Critique of the requirement for vitamin E[1–3]

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ABSTRACT The Food and Nutrition Board of the Institute of Medicine recently published a comprehensive evaluation of antioxidants in human diets that includes dietary reference intakes for vitamin E. The new dietary reference intake is 15 mg (35 μmol)/d for adults, which is 50% greater than the generous allowance in the 10th edition of *Recommended Dietary Allowances* published in 1989. Much of the data interpreted in these publications came from studies sponsored by the Committee of Nutritional Studies at Elgin State Hospital (Elgin, IL) of an earlier Food and Nutrition Board. The 50% increase in the recommended dietary allowances for vitamin E is not supported by any new data. It is possible that the publication of the Institute of Medicine did not take into consideration the effects of the oxidized lipids in the diets used to promote the development of vitamin E deficiency. If lipids, oxidized to remove tocopherols, had not been a part of the experimental diets, the minimum requirement for vitamin E would have been too small for possible evaluation. Studies on the different effects of saturated and oxidized lipids in the production of encephalomalacia in chicks and muscular dystrophy in rats are reviewed. The tolerable upper intake level of vitamin E supplementation is reported to be 1000 mg/d. It is possible that the universal consumption of aspirin may not have been taken into consideration when this level was determined. Vitamin E plus aspirin may increase the tendency to hemorrhage, which makes a lower upper intake level worth consideration. *Am J Clin Nutr* 2001;73:1003-5.

KEY WORDS Vitamin E requirement, Food and Nutrition Board, Elgin Project, oxidized lipids, Institute of Medicine, antioxidants, platelet adhesion, aspirin

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INTRODUCTION

In a comprehensive report that deserves sincere commendations (1), the Food and Nutrition Board (FNB) has, for the second time, recommended a vitamin E requirement for adults that is more than can be practically obtained in most American diets. This recommendation was largely based on the studies in the Elgin Project reported in 1960 (2). The recommendation was not easily decided on and it should be subject to additional scientific debate. For example, I recall requesting in my citation for an Osborne and Mendel Award in 1961 that no specific requirement for vitamin E be adopted on the basis of these studies, despite my involvement in them.

The new dietary reference intake for vitamin E of 15 mg (35 μmol) α-tocopherol/d for both men and women (1) is, by recent interpretation (3, 4), not much different from the 1968 recommended dietary allowance (RDA; 5) of 30 IU (30 mg), which was halved by the next RDA Committee, who based their recommendation on the same published data (6).

Having been a member of 3 other RDA committees, I am aware of the extensive debate that occurs at each meeting. It is my judgment that more attention should have been paid to the amount of vitamin E consumed by millions of healthy individuals. When supplements that provide more than the RDA are desirable, the amount greater than the RDA is a pharmacologic dose, not a nutritional requirement. Based on a representative report (7), the mean consumption of vitamin E by American men and women is 21.4 ± 7.2 and 16.5 ± 7.0 μmol/d, respectively. Accordingly, the average unsupplemented consumption of vitamin E for many individuals is about one-half that of the 1989 RDA (8) without any known apparent harm to the subjects evaluated. Data on consumption of vitamin E can be complicated by the relation of plasma tocopherol with plasma lipid concentrations (9), a relation that should be evaluated in studies of vitamin E.

Many of the data presented here are from experiments conducted at the LB Mendel Research Laboratory during the tenure of the last committee of the FNB that cooperated with the Elgin State Hospital. As shown by the examples in the following sections, nature has provided living organisms with many antioxidants to counter the action of some of the free radicals that normally occur. Thus, when lipids can be absorbed, the tissues have to be overwhelmed with the products of oxidized lipids to study vitamin E deficiency.

ANIMAL STUDIES

Our own evaluations of the relation of saturated and oxidized unsaturated fats to vitamin E metabolism began with studies of chick encephalomalacia (10). The data showed that corn oil or lard from which tocopherol had been removed promoted chick encephalomalacia, whereas coconut oil and butter did not. This finding confirmed earlier reports by Briggs et al

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(11), who showed that chick encephalomalacia did not occur in chicks fed a fat-free diet and that chicks could be raised to full egg-laying capacity in the absence of dietary vitamin E. Other studies showed a relation between the degree of unsaturated lipid with the need for vitamin E (12): the higher the concentration of unsaturated lipid, the more tocopherol that was required. Additionally, substituting coconut oil for corn oil decreased the incidence of chick encephalomalacia.

