Vitamin E: too much or not enough?1,2

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The latest recommended vitamin E requirements, the dietary reference intakes, were published in 2000 by the Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences (1). These new requirements were based largely on the studies by Horwitt in the 1950s and 1960s at the Elgin State Hospital (2–5). Horwitt was a pioneer in the field of clinical nutrition, a gentleman, and an exceptional scientist. It is with great sadness that I note his passing and with chagrin that I write this editorial, which is critical of his claim that the new recommendation is too high (6).

The new dietary reference intake for vitamin E (1) also includes advances in the field of vitamin E research. These advances include the observation that vitamin E deficiency occurs in humans and that it can be caused by fat malabsorption or by defects in the gene for the α-tocopherol transfer protein (α-TTP). In the early stages of deficiency, rather subtle symptoms are observed, which can be reversed by α-tocopherol supplementation. The prevalence of α-TTP deficiency is unknown, as is the extent to which vitamin E deficiency is the cause of peripheral neuropathy of “no known etiology.” However, it is generally accepted that the prevalence of vitamin E deficiency in humans is rare.

Neurologic symptoms, therefore, were not the basis for establishing the new vitamin E requirements. Instead, erythrocyte hemolysis in response to in vitro additions of peroxide was used as a marker of adequacy because this is the test that was used in the Elgin Project studies. Horwitt suggested that the diets consumed by his subjects were high in polyunsaturated fatty acids and were stripped of tocopherols; therefore, the requirements of his subjects were higher than those of free-living humans. It was agreed that the intake of unsaturated fat and other antioxidants and the subjects’ oxidative stress modulate the vitamin E requirement. However, the extent of the change in requirements was unknown; therefore, it was impossible to make numerical adjustments to the dietary reference intake.

Horwitt questions the dietary reference intake of 15 mg α-tocopherol because the usual North American diet might not contain this amount. Indeed, Horwitt is correct: a diet rich in fruit and vegetables and low in fat probably contains <15 mg α-tocopherol, unless particular nuts, oils, and whole grains are consumed. Yet, requirements for other nutrients are based on physiologic needs, not on dietary contents. For example, when humans became deficient because their diets were inadequate in thiamine, riboflavin, or niacin, flour was fortified to resupply these nutrients lost in milling. Vitamins A and D are routinely added to milk to ensure that blindness and rickets are prevented. Dietary α-tocopherol contents have probably decreased over time because of attempts to improve the dietary fat composition by increasing the vegetable oil content of manufactured foods. These corn and soybean oils are rich in γ-tocopherol, which increases γ-tocopherol intakes—a fact taken into account in the 1989 recommended dietary allowance (RDA) for vitamin E (7).

The 1989 RDA was expressed in α-tocopherol equivalents, for which γ-tocopherol was estimated to be equivalent to 10% of the activity of α-tocopherol (7). In contrast, the 2000 dietary reference intake indicates that the vitamin E requirement can be met by α-tocopherol only and further specifies that the structure recognized by α-TTP limits the activity of synthetic all-rac-α-tocopherol, which contains 8 stereoisomers, to half its component stereoisomers, the 2R and not the 25 structural forms. Thus, the 2000 dietary reference intake for vitamin E is not based on antioxidant activities of the various dietary tocopherols and tocotrienols, but rather on the observation that α-TTP only maintains plasma α-tocopherol concentrations; therefore, α-tocopherol must be required for some specific as yet undefined function.

The key to establishing human vitamin E requirements is identifying the function of the vitamin. The functional role of α-tocopherol as an antioxidant is difficult to justify because a variety of dietary phenolic antioxidants exist that are more potent than α-tocopherol. However, in contrast with these phenolic antioxidants, only α-tocopherol has a protein, α-TTP, that regulates plasma α-tocopherol concentrations. It may be that α-tocopherol itself, or the antioxidant activity provided by α-tocopherol in a specific cellular location, is required for a unique function. One possibility is that α-tocopherol modulates protein kinase C–dependent pathways, which in turn regulate the expression of a variety of signal transduction pathways. Thus, α-tocopherol’s role in human nutrition may be in modulating the phosphorylation and dephosphorylation of key pathways for the regulation of cell proliferation and inflammatory responses.

The difficulty in assessing the adequacy of vitamin E status is that it takes decades for an adult to exhibit the neurologic symptoms associated with vitamin E depletion. However, mark-

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ers of oxidative stress may be pertinent. Oxidative stress is generally accepted to mean that the generation of free radicals exceeds the body's ability to detoxify free radicals. Free radical damage is a recognized component of atherosclerosis, neurodegenerative diseases, chronic inflammation, cancer, and aging. However, it is not clear whether this oxidative damage is a cause or a consequence of the disease process. The hypothesis that antioxidant protection could modulate the outcome of such disorders is the basis for many clinical intervention studies with vitamin E supplements. Horwitt concluded that <15 mg vitamin E was required daily; however, he took 200 mg/d for its potential pharmacologic benefit (6).

The 2000 dietary reference intakes include not only the recommended amounts but the upper limit (UL), an intake that should not cause adverse effects (1). An increased tendency to bleed was the adverse effect that was used as a marker to set the UL for vitamin E. Horwitt noted that many individuals routinely consume aspirin for its antiplatelet activity. Thus, an increased incidence of bleeding could result from a combination of aspirin and vitamin E supplements. Unfortunately, relatively few studies of the relation of vitamin E dose with changes in platelet number and function have been conducted. Thus, the UL was based on rat studies because the data available from long-term, high-dose vitamin E intakes in humans were limited.

The dietary reference intake for vitamin E is based on the best data currently available. Despite Horwitt’s protestations, his studies at the Elgin Hospital defining the reversal of markers of oxidative stress by vitamin E are currently the best available data. Until α-tocopherol’s physiologic role is described, optimal concentrations for function are defined and related to intakes, it is likely that Horwitt’s data will remain the best available.

REFERENCES