ANTIOXIDANTS & REDOX SIGNALING
Volume 2, Number 3, 2000
Mary Ann Liebert, Inc.

# Forum Review Article

# Mechanisms of Vitamin E Regulation: Research Over the Past Decade and Focus on the Future

ELIZABETH PARKS[1] and MARET G. TRABER[2]

## ABSTRACT

**This paper discusses the developments in human vitamin E research since 1990. New methodologies such as the use of stable isotopes, advances in vitamin E measurements, and isolation and cloning of specific α-tocopherol binding proteins have facilitated investigation of α-tocopherol absorption, metabolism, and transport in humans *in vivo.* Changes in food production in the United States and dietary intake impacted vitamin E availability and intake. Epidemiologic and therapeutic studies have pointed to its role in disease prevention and in healing processes. Specific molecular functions of α-tocopherol have been the most recent and surprising new findings and are an important area for future experimentation. Given the aging of the American population and the potential role for α-tocopherol in preventive medicine, the study of the molecular functions of vitamin E promises to provide some of the most exciting discoveries of the next decade.** Antiox. Redox Signal. 2, 405–412.

## VITAMIN E FUNCTION

VITAMIN E is the primary fat-soluble, chain-breaking antioxidant in the human body. This description has been repeated so often over the past decade that the real meanings of these adjectives, as they relate to basic science and human health, have been somewhat obscured. The term "primary" reminds us of the continuing role α-tocopherol plays in human physiology and metabolism across the lifespan. It also glosses over the fact that vitamin E includes eight different naturally occurring related antioxidants, only one of which, α-tocopherol, has been demonstrated to be required by humans (Traber, 1999). Therefore, the term "vitamin E" will be used for the properties that the tocopherols and tocotrienols share, and the use of the term "α-tocopherol" will focus on the characteristics of this required nutrient.

The fat-soluble nature of the vitamin E indicates how the complexity of food sources in the diet and the level of dietary fat intake govern vitamin E absorption and transport in the body. Last, it is the chain-breaking antioxidant quality of vitamin E that supports its unique role as a fat-soluble antioxidant. This latter role may be significant in disease prevention and in healing processes; however, specific molecular functions of α-tocopherol may also play critical roles that are just beginning to be defined. This paper will review these attributes of vitamin E with respect to the most recent scientific findings and what remains to be discovered about vitamin E with emphasis on its pertinence to the aging of the American population.

[1]Department of Food Science and Nutrition, University of Minnesota, Twin Cities, St. Paul, MN 55108-6099.
[2]Department of Nutrition and Food Management, Linus Pauling Institute, Oregon State University, Corvallis, OR, 97331-6512.

## VITAMIN E IN THE FOOD SUPPLY

The fat-soluble nature of vitamin E causes it to be impacted by alterations in the U.S. food supply. Statistics have indicated a reduction in the percentage of dietary energy consumed as fat during the period from 1987 to 1994 (Stephen *et al.,* 1995). Seed oil consumption represents the primary source of vitamin E in U.S. diets (Sheppard *et al.,* 1993), and, therefore, any reduction in the consumption of dietary fat could potentially reduce vitamin E intake. On the other hand, recent epidemiological studies demonstrating that increased intakes of whole grains and nuts reduces the incidence of heart disease (Fraser *et al.,* 1992; Hu *et al.,* 1998), may lead to an increase in vitamin E intake, which is concentrated in the germ of grains and nuts. Future questions to be addressed concern the amount and type of dietary fat needed to facilitate efficient vitamin E absorption, and to assess whether the elderly have a decrease in the fractional absorption of vitamin E.

### *Increasing vitamin E in the food supply by genetic engineering*

Because vitamin E intake is correlated with fat intake (Peterson and Sigman-Grant, 1997; Peterson *et al.,* 1999), dramatic reductions in the consumption of dietary fat by Americans through the use of reduced-fat and fat-free products will likely impact the vitamin E intake of Americans. Food companies are already supplementing low-fat prepared foods with vitamin E. As vitamin E nutriture takes a more prominent role in strategies designed at disease prevention, efforts should be made to increase the information available regarding the vitamin E content of unprocessed foods. Furthermore, it may become necessary to add this information to the label on processed food products.

