History of vitamin E in infant nutrition[1,2]

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ABSTRACT Vitamin E was discovered by Evans and Bishop in 1922. Work in the 1930s revealed the chemical structure and the biological function of α-tocopherol. In the 1940s Filer and others demonstrated that vitamin E protects tissue unsaturated fatty acids against oxidation. The 1940s and the 1950s marked the beginning of interest in the role of vitamin E in infant nutrition. During this period, investigators examined the intestinal absorption of vitamin E in infants and its use for the prevention of hemolysis, retrolental fibroplasia, intracranial hemorrhage, and pulmonary oxygen toxicity. These studies were the forerunners of more recent studies examining possible benefits of vitamin E therapy in premature infants. Recent studies confirmed earlier reports indicating that enteral administration of vitamin E is the safest and most effective route in infants. Although preventing vitamin E deficiency is clearly necessary, neither earlier nor more recent work has shown any benefit from high-dose vitamin E therapy (> 20 $IU \cdot kg^{-1} \cdot d^{-1}$) for premature infants. *Am J Clin Nutr* 1987;46:183–6.

KEY WORDS Vitamin E, tocopherol, history, infant

Discovery, structure, and function of vitamin E

Although Evans and Bishop (1) are rightly credited with the discovery of vitamin E in 1922, other investigators (2, 3) had recognized a few years earlier that semipurified diets containing vitamins A, B, C, and D supported growth but not reproduction in rats (4). Evans and Bishop (1, 5, 6) produced sterility in rats by feeding them a diet composed of casein, cornstarch, lard, butterfat, salt, and yeast. They found that fertility could be restored by the feeding of lettuce or wheat germ oil, but not cod liver oil or the flour or chaff of wheat. They concluded that a factor X present in certain plant oils was an essential dietary ingredient. Sure (7) was the first to suggest the name vitamin E, which was soon adopted by Evans and Bishop and others.

Olcott and Mattill (8) in 1931 were the first to describe the antioxidant function of vitamin E, a property subsequently recognized as its most important biological function. Also in 1931 Pappenheimer and Goetsch reported the occurrence of encephalomalacia in chicks fed diets deficient in vitamin E (9) and nutritional muscular dystrophy in young guinea pigs and rabbits fed similar diets (10).

In 1936 α-tocopherol was first isolated (11), and the name *tocopherol* was suggested to Evans by George M Calhoun, Professor of Greek at the University of California (5, 12), where Evans and his colleagues also worked. The word was constructed from the Greek words *tokos,* meaning offspring, and *phero,* meaning to bear. In 1938 Fernholz (13) described the chemical structure of α-tocopherol and Karrer et al (14) were the first to synthesize α-tocopherol.

Filer and Mason (15, 16) were among the first to demonstrate the important role of vitamin E in protecting unsaturated fatty acids from oxidation in vivo. These investigators (17, 18) also studied the manifestations of vitamin E deficiency in rhesus monkeys. These were the first such studies in any primate species, including man.

Early studies of vitamin E in infant nutrition

The first therapeutic trial of vitamin E administration to infants was conducted by Widenbauer (19) in 1938. He administered wheat germ oil to 17 premature infants with growth failure; 11 of the infants resumed weight gain after treatment. Widenbauer proposed that vitamin E may have promoted growth in these infants and called for further investigation.

In the late 1940s and 1950s a number of studies of vitamin E treatment of infants were published that were forerunners of more recent work. György and Rose (20) demonstrated that vitamin E-deficient rats developed

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hemolysis and that this hemolysis could be corrected by giving the rats tocopherol. A few years later, György et al (21) showed that the erythrocytes of term newborn infants were susceptible to hemolysis in the presence of hydrogen peroxide and that vitamin E supplements prevented this hemolysis. Gordon and de Metry (22) demonstrated that the same was true for premature infants. This susceptibility to hemolysis was the basis for the hemolytic anemia that was described in the 1960s (23–25) in premature infants who were fed formulas that contained little vitamin E but abundant polyunsaturated fatty acids and iron (26, 27). Improvements in the composition of infant formulas have eliminated the hemolytic anemia of vitamin E deficiency except in rare cases of prolonged total parenteral nutrition with lipid emulsion or in cases of fat malabsorption resulting from cholestatic liver disease or cystic fibrosis of the pancreas.