Then a serendipitous observation was made by Bailey, a distinguished neurosurgeon who was a member of one of the FNB Elgin Project committees and had excellent histologic facilities nearby in Chicago. Bailey conducted histologic studies on the brains of the chicks we were studying at the time (13). At the same time, he studied the brain of an infant who had been fed intravenously for 19 d with a sterilized commercial emulsion that contained no tocopherol. He concluded that the cerebral hemorrhage and absence of Purkinje cells noted in the infant's brain and in the chick's brain were identical. The sterilized commercial emulsion contained 15% coconut oil. Although 15% coconut oil fed to chicks produced no encephalomalacia in 13 chicks, 12% coconut oil plus 3% safflower oil produced encephalomalacia in all 11 of the chicks studied (12). With the development of gas chromatography, we learned that the brain contains little linoleic acid (12) but contains high amounts of fatty acids with 4, 5, and 6 double bonds (13). This means that the brain mitochondria are more susceptible to oxidation in the absence of vitamin E (14, 15).

Evaluation of the appearance of muscular dystrophy in rats (16) made it apparent that unless the diet contains liberal amounts of peroxidized lipids, creatinuria does not develop. Although vitamin E–deficient diets containing 15% coconut oil or 0.2% corn oil produce no significant increase in creatinuria, consumption of 15% stripped corn oil or 7% stripped linseed oil results in creatinuria and decreased growth. The amount of vitamin E added to the diet to achieve normal growth and prevent increases in creatinuria is related to the amount of peroxidized lipids in the diet and in the tissues (16–18). Thus, for the study of vitamin E deficiency in animals, it is necessary to add oxidized lipids to their diets.

STUDIES IN INFANTS

In 1967–1968, I engaged in a study of nutritionally deficient infants at the Anemia and Malnutrition Center of the Chiang Mai Medical School and St Louis University. Many of the infants were severely deficient in protein and some were also deficient in vitamins. Five of these infants, a small percentage of the total, often had marked variations in serum lipoproteins, the reason for which was unknown. Daily changes in serum lipoprotein concentrations correlated with changes in serum tocopherols (19). In other words, infants who we thought were quite deficient in vitamin E had vitamin E in their tissues that could be transferred to their blood serum and thus may not have been deficient after all. This phenomenon was studied in rats whose blood lipids increased greatly after being fed an atherogenic diet that included 0.3% propylthiouracil and 3% cholesterol. A 10-fold increase in the serum lipids of these animals was accompanied by an approximate 10-fold increase in serum tocopherol and 3-fold increase in vitamin A. Serum cholesterol and phospholipid concentrations were similarly affected (19). Thus, serum vitamin E concentrations need to be evaluated in light of previous vitamin E consumption, which affects the amount of tocopherols stored in the tissues.

STUDIES IN MEN

The recent FNB report (1) paid considerable attention to results of the fourth Elgin Project, which was sponsored by the FNB Committee of Nutritional Studies at Elgin State Hospital. By this time, the nearby LB Mendel Research Laboratory (Elgin, IL) had its own building with a kitchen, a metabolic ward, and research facilities that were particularly suited for the intended research.

Briefly, one group of 19 subjects was fed a basal diet containing 3–4 mg tocopherol/d, another group of 9 subjects received the same diet plus a supplement of 15 mg *RRR*-α-tocopheryl acetate/d, and a third group of 10 subjects was fed the regular hospital diet. (The plan was similar to 3 previous long-term studies of thiamine, riboflavin, and niacin plus tryptophan.)

The critical component of the basal diet was 30 g stripped lard/d. After 2.5 y the lard was replaced by 30 g stripped corn oil to increase the unsaturation of the lipids in the basal diet. Nine months later, the amount of corn oil was increased to 60 g/d. The effects of oxidized lipids on serum tocopherol concentrations and on the results of the peroxide hemolysis test were similar to those observed in the animals. In subjects who consumed the depleted basal diet for 54 mo, who presumably had high concentrations of polyunsaturated lipids in their tissues, low serum concentrations returned to reference concentrations after consumption of either 7.5 or 15 mg *RRR*-α-tocopherol/d. Greater than reference serum tocopherol concentrations were observed at all times in subjects in the control group, who had consumed supplements providing 15 mg *RRR*-α-tocopherol/d. In addition, the diet of the control subjects provided 3–4 mg *RRR*-α-tocopherol/d. The results of the peroxide hemolysis test were normal until 60 mo, when the 15-mg supplement was discontinued. In evaluations of the data from these long-term studies it should be emphasized that the experimental diets contained large amounts of oxidized unsaturated fats not found in habitual diets.