Over the past decade, dramatic gains in plant genetic engineering have resulted in the ability to modify plants to increase their content of potentially beneficial components. Attempts to increase the vitamin E content of plant oils will be based on the cloning of enzymes in its biosynthetic pathway, which is known (Trelfall and Whistance, 1971). Genes encoding one enzyme have already been cloned (Garcia *et al.,* 1997; Norris *et al.,* 1998). A recent strategy to increase plant $\alpha$-tocopherol took advantage of the fact that in many seed oils (corn, soybean, canola) the majority of tocopherol is $\gamma$-tocopherol, a less biologically potent, biosynthetic precursor of $\alpha$-tocopherol. Overexpression of the methyltransferase that converts $\gamma$-tocopherol to $\alpha$-tocopherol led to a significant increase in the content of the latter (Shintani and DellaPenna, 1998). Whether such a strategy is the most efficient way to increase vitamin E intake of Americans is highly controversial.

## VITAMIN E ABSORPTION, TRANSPORT, AND METABOLISM

### *Intestinal fat is needed for efficient vitamin E absorption*

Bile acid secretion and micellarization are required for vitamin E absorption (Traber, 1999). With regard to the amount of fat necessary to aid vitamin E absorption, studies in rats suggest that very low-fat diets and high-fat diets result in similar vitamin E absorption (Brink *et al.,* 1996). Furthermore, individuals who consume very low-fat diets can have adequate vitamin E intakes, especially if they consume diets rich in whole grains (Parks *et al.,* 1995; Swinburn *et al.,* 1999). Furthermore, as dietary fat and cholesterol are reduced, the concentration of blood lipids is reduced in kind; thus, the need for vitamin E may be diminished.

Dose-response studies have shown that plasma $\alpha$-tocopherol levels in healthy subjects can be increased maximally about two- to three-fold, regardless of the duration, size ($>$100 mg), or frequency of vitamin E supplementation (Dimitrov *et al.,* 1991; Princen *et al.,* 1992, 1995; Jialal *et al.,* 1995; Reaven *et al.,* 1995). However, this limitation on plasma $\alpha$-tocopherol concentrations is not due to a limitation on absorption because increasing doses of deuterated $\alpha$-tocopherol resulted in increasing areas under the curve (Traber *et al.,* 1998). Plasma $\alpha$-tocopherol concentrations appear to be regulated by the hepatic $\alpha$-tocopherol transfer protein, as discussed below.

Two developments in the 1990s have spurred an increase in research on the interrelationship between the presence of fat in the duodenum and vitamin E absorption. The first was the FDA approval of Olestra®, a fat-substitute made by Proctor and Gamble (Hunt *et al.*, 1998). This sucrose polyester cannot be hydrolyzed in the intestine and therefore it is not absorbed and passes out of the body through the stool. Reductions in fat-soluble vitamin absorption from Olestra®-containing products led to the required supplementation of these products with vitamin E and $\beta$-carotene (Schlagheck *et al.*, 1997). A second product, Orlistat®, is a pharmaceutical designed to cause weight loss in obese persons by reducing fat absorption through the inhibition of intestinal lipase. Significant fecal loss of vitamin E was observed (Melia *et al.*, 1996), which has resulted in a recommendation for vitamin E supplementation of patients on this medication. It is likely that the high incidence of obesity in the United States, first identified as a growing public health concern in the 1990s, will continue to increase into the next decade. Strategies aimed at altering dietary fat intake and intestinal fat absorption should continue to include research as to the impact of these therapies on fat-soluble vitamin status.

*What kind of fat?*

Not only the amount of fat, but also the kind of fat may affect vitamin E absorption. Tijburg *et al.*, (1997) have shown that vitamin E absorption is similar whether the diet contains 15% or 30% energy from fat, at least in rats. However, the fecal excretion of vitamin E was significantly lower in rats fed on diets with high levels of linoleic acid compared with rats fed on lower levels of linoleic acid, irrespective of the dietary fat content. This suggests that high levels of linoleic acid improved vitamin E absorption.