Gerlóczy (28) administered *dl*-α-tocopheryl acetate to premature infants for the prevention and cure of edema (scleroedema). He noted that tocopheryl acetate was effective in oral doses of 5 mg, whereas intramuscular doses of 30 mg were not effective in preventing or mobilizing the edema. This unusual property of tocopheryl acetate was subsequently confirmed by others (29, 30). Tocopheryl acetate remains relatively inactive until deesterified by hydrolytic enzymes that are present mainly in the gut; this form of vitamin E may thus be ineffective if given parenterally. Filer et al (31) showed that vitamin E is well absorbed from the gastrointestinal tract, even in small premature infants. Although some data (32) do not support this observation, more recent studies (33, 34) confirmed that most small premature infants rapidly achieve adequate blood levels of vitamin E with enteral dosing.

In 1949 Owens and Owens (35) published their results of a trial of vitamin E supplementation to premature infants for the prevention of retrolental fibroplasia (RLF). Alternate infants weighing < 1.36 kg (3 lb) were given 150 mg of *dl*-α-tocopheryl acetate daily. None of the 11 infants receiving vitamin E developed RLF, but 5 of 15 control infants did. The mean serum tocopherol levels in the treated and control groups were 4.12 mg/dL and 0.25 mg/dL, respectively. Soon thereafter oxygen was identified as the major cause of RLF, and these observations of Owens and Owens were set aside for 25 years. When RLF persisted despite more careful use of oxygen therapy for premature infants, Johnson et al (36) initiated further studies of vitamin E for the prevention of RLF. Investigation and discussion of the relation between vitamin E therapy and RLF continues to the present (37–40).

The same year that Owens and Owens published their landmark study of vitamin E for prevention of RLF, Minkowski (41) reported the first trial of vitamin E for the prevention of intracranial hemorrhage (ICH) in premature infants. He found that α-tocopherol (300–600 mg) given to mothers in premature labor reduced the incidence of ICH in their infants from 13% (6 of 45) to 2% (1 of 45). This result is somewhat surprising, as tocopherol is poorly transported across the placenta; blood plasma levels of vitamin E are lower in newborn infants than in their mothers (42, 43). Tissue concentrations and whole body stores of tocopherol are also low in newborn infants (44). Interest in a possible role for vitamin E in the prevention of ICH has been renewed in recent years. Several trials of tocopherol given directly to premature infants showed a decrease in the incidence (45) or severity (46) of ICH with vitamin E, but other investigations found an increase in intraventricular (40) and retinal hemorrhage (47) among infants given tocopherol intravenously. This latter observation may be explained by the known effects of vitamin E on coagulation. Tocopherol decreases platelet aggregation (48) and interferes with the vitamin K-dependent coagulation factors (49).

In 1958 Taylor (50) reported that vitamin E-deficient rats were more susceptible to pulmonary oxygen toxicity than rats receiving a regular dietary source of tocopherol. This and subsequent animal experiments prompted trials of vitamin E supplements for the prevention of bronchopulmonary dysplasia (BPD), a disease of chronic lung injury in premature infants who required oxygen therapy or positive-pressure ventilation. The first study (51) of vitamin E for the prevention of BPD in infants showed a benefit; the control infants were probably vitamin E deficient because of the low vitamin E intakes and high intakes of polyunsaturated fatty acids that were common then (52). Subsequent studies (52, 53), conducted with better vitamin E nutritional practices, showed no additional protection against BPD by larger, supplemental doses of vitamin E.

Conclusion

Recent interest in vitamin E therapy to prevent various complications of prematurity originated with landmark experiments conducted in the 1940s and 1950s. This is true for hemolytic anemia (1948) (20), retrolental fibroplasia (1949) (35), intracranial hemorrhage (1949) (41), and bronchopulmonary dysplasia (1958) (50). In addition, the neurologic syndrome reported (54–56) in children with vitamin E deficiency resulting from chronic malabsorption due to hepatic cholestasis or other causes bears considerable resemblance to the brain degeneration and myopathy described many years earlier in animals (5, 9, 10).

