ALTHOUGH the existence of vitamin E has been known for approximately 40 years, and vitamin E deficiency states have been induced experimentally in many species, including fish, birds, and mammals, its importance in human nutrition is not yet clearly understood. Excellent studies of vitamin E deficiency in the Rhesus monkey by Dinning and Day and Finch et al. extended the earlier observations of Mason and Telford and Filer and co-workers and are probably predictive of the deficiency syndrome to be found in man. Manifestations of vitamin E deficiency in human subjects consist of decreased concentrations of tocopherol in serum, oxidative hemolysis of erythrocytes, creatinuria, and pathologic changes in certain tissues. Clinical correlates of these laboratory evidences of deficiency have not been detected in human subjects.

Seven clinically related compounds—alpha-, beta-, gamma-, delta-, epsilon-, zeta- and eta-tocopherol—exert vitamin E activity. Of these, alapha-tocopherol is most potent. Although the only rich sources of tocopherols are some vegetable oils, smaller quantities are present in a wide variety of foods. Tocopherols are important natural antioxidants in foods and are especially effective in preventing oxidation of fats.

Since vitamin E is fat-soluble, it seemed reasonable to seek evidence of human deficiency of vitamin E in individuals with abnormalities in intestinal absorption of fat. In searching for such evidence, Pappenheimer and Victor, Woodruff, Gordon et al., and Goldbloom determined concentrations of tocopherol in plasma or serum of individuals with steatorrhea, studied the extent of its absorption from the gastrointestinal tract, the susceptibility of erythrocytes to hemolysis in weak solutions of oxidizing agents, and rates of urinary excretion of creatine and creatinine. In addition, deposition of ceroid pigment in various muscles has been reported and is believed to be an evidence of deficiency. While these studies suggested that vitamin E deficiency occurs in the human, confirmatory evidence provided by a direct depletion study with human subjects was necessary.

INDUCTION OF VITAMIN E DEFICIENCY IN HUMAN ADULT

Induction of vitamin E deficiency in normal man under controlled conditions was necessary in order to delineate the characteristics of the deficiency state and to estimate the human requirement for the vitamin. In studies begun in 1953, Horwitt and co-workers have been successful in inducing vitamin E deficiency in adult man. Three groups of subjects were studied: (1) adult males fed a basal diet (37% of the calories as fat) which supplied approximately 2 mg of tocopherol daily; (2) adult males fed the basal diet plus a daily supplement of 15 mg of d-alpha-tocopheryl acetate; and (3) adult males fed the regular hospital diet, probably supplying from 10 to 20 mg of tocopherol daily. In early studies, fat in the basal diet consisted of lard from which vitamin E had been removed by molecular distillation, but in later studies stripped corn oil (i.e., corn oil low in vitamin E) was employed to increase the intake of polyunsaturated fatty acids and thus to increase the requirement for the vitamin. After ingestion of the basal diet containing lard for 28 months,
concentration of tocopherol in plasma decreased to approximately 0.5 mg/100 ml (normal concentration,\textsuperscript{15} 1.0 mg/100 ml), and about 80\% of erythrocytes of these subjects demonstrated abnormal tendency to hemolysis in weak oxidizing solutions. After substitution of stripped corn oil for lard, concentrations of tocopherol in plasma decreased further, reaching a mean value of 0.3 mg/100 ml by the forty-fifth month of study, but susceptibility of erythrocytes to hemolysis was not appreciably greater than it had been at the twenty-eighth month.

Average concentrations of vitamin E in plasma of control subjects who received the same diets with the addition of 15 mg of d-alpha-tocopheryl acetate daily remained at approximately 0.9 mg/100 ml even after prolonged daily ingestion of 30 gm of stripped corn oil. Susceptibility of erythrocytes to hemolysis was not increased. After 3 years of such supplemental feeding, the amount of stripped corn oil given to the control subjects was increased to 60 gm daily, and it was found that an intake of 30 mg of d-alpha-tocopheryl acetate was required to maintain concentrations of vitamin E in plasma in the normal range. When daily administration of d-alpha-tocopheryl acetate was discontinued (fifth year of the study), a sudden decrease in concentration of tocopherol in the plasma was evident and was followed by progressive increase in sensitivity of erythrocytes to hemolysis by oxidizing solutions.