More research is needed to determine whether humans absorb the same amount of vitamin E if a given dose is administered with a bolus of saturated versus *trans*-fatty acids, poly-, or monounsaturated fatty acids. Fatty acid composition impacts the postprandial handling of dietary triglycerides (Tinker *et al.*, 1999) and would therefore presumably impact vitamin E transport in the blood once the molecule is absorbed. In addition to understanding the impact of quantity and type of fat on vitamin E absorption, factors that impact vitamin E absorption in a more physiologic setting of eating need to be investigated. Normal meals are composed of components other than fat (carbohydrates, fiber, etc.) which may interact with the type of fat to affect vitamin E absorption. Age-related changes in the production of bile may impact fat-soluble vitamin absorption, although studies of vitamin E absorption in the elderly have not controlled for this variable. There is currently very little known regarding the how vitamin E absorption changes with age, as reviewed by Kasper (1999).

*Regulation of hepatic vitamin E*

Much information on the regulation of human vitamin E transport has been gained through the study of individuals with a genetic form of vitamin E deficiency (Cavalier *et al.*, 1998). As early as 1975, Catignani first identified a cytosolic protein that bound $\alpha$-tocopherol from rat liver (Catignani, 1975). However, it was not until the 1990s that genetic defects in the human $\alpha$-tocopherol transfer protein were found to be associated with a characteristic syndrome, ataxia with vitamin E deficiency (AVED). AVED patients have neurologic abnormalities, which are similar to those of Friedreich's ataxia (Ben Hamida, 1993; Ouahchi *et al.*, 1995), but they also have characteristic neurologic abnormalities of human vitamin E deficiency (Sokol, 1993). In 1993, Ben Hamida *et al.* reported that autosomal recessive AVED is associated with a Friedreich ataxia-like phenotype in six Mediterranean families (four of them from Tunisia). Using stable, non-radioactive isotopes of tocopherols (deuterated tocopherols), Traber *et al.* (Traber *et al.*, 1990b, 1993) investigated the transport of vitamin E in patients with this syndrome. Traber *et al.* suggested that secretion of $\alpha$-tocopherol from the liver was abnormal and proposed that this could be the function of the hepatic $\alpha$-tocopherol transfer protein. Their other studies suggested that *RRR*-$\alpha$-tocopherol was preferentially incorporated into very-low-density

lipoproteins (VLDL) via secretion in nascent VLDL (Traber *et al.,* 1990a; Traber *et al.,* 1992).

*Vitamin E metabolites*

Stable isotopes of vitamin E have also been used to study the human urinary excretion of its metabolites. These include both the metabolite of $\alpha$-tocopherol (2,5,7,8-tetramethyl-2(2′-carboxyethyl)-6-hydroxychroman, $\alpha$CEHC) (Schultz *et al.,* 1995, 1997) and that of $\gamma$-tocopherol (2,7,8-trimethyl-2-(2′carboxyethyl)-6-hydroxychroman, LLU$\alpha$) (Wechter *et al.,* 1996). Surprisingly, LLU$\alpha$ (the $\gamma$-tocopherol metabolite) has a unique role as a natriuretic factor in regulating kidney function (Wechter *et al.,* 1996). $\alpha$CEHC, the analogous metabolite of $\alpha$-tocopherol, is neither natriuretic nor inhibitory of the $K^+$ channels (Murray *et al.,* 1997). The importance of LLU$\alpha$ in human physiology remains to be elucidated.

The relationship between plasma vitamin E and urinary metabolites is unclear because $\alpha$CEHC is present at very low concentrations in unsupplemented subjects (Lodge *et al.,* 2000), but it increases in the urine with increasing vitamin E supplements (Schultz *et al.,* 1995). Vitamin E supplements decrease plasma concentrations of $\gamma$-tocopherol (Handelman *et al.,* 1095; Baker *et al.,* 1986), which may increase liver $\gamma$-tocopherol concentrations, and thereby increase production of LLU$\alpha$. This has not yet been demonstrated; however, the importance of the liver in regulating plasma vitamin E concentrations and excretion suggests that this is a key area for future studies.

