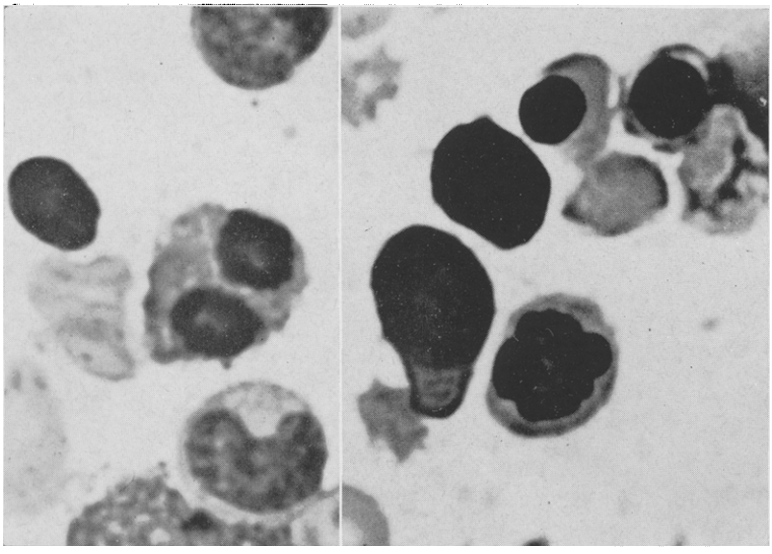

Fig. 5. Normoblasts in the bone marrow of a vitamin E–deficient infant. One nucleus is diploid and another is polyploid. Clumping of chromatin with central area of pallor can be observed. (×1,000.)

Vitamin E and hemolysis. Monkeys with vitamin E deficiency have a shortened red cell survival.[23] Recently Binder and associates[24] have recorded shortening of red cell survival in vitamin E–deficient adults with malabsorption syndromes. In some of these patients Heinz bodies could be demonstrated in the absence of glucose-6-phosphate dehydrogenase deficiency. Heinz bodies were observed in increased numbers in some of the vitamin E–deficient premature infants.

The mechanism of hemolysis. The mechanism of hemolysis in vitamin E deficiency is not known. Tocopherol is recognized as a potent antioxidant.[25] Lipid peroxides accumulate rapidly in the presence of vitamin E deficiency.[26] Newborn infants in general have an increase in the peroxidizable lipids of the red cell membrane[27] which can be reduced by the administration of vitamin E. Lipid peroxides bind free sulfhydryl groups.[28] When red cell membrane sulfhydryl groups are bound, a shortening of red cell life-span is observed.[29] It is possibly through this mechanism of lipid peroxidation that the red cell is damaged in these infants.

Other aspects of vitamin E deficiency. In the laboratory animal vitamin E deficiency can produce encephalomalacia, muscular dystrophy, liver necrosis, exudative enteropathy, axonal swelling and demyelinization, and retinitis in addition to the hematologic changes previously described. Although several infants tested have had muscle biopsies, electroencephalograms, and fundoscopic examinations interpreted as normal, it cannot be stated that a hemolytic anemia is the sole manifestation of their deficiency state.

Further, creatinuria was not demonstrated in these infants. Marked changes in creatine excretion were not observed following the administration of vitamin E. Since creatinuria is regularly seen in severe vitamin E–deficient states, the disease reported here may be a manifestation of mild vitamin E deficiency superimposed on an unusual fatty acid composition of the red cell membrane.

The requirement for vitamin E. The daily supplement of 9 mg. of *d*-alpha tocopherol appeared to be sufficient to prevent the development of a hemolytic anemia in infants of low birth weight. Smaller quantities may prove to be sufficient.[30] An increase in the quantity of unsaturated fatty acids in the diet will increase tocopherol requirements[31] in certain states. Tocopherol requirements of premature infants may also depend on other dietary components; the dietary content of iron, vitamin B_{12}, and folic acid

appears to influence tocopherol requirements.[32, 33]

Goldbloom and Cameron,[9] who studied somewhat larger infants with a mean birth weight of 1,808 grams, could find no influence of tocopherol on the hematologic status of premature infants. Although the vitamin E–deficient infants had lower hemoglobin values, particularly at 1 month of age, the authors state that these differences were not statistically significant. Reticulocyte counts were not performed so one cannot be certain that a compensated hemolytic state was not present.

Certain factors may have prevented the earlier recognition of the vitamin E–responsive state. Some of the proprietary prepared milks, as in this study, contain widely varying amounts of vitamin E. Some milks have sufficient vitamin E to prevent the development of this state.

"Spontaneous" correction of this reticulocytosis and anemia has been recognized to occur in small premature infants at 1 to 3 months of age. This is frequently the time of changing diet, and if such foods as cereals which are known to be rich in vitamin E are added, it might appear that the state is reversing spontaneously.

The recent addition of iron to formulas may have affected the incidence of the vitamin E responsive state. It is known that iron is antagonistic to vitamin E,[32] and thus may lower the vitamin E available to the infant. Likewise, ascorbic acid which is routinely given to premature infants may increase the vitamin E requirement. The older regimen of a low fat diet for premature infants contains little vitamin E; on the other hand, the newer diets for premature infants may have vitamin E but many are simultaneously enriched in unsaturated fatty acids, thus increasing antioxidant requirements.

It would appear that the infant of low birth weight frequently develops a hemolytic anemia. In some instances this can be partially or totally corrected or prevented by the administration of vitamin E. The mechanism of action of vitamin E, its role in other hematologic entities, its total role in human nutrition, and its minimal daily requirement still remain to be determined.

SUMMARY

Hemolytic anemia was found in 11 low-birth-weight infants at 6 to 11 weeks of age. The anemia was characterized by marked reticulocytosis, pyknocytosis, and other abnormal red cell forms, and by shortened red cell survival times. Serum tocopherol was low, and in vitro peroxide hemolysis was increased. Signs of hemolysis decreased after the administration of vitamin E.

Prospectively, 10 infants were given vitamin E supplements starting shortly after birth. Hemolysis in these was prevented or occurred at a lesser rate than it did in control infants studied simultaneously. The mean of the hemoglobin levels of the vitamin E–sufficient group was 9.2 Gm. compared with 7.7 for the deficient group. The reticulocyte counts of the treated infants averaged 3.1 per cent compared with 7.4 per cent in the untreated infants.

Variability in the occurrence of this vitamin E–responsive state is related to a variety of factors which include dietary variations in level of unsaturated fatty acids and in total fat, iron, ascorbate, and vitamin E. One of the commercial milk formulas used in this study had marked variability of vitamin E content.

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