Finally, appreciation of two early discoveries—that vitamin E is well absorbed from the gastrointestinal tract in premature infants (31) and that tocopheryl acetate has relatively little biological activity when given parenterally (28)—would have indicated that intravenous administration of high doses of tocopheryl acetate to premature infants was not advisable, particularly in the absence of adequate pharmacokinetic and toxicologic studies. Animal studies had shown that parenteral vitamin E can be toxic to the liver (57). One example of the possible consequences of forgetting these lessons from the past is well documented (58–60) in the case of the E-Ferol tragedy. E-Ferol was a preparation of α-tocopheryl acetate that was marketed for intravenous administration to premature infants. A syndrome of ascites, liver failure, and kidney failure led to the deaths of 38 infants and the serious illness of many others (60).

Vitamin E deficiency is quite unlikely to occur in enterally nourished infants except those with cholestatic liver disease or chronic malabsorption from other causes (27). Infants receiving total parenteral nutrition that includes lipid emulsion may also be at increased risk for vitamin E deficiency. Except for preventing or correcting these rare cases of vitamin E deficiency, there is no clearly established indication for high-dose vitamin E therapy (> 20 $IU \cdot kg^{-1} \cdot d^{-1}$) for premature infants. While some studies suggest a protective effect of vitamin E against retrolental fibroplasia or intracranial hemorrhage, further examination of the efficacy and safety of vitamin E treatment for these indications is required before any routine supplementation practice is instituted.