## VITAMIN E AND AGING

Vitamin E plays a significant role in human health across the life-span. Blood $\alpha$-tocopherol levels increase with age. Winklhofer-Roob *et al.* (1997) reported in 208 Swiss individuals ages 0.4–38.7 years that plasma $\alpha$-tocopherol increased 0.24 $\mu M$ per year from approximately 19 $\mu M$ to 29 $\mu M$. This increase disappeared when the values were corrected for the observed age-related increase in plasma cholesterol. Ford and Sowell (1999), using data from the Third National Health and Nutrition Examination Survey (1988–1994), reported that the mean serum $\alpha$-tocopherol among 16,295 U.S. adults aged 18 or more years was 26.8 $\mu M$; the 25th 50th, and 75th percentiles were 19.6, 24.1, and 30.4 $\mu M$, respectively. The mean $\alpha$-tocopherol/cholesterol ratio was $5.1 \times 10^{-3}$; the 25th, 50th, and 75th percentiles were 4.1, 4.7, and $5.5 \times 10^{-3}$, respectively. For these adult participants, serum $\alpha$-tocopherol concentrations were directly related to age and serum cholesterol. In contrast to the data in children, $\alpha$-tocopherol concentrations increased with age, even when corrected for increasing cholesterol (Ford and Sowell, 1999). Whether the need for vitamin E increases with age is not known. Increased requirements during the normal aging process may be related to an elevation in blood lipid concentration that occurs during adulthood, or to an increase in body mass index, which at any one time is significantly associated with serum $\alpha$-tocopherol concentrations (Gascón-Vila *et al.,* 1997). Fat accrual increases during puberty and how the metabolic changes associated with puberty affect vitamin E stores is not known. In adulthood, body fatness peaks in the fifth and sixth decade of life, a time in which symptoms of slowly progressing diseases come to the forefront (Burton and Foster, 1985). In women, the onset of menopause is associated with increases in body weight and changes the pattern of blood lipids—decreasing high-density lipoprotein (HDL) and increasing LDL and triglyceride). It will be important to ascertain whether these lipid changes are accompanied by changes in the distribution of vitamin E among the lipoproteins.

## VITAMIN E AND ITS RELATION TO CHRONIC DISEASE

Epidemiological data generated over the past decade have shown an inverse relationship between vitamin E intake and the incidence of chronic diseases (Rimm *et al.,* 1993; Stampfer *et al.,* 1993; Kushi *et al.,* 1996). Most of these data have been obtained using food records, dietary recalls, and food frequency analysis. Some caution should be used when interpreting the results of vitamin E intake data

as determined by nutrient analysis software because the content of vitamin E is missing from some foods in these databases. Efforts should be made in the future to expand the information on the vitamin E content of foods listed in diet analysis software.

A highly debated issue has been whether vitamin E supplementation should be added to strategies designed to reduce chronic disease. Over the past decade, the governmental approach to answering this question has taken a slow, cautious path, which is somewhat surprising given the relative low toxicity of this micronutrient. A recent position statement by the American Heart Association has not advocated vitamin E supplementation for individuals with documented atherosclerosis (Tribble, 1999). Notably, epidemiological studies report a strong correlation of decreased risk of coronary heart disease with increased vitamin E intakes (Rimm *et al.,* 1993; Stampfer *et al.,* 1993; Kushi *et al.,* 1996). However, intervention studies with supplemental vitamin E have yielded conflicting results. In contrast to the 77% reduction in second heart attacks seen in one trial (Stephens *et al.,* 1996), little benefit was reported in another (Marchioli, 1999), and no additional benefit of vitamin E supplementation above the use of ACE-inhibitors, was found in a third (Kleinert, 1999).

Other research has suggested the beneficial effects of $\alpha$-tocopherol supplementation in the diseases of diabetes (Davi *et al.,* 1999), cataracts (Rouhiainen *et al.,* 1996). Alzheimer's disease (Sano *et al.,* 1997), and impaired immune function (Meydani *et al.,* 1997). However, testing has been limited and it is premature to advocate beneficial effects of vitamin E based solely on these studies. Questions that will be critical to answer are whether supplementation postpones the onset of disease in individuals predisposed to premature onset due to family history or whether it provides benefit in individuals with other lifestyle risk factors (*e.g.,* smoking).