The subjects who were fed the uncontrolled hospital diet, who ate in a separate dining room, always had reference serum tocopherol concentrations and normal results of hemolysis tests. Their diet, which was low in fruit and vegetables, provided <8 mg vitamin E/d. The average plasma tocopherol concentrations were similar to those found in population surveys, ≈18.5 mmol/L, and varied greatly from month to month for 7 y. Many of the plasma tocopherol concentrations were <2 mmol/L (0.8 mg/dL). No pathologic changes were ever noted in this group, who received the same clinical supervision as did the other groups.

A larger difference in the potency of *RRR*-α-tocopherol than of *all-rac*-α-tocopherol was first recorded after 2 subjects in the supplemented group received 105 mg *RRR*-α-tocopheryl acetate and 140 mg *all-rac*-α-tocopheryl acetate, respectively, for 7 mo (Table 1 of reference 2). The natural vitamin E seemed to be more potent than expected. After 54 mo, 6 of the depleted subjects were supplemented with what was then considered equal potencies of the natural compared with the synthetic vitamin E preparation (Table 3 of reference 2). [There is an error in patient identification in this table that was corrected in a later publication (20)]. These data also showed that *RRR*-α-tocopherol had at least twice the physiologic potency of *all-rac*-α-tocopherol in men. Years later, studies of the different relative potencies of synthetic and natural forms of vitamin E were confirmed (3, 4, 21). It is hoped that these relations will be recognized officially to avoid further confusion by consumers.

On the basis of the information described above, the 1989 RDA committee concluded that the requirement for men should

be 10 mg tocopherol equivalents vitamin E/d, although it was known that millions of persons have lived long lives while consuming much less. An increasing in this requirement to 15 mg/d benefits only the commercial interests involved in the sale of vitamin E. To help consumers, the distinction between nutritional requirements and the possible pharmacologic benefits of an antioxidant should be emphasized. Because of common knowledge that I have been involved in the field of vitamin E research for >65 y, "I am frequently asked by both professionals and laymen how much I take." The answer is 200 mg *RRR*-α-tocopherol/d, but often with the proviso that I am not completely certain of the benefit of such a pharmacologic dose of an antioxidant.

TOXICITY

Although a slight increase in hemorrhagic stroke as a result of vitamin E consumption was discussed in the current FNB report (1), the possible influence of aspirin, which millions of persons swallow each day, may not have been considered. It was previously shown that the antiadhesive effects of α-tocopherol on platelets combined with the antiaggregatory effects of aspirin reduce platelet adhesion by a highly significant 40% (22, 23). This effect on platelets, which is dependent on many variables, could be considered either beneficial or undesirable in the prevention of stroke. However, inhibition of platelet function could lead to an increased tendency to bleed (24). Accordingly, it is my judgment that a tolerable upper intake level of 1000 mg *RRR*-α-tocopherol/d for adults is too high. The daily intake of less than one-half that amount produces high concentrations of vitamin E in the tissues.

Many people who supplement their diet believe that if a little is good, more is better. An official statement that 1000 mg *RRR*-α-tocopherol/d is safe may encourage some consumers to take the maximum amount of vitamin E recommended regardless of their consumption of other antithrombotic compounds. The precautionary principle should be applied in this situation.

SUMMARY

I suggest that no change be made to the 1989 RDA for vitamin E—10 mg *RRR*-α-tocopherol/d for men (8). It is reasonable that the requirement for women be the same. To produce diets that provide 15 mg vitamin E/d (1), large amounts of foods that contain large amounts of unsaturated lipids are required. Paradoxically, the more unsaturated lipids in a food, the higher the requirement for vitamin E, especially if the lipid is oxidized.

Choosing an upper limit for a vitamin E supplement is tough. A recommendation of <1000 mg *RRR*-α-tocopherol/d is suggested to account for the additive effect of aspirin on platelet adhesion and aggregation in inducing bleeding. Persons with high blood pressure are more susceptible to hemorrhagic stroke and they are among those who consume aspirin.

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