It should be recognized that the studies reported by Horwitt were conducted by feeding a source of polyunsaturated fatty acids from which most of the tocopherols or natural antioxidants have been removed. Fresh edible-grade corn oil with its natural content of tocopherols would not be expected to produce comparable experimental results.

**FULL-TERM AND PREMATURE INFANT**

**Body Content of Vitamin E**

Dju et al.\textsuperscript{16} have demonstrated that the accumulation of vitamin E in the developing fetus follows a linear log-log relationship with increase in fetal mass. A similar relationship can also be demonstrated for the accumulation of fetal fat. Calculations based on these data indicate that the total body content of vitamin E of the fetus weighing 1,800 gm is approximately 8 mg, while that of a modern infant weighing 3,400 gm is approximately 20 mg.

**Influence of Diet on Concentration of Tocopherol in Plasma or Serum**

The concentration of tocopherol in plasma of the pregnant woman increases from an average adult value of approximately 1.0 mg/100 ml\textsuperscript{15} to 1.5-2.0 mg/100 ml at term.\textsuperscript{17} Mean concentrations of tocopherol in plasma or serum of full-term and premature infants at birth have generally been reported to be less than 0.5 mg/100 ml.\textsuperscript{18-20} Concentrations increase rather rapidly in plasma or serum of breast-fed infants and of infants receiving formulas containing mixtures of vegetable oils. However, Wright et al.\textsuperscript{18} and Gordon et al.\textsuperscript{8} have demonstrated that the increase in concentration occurs less rapidly when infants are fed an evaporated milk formula, the difference being attributed to the greater content of vitamin E in human milk than in cow milk.

Recently Goldbloom\textsuperscript{21} has investigated the relationship between the type of fat and concentration of vitamin E in the formula and the concentration of tocopherol attained in serum of premature infants. When fat was supplied as a mixture of coconut oil, olive oil, and stripped corn oil, the formula thus being low in content of tocopherols and relatively high in content of polyunsaturated fatty acids, mean concentrations of tocopherol in serum ranged between 0.1 and 0.2 mg/100 ml from the second through the sixth month of life, and at six months of age, from 0.04 to 0.28 mg/100 ml with a mean value of 0.14 mg/100 ml. A second group of premature infants received an identical feeding except that corn oil with natural content of tocopherol
equivalent to 3 mg of vitamin E per quart of formula was included instead of stripped corn oil, while a third group received a formula in which the corn oil was supplemented with d-alpha-tocopheryl acetate equivalent to 5 to 8 mg of vitamin E per quart. Concentrations of tocopherol in serum of infants in the second and third groups averaged 0.7 mg/100 ml at 1 month of age and 1.0 mg/100 ml by 6 months of age. Growth of all infants was normal, and hematologic indices were within normal limits. Since the mean volume of intake was 800 ml/day, these observations suggest that the requirement for tocopherol by premature infants, even those receiving considerable amounts of polyunsaturated fatty acids, is less than 3 mg daily. From the data of Goldbloom it would seem likely that premature infants effectively utilize the small quantity of tocopherol acquired in utero.

**Oxidative Hemolysis of Erythrocytes**

Susceptibility of erythrocytes to oxidative hemolysis is influenced by at least two variables: the quantity of tocopherol attached to the erythrocyte and the nature of the lipids found in the stroma. Each variable is influenced by diet and tissue stores. Gyorgy et al., Gordon and deMetry, and MacKenzie obtained evidence that the erythrocytes of the newborn, particularly the premature infant, are sensitive to hemolysis in dilute solutions of hydrogen peroxide. Appreciable hemolysis is absent in 95% of subjects with plasma concentrations of tocopherol above 0.5 mg/100 ml, but is much more common in subjects with lower plasma concentrations. As noted previously, concentration in plasma of newborn infants is often about 0.25 mg/100 ml. Erythrocytes of normal newborn infants consuming human milk or formulas other than those based on skim milk, rapidly become resistant to hemolysis in such weak oxidizing solutions, although erythrocytes of infants with steatorrhea continue to manifest hemolysis.