## CONCLUSIONS

In the past decade, vitamin E research has substantially increased our understanding of the metabolism of $\alpha$-tocopherol in humans. Changes Americans are making in the food supply, medicines, and in their dietary intake will likely impact vitamin E status. Research has supported the biological importance of the antioxidant role of vitamin E and future work will now extend to the molecular level of regulation by this molecule. The influence of $\alpha$-tocopherol on cellular and genetic activity, whether through direct antioxidant effects or through specific molecular effects (Azzi *et al.,* 1998; Devaraj and Jialal, 1998; Keaney *et al.,* 1999), will be a fertile area of future research. Finally, given the shift in the distribution of the population with respect to an older age, the effects of vitamin E on the processes of aging will be a critical focus in the new millennium.

## ABBREVIATIONS

AVED, Ataxia with vitamin E deficiency; $\alpha$CEHC, 2,5,7,8-tetramethyl-2(2′-carboxyethyl)-6-hydroxychroman; $\alpha$-tocopherol, only form of vitamin E required by humans; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LLU$\alpha$, 2,7,8-trimethyl-2-(2′-carboxyethyl)-6-hydroxychroman; VLDL, very-low-density lipoproteins; vitamin E, includes all forms.

## REFERENCES

AZZI, A., ARATRI, E., BOSCOBOINIK, D., CLEMENT, S., OZER, N.K., RICCIARELLI, R., and SPYCHER, S. (1998). Molecular basis of alpha-tocopherol control of smooth muscle cell proliferation. Biofactors **7,** 3–14.

BAKER, H., HANDELMAN, G.J., SHORT, S., MACHLIN, L.J., BHAGAVAN, H.N., DRATZ, E.A., and FRANK, O. (1986). Comparison of plasma $\alpha$- and $\gamma$-tocopherol levels following chronic oral administration of either all-rac-$\alpha$-tocopheryl acetate or RRR-$\alpha$-tocopheryl acetate in normal adult male subjects. Am. J. Clin. Nutr. **43,** 382–387.

BEN HAMIDA M, B.S., SIRUGO G, BEN HAMIDA C, PANAYIDES K, IONANNOU P, BECKMANN J, MANDEL JL, HENTATI F, KOENIG M, *et al.* (1993). Friedreich's ataxia phenotype not linked to chromosome 9 and associated with selective autosomal recessive vitamin E deficiency in two inbred Tunisian families. Neurology **43,** 2179–2183.

BRINK, E.J., HADDEMAN, E., and TIJBURG, L.B. (1996). Vitamin E incorporated into a very-low-fat meal is absorbed from the intestine of young rats. Br. J. Nutr. **75,** 939–948.

BURTON, B.T., and FOSTER, W.R. (1995). Health implications of obesity: an NIH Consensus Development Conference. J. Am. Diet. Assoc. **85,** 1117–1121.

CATIGNANI, G.L. (1975). An alpha-tocopherol binding protein in rat liver cytoplasm. Biochem. Biophys. Res. Commun. **67,** 66–72.

CAVALIER, L., OUAHCHI, K., KAYDEN, H.J., DI DONATO, S., REUTENAUER, L., MANDEL, J.L., and KOENIG, M. (1998). Ataxia with isolated vitamin E deficiency: heterogeneity of mutations and phenotypic variability in a large number of families. Am. J. Hum. Genet. **62,** 301–310.

DAVI, G., CIABATTONI, G., CONSOLI, A., MEZZETTI, A., FALCO, A., SANTARONE, S., PENNESE, E., VITACOLONNA, E., BUCCIARELLI, T., COSTANTINI, F., CAPANI, F., and PATRONO, C. (1999). In vivo formation of 8-iso-prostaglandin F2{alpha} and platelet activation in diabetes mellitus: effects of improved metabolic control and vitamin E supplementation. Circulation **99,** 224–229.

DEVARAJ, S., and JIALAL, I. (1998). The effects of alpha tocopherol on crucial cells in atherogenesis. Curr. Opin. Lipidol. **9,** 11–15.

DIMITROV, N.V., MEYER, C., GILLILAND, D., RUPPENTHAL, M., CHENOWETH, W., and MALONE, W. (1991). Plasma tocopherol concentrations in response to supplemental vitamin E. Am. J. Clin. Nutr. **53,** 723–729.