References

1. Evans HM, Bishop KS. On the existence of a hitherto unrecognized dietary factor essential for reproduction. Science 1922;56:650–1.
2. Osborne TB, Mendel LB. The nutritive value of yeast protein. J Biol Chem 1919;38:223–7.
3. Mattill HA, Conklin RE. The nutritive properties of milk, with special reference to reproduction in the albino rat. J Biol Chem 1920;44: 137–58.
4. Mason KE. The first two decades of vitamin E. Fed Proc 1977;36: 1906–10.
5. Evans HM. The pioneer history of vitamin E. Vitam Horm 1962;20: 379–87.
6. Evans HM, Bishop KS. The production of sterility with nutritional regimes adequate for growth and its cure with other foodstuffs. J Metab Res 1923;3:233–316.
7. Sure B. Dietary requirements for reproduction. II The existence of a specific vitamin for reproduction. J Biol Chem 1924;58:693–709.
8. Olcott HS, Mattill HA. The unsaponifiable lipids of lettuce. II Fractionation. J Biol Chem 1931;93:59–64.
9. Pappenheimer AM, Goetsch M. A cerebellar disorder in chicks, apparently of nutritional origin. J Exp Med 1931;53:11–26.
10. Goetsch M, Pappenheimer AM. Nutritional muscular dystrophy in the guinea pig and rabbit. J Exp Med 1931;54:145–65.
11. Evans HM, Emerson OM, Emerson GA. The isolation from wheat germ oil of an alcohol, α-tocopherol, having the properties of vitamin E. J Biol Chem 1936;113:319–32.
12. Parkes AS, Simpson M, Lyons WR. Dr. Herbert M. Evans. An interview. J Reprod Fertil 1969;19:3–19.
13. Fernholz E. On the constitution of α-tocopherol. J Am Chem Soc 1938;60:700–5.
14. Karrer P, Fritzsche H, Ringier BH, Salomon H. α-Tocopherol. Helv Chim Acta 1938;21:520–5.
15. Filer LJ Jr, Rumery RE, Mason KE. Specific unsaturated fatty acids in the production of acid-fast pigment in the vitamin E-deficient rat and the protective action of tocopherols. In: Transactions of the First Conference on Biological Antioxidants. New York: Josiah Macy, Jr Foundation, 1946:67–76.
16. Mason KE, Filer LJ Jr. Interrelationships of dietary fat and tocopherols. J Am Oil Chem Soc 1947;24:240–2.
17. Mason KE, Telford IR. Some manifestations of vitamin E deficiency in the monkey. Arch Pathol 1947;43:363–73.
18. Filer LJ Jr, Rumery RE, Yu PNG, Mason KE. Studies on vitamin E deficiency in the monkey. Ann NY Acad Sci 1949;52:284–91.
19. Widenbauer F. Versuche mit Weizenkeimöl (Vitamin E) bei der Aufzucht von Frühgeburten. Z Kinderheilkd 1938;60:216–21.
20. György P, Rose CS. Effect of dietary factors on early mortality and hemoglobinuria in rats following administration of alloxan. Science 1948;108:716–8.
21. György P, Cogan G, Rose CS. Availability of vitamin E in the newborn infant. Proc Soc Exp Biol Med 1952;81:536–8.
22. Gordon HH, de Metry JP. Hemolysis in hydrogen peroxide of erythrocytes of premature infants. Effects of alpha-tocopherol. Proc Soc Exp Biol Med 1952;79:446–50.
23. Hassan H, Hashim SA, Van Itallie TB, Sebrell WH. Syndrome in premature infants associated with low plasma vitamin E levels and high polyunsaturated fatty acid diet. Am J Clin Nutr 1966;19:147–57.
24. Oski FA, Barness LA. Vitamin E deficiency: a previously unrecognized cause of hemolytic anemia in the premature infant. J Pediatr 1967;70:211–20.
25. Ritchie JH, Fish MB, McMasters V, Grossman M. Edema and hemolytic anemia in premature infants: a vitamin E deficiency syndrome. N Engl J Med 1968;279:1185–90.
26. Williams ML, Shott RJ, O'Neal PL, Oski FA. Role of dietary iron and fat on vitamin E deficiency anemia of infancy. N Engl J Med 1975;292:887–90.
27. Bell EF, Filer LJ Jr. The role of vitamin E in the nutrition of premature infants. Am J Clin Nutr 1981;34:414–22.
28. Gerlóczy F. Clinical and pathological role of d,l-α tocopherol in premature infants (studies on the treatment of scleroedema). Ann Paediatr (Basel) 1949;173:171–86.
29. Newmark HL, Pool W, Bauernfeind JC, DeRitter E. Biopharmaceutic factors in parenteral administration of vitamin E. J Pharm Sci 1975;64:655–7.
30. Knight ME, Roberts RJ. Tissue vitamin E levels in newborn rabbits after pharmacologic dosing. Influence of dose, dosage form, and route of administration. Dev Pharmacol Ther 1985;8:96–106.
31. Filer LJ Jr, Wright SW, Manning MP, Mason KE. Absorption of α-tocopherol and tocopheryl esters by premature and full term infants and children in health and disease. Pediatrics 1951;8:328–39.
32. Melhorn DK, Gross S. Vitamin E-dependent anemia in the premature infant. II Relationships between gestational age and absorption of vitamin E. J Pediatr 1971;79:581–8.
33. Bell EF, Brown EJ, Milner R, Sinclair JC, Zipursky A. Vitamin E absorption in small premature infants. Pediatrics 1979;63:830–2.
34. Jansson L, Lindroth M, Työppönen J. Intestinal absorption of vitamin E in low birth weight infants. Acta Paediatr Scand 1984;73: 329–32.
35. Owens WC, Owens EU. Retrolental fibroplasia in premature infants. II Studies on the prophylaxis of the disease: the use of alpha tocopheryl acetate. Am J Ophthalmol 1949;32:1631–7.
36. Johnson L, Schaffer D, Boggs TR Jr. The premature infant, vitamin E deficiency and retrolental fibroplasia. Am J Clin Nutr 1974;27: 1158–73.
37. Hittner HM, Godio LB, Rudolph AJ, et al. Retrolental fibroplasia: efficacy of vitamin E in a double-blind clinical study of preterm infants. N Engl J Med 1981;305:1365–71.
38. Puklin JE, Simon RM, Ehrenkranz RA. Influence on retrolental fibroplasia of intramuscular vitamin E administration during respiratory distress syndrome. Ophthalmology 1982;89:96–103.
39. Finer NN, Schindler RF, Grant G, Hill GB, Peters KL. Effect of intramuscular vitamin E on frequency and severity of retrolental fibroplasia. A controlled trial. Lancet 1982;1:1087–91.
40. Phelps DL, Rosenbaum AL, Isenberg SJ, Leake RD, Dorey FJ. Tocopherol efficacy and safety for preventing retinopathy of prematurity: a randomized, controlled, double-masked trial. Pediatrics 1987;79:489–500.
41. Minkowski A. Essai de prévention des hémorragies cerebro-meningees des prématurés par l'administration a la mère, pendant le travail, de substances "anti-fragilité vasculaire." Arch Fr Pediatr 1949;6:276–80.
42. Wright SW, Filer LJ Jr, Mason KE. Vitamin E blood levels in premature and full term infants. Pediatrics 1951;7:386–93.
43. Leonard PJ, Doyle E, Harrington W. Levels of vitamin E in the

plasma of newborn infants and of the mothers. Am J Clin Nutr 1972;25:480–4.
44. Dju MY, Mason KE, Filer LJ Jr. Vitamin E (tocopherol) in human fetuses and placentae. Etud Néo-natales 1952;1:49–62.
45. Speer ME, Blifeld C, Rudolph AJ, Chadda P, Holbein MEB, Hittner HM. Intraventricular hemorrhage and vitamin E in the very low-birth-weight infant: evidence for efficacy of early intramuscular vitamin E administration. Pediatrics 1984;74:1107–12.
46. Chiswick ML, Johnson M, Woodhall C, et al. Protective effect of vitamin E (DL-alpha-tocopherol) against intraventricular haemorrhage in premature babies. Br Med J 1983;287:81–4.
47. Rosenbaum AL, Phelps DL, Isenberg SJ, Leake RD, Dorey F. Retinal hemorrhage in retinopathy of prematurity associated with tocopherol treatment. Ophthalmology 1985;92:1012–4.
48. Stuart MJ, Oski FA. Vitamin E and platelet function. Am J Pediatr Hematol Oncol 1979;1:77–82.
49. Corrigan JJ Jr. Coagulation problems relating to vitamin E. Am J Pediatr Hematol Oncol 1979;1:169–73.
50. Taylor DW. Effects of tocopherols, methylene blue and glutathione on the manifestations of oxygen poisoning in vitamin E-deficient rats. J Physiol (Lond) 1958;140:37–47.
51. Ehrenkranz RA, Bonta BW, Ablow RC, Warshaw JB. Amelioration of bronchopulmonary dysplasia after vitamin E administration. A preliminary report. N Engl J Med 1978;299:564–9.
52. Ehrenkranz RA, Ablow RC, Warshaw JB. Effect of vitamin E on the development of oxygen-induced lung injury in neonates. Ann NY Acad Sci 1982;393:452–65.
53. Saldanha RL, Cepeda EE, Poland RL. The effect of vitamin E prophylaxis on the incidence and severity of bronchopulmonary dysplasia. J Pediatr 1982;101:89–93.
54. Tomasi LG. Reversibility of human myopathy caused by vitamin E deficiency. Neurology (NY) 1979;29:1182–6.
55. Rosenblum JL, Keating JP, Prensky AL, Nelson JS. A progressive neurologic syndrome in children with chronic liver disease. N Engl J Med 1981;304:503–8.
56. Elias E, Muller DPR, Scott J. Association of spinocerebellar disorders with cystic fibrosis or chronic childhood cholestasis and very low serum vitamin E. Lancet 1981;2:1319–21.
57. Phelps DL. Local and systemic reactions to the parenteral administration of vitamin E. Dev Pharmacol Ther 1981;2:156–71.
58. Lorch V, Murphy D, Hoersten LR, Harris E, Fitzgerald J, Sinha SN. Unusual syndrome among premature infants: association with a new intravenous vitamin E product. Pediatrics 1985;75:598–602.
59. Bove KE, Kosmetatos N, Wedig KE, et al. Vasculopathic hepatotoxicity associated with E-Ferol syndrome in low-birth-weight infants. JAMA 1985;254:2422–30.
60. Balistreri WF, Farrell MK, Bove KE. Lessons from the E-Ferol tragedy. Pediatrics 1986;78:503–6.