**OLDER CHILDREN WITH STEATORRHEA**

Certain children with cystic fibrosis of the pancreas or biliary atresia demonstrate decreased concentrations of tocopherol in plasma, increased susceptibility of erythrocytes to hemolysis, and creatinuria, findings that can generally be reversed by administration of vitamin E. In addition, deposits of ceroid pigment are present in tissues of most children with cystic fibrosis of the pancreas, especially those who are more than 2 years of age, and in tissues of a smaller percentage of children with biliary atresia and portal cirrhosis.

No clinical counterpart to the nutritional muscular dystrophy of vitamin E-deficient experimental animals has been found in man, although it has been possible to demonstrate the biochemical and histopathologic evidences of vitamin E deficiency in children with cystic fibrosis of the pancreas. In a double-blind study by Levin and coworkers, 45 children with cystic fibrosis of the pancreas received either tocopherol or a placebo and increases in muscle strength in children of both groups were detected after two months of observation and after 6 months of observation. No difference in muscle strength was noted between the two groups.

Water-miscible preparations of vitamin E given orally in daily doses of 10 mg/kg have been found to raise the content of creatine in muscle, to lower the concentration in plasma and to decrease creatinuria, but beneficial clinical effects of providing tocopherol have not been demonstrated.

**CONCLUSION**

The current situation with respect to vitamin E is quite comparable to that which prevailed in 1959 when the Food and Drug Administration declared vitamin E essential for man but noted that diets in this country are amply supplied with the vitamin. On the basis of currently available evidence, the Committee concludes that premature and full-term infants receiving human milk or formulas of cow
milk do not require supplementary administration of vitamin E except, possibly, when dietary intake of fat is markedly reduced, as is sometimes practiced in feeding premature infants.

It seems desirable to provide dietary supplements of vitamin E to patients with prolonged steatorrhea from any cause. Relatively large doses may be required to maintain normal plasma concentrations.

**Committee on Nutrition**

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Michael J. Sweeney, M.D.
Samuel J. Fomon, M.D., *Chairman*

**REFERENCES**


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This book has been a source book of speech training for children with cleft palates ever since it was first published in 1945. Since then it has gone through five editions. In those 17 years there have been many modifications in the treatment of cleft palates. The surgery, in general, has improved tremendously, aiming always for physiological closure of the enlarged nasopharynx during speech. Antibiotics and greatly superior anesthesia have cut down the mortality appreciably. Miss Morley has attempted to bring all this data up to date in this fifth edition.

The first half of the book is concerned primarily with the anatomy, embryology, physiology, and the surgical correction of the palatal defects. All of the work is based principally on the English school of thought, although there are many references made to the published works of the International Group of Plastic Surgeons dealing with this problem. The illustrations on the whole are very clear and well explained. There is a section devoted to the secondary repair of the scarred palate, and it is rather refreshing to find no great emphasis on the use of posterior pharyngeal flaps as an adjunct to the routine closure of the palate. The role of the orthodontist has increased with the years, and there is a section included to explain the use of the newer type of obturators.

The second half of the book is concerned with the development in speech in these children and the various forms of instruction for obtaining good speech in those who have not obtained it spontaneously. This portion of the book is far stronger in depth and detail than is the first half and should be part of every speech therapist's library.

To quote the author in her preface to this fifth edition: "A failed surgical result is becoming increasingly something of the past and the speech therapist no longer encounters large numbers of patients with inadequate nasopharyngeal closure. Speech therapy is changing from a hopeless struggle against insuperable odds to achieve speech, which was at least intelligible, to that of post operative observation and assessment of speech which is developing gradually but surely towards the normal. Clinically we now find that the majority of children have normal voice tone and resonance following primary repair of the cleft palate in infancy. Nasopharyngeal closure is adequate and articulation develops spontaneously without speech therapy. By four years of age the great majority of children seen in recent years had attained normal articulation, speech therapy being required only in those few who had failed to do so."

This book may be recommended to all people who have to deal with any kind of speech training since the basic fundamentals are all here with a special emphasis on the cleft palate patient.

Donald W. MacCollum, M.D.
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