FORD, E.S., and SOWELL, A. (1999). Serum alpha-tocopherol status in the United States population: findings from the Third National Health and Nutrition Examination Survey. Am. J. Epidemiol. **150,** 290–300.

FRASER, G.E., SABATE, J., BEESON, W.L., and STRAHAN, T.M. (1992). A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist Health Study. Arch. Intern. Med. **152,** 1416–1424.

GARCIA, I., RODGERS, M., LENNE, C., ROLLAND, A., SAILLAND, A., and MATRINGE, M. (1997). Subcellular localization and purification of a p-hydroxyphenylpyruvate dioxygenase from cultured carrot cells and characterization of the corresponding cDNA. Biochem. J. **325,** 761–769.

GASCÓN-VILA, P., GARCIA-CLOSAS, R., SERRA-MAJEM, L., PASTOR, M.C., RIBAS, L., RAMON, J.M., MARINE-FONT, A., and SALLERAS, L. (1997). Determinants of the nutritional status of vitamin E in a non-smoking Mediterranean population. Analysis of the effect of vitamin E intake, alcohol consumption and body mass index on the serum alpha-tocopherol concentration. Eur. J. Clin. Nutr. **51,** 723–728.

HANDELMAN, G.J., MACHLIN, L.J., FITCH, K., WEITER, J.J., and DRATZ, E.A. (1985). Oral $\alpha$-tocopherol supplements decrease plasma $\gamma$-tocopherol levels in humans. J. Nutr. **115,** 807–813.

HU, F.B., STAMPFER, M.J., MANSON, J.E., RIMM, E.B., COLDITZ, G.A., ROSNER, B.A., SPEIZER, F.E., HENNEKENS, C.H., and WILLETT, W.C. (1998). Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study. Br. Med. J. **317,** 1341–1345.

HUNT, R., ZORICH, N.L., and THOMSON, A.B. (1998). Overview of olestra: a new fat substitute. Canad. J. Gastroenterol. **12,** 193–197.

JIALAL, I., FULLER, C.J., and HUET, B.A. (1995). The effect of alpha-tocopherol supplementation on LDL oxidation. A dose-response study. Arterioscler. Thromb. Vasc. Biol. **15,** 190–198.

KASPER, H. (1999). Vitamin absorption in the elderly. Int. J. Vit. Nutr. Res. **69,** 169–172.

KEANEY, J.F.J., SIMON, D.I., and FREEDMAN, J.E. (1999). Vitamin E and vascular homeostasis: implications for atherosclerosis. FASEB J. **13,** 965–975.

KLEINERT, S. (1999). HOPE for cardiovascular disease prevention with ACE-inhibitor ramipril. Heart Outcomes Prevention Evaluation. Lancet **354,** 841.

KUSHI, L.H., FOLSOM, A.R., PRINEAS, R.J., MINK, P.J., WU, Y., and BOSTICK, R.M. (1996). Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. N. Engl. J. Med. **334,** 1156–1162.

LODGE, J.K., TRABER, M.G., ELSNER, A., and BRIGELIUS-FLOHÉ, R. (2000). A rapid method for the extraction and determination of vitamin E metabolites in human urine. J. Lipid Res. **41,** 148–154.

MARCHIOLI, R. (1999). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet **354,** 447–455.

MELIA, A.T., KOSS-TWARDY, S.G., and ZHI, J. (1996). The effect of orlistat, an inhibitor of dietary fat absorption, on the absorption of vitamins A and E in healthy volunteers. J. Clin. Pharmacol. **36,** 646–653.

MEYDANI, S.N., MEYDANI, M., BLUMBERG, J.B., LEKA, L.S., SIBER, G., LOSZEWSKI, R., THOMPSON, C., PEDROSA, M.C., DIAMOND, R.D., and STOLLAR, B.D. (1997). Vitamin E supplementation and in vivo immune response in healthy elderly subjects. A randomized controlled trial. J. Am. Med. Assn. **277,** 1380–1386.

MURRAY, E.D.J., WECHTER, W.J., KANTOCI, D., WANG, W.H., PHAM, T., QUIGGLE, D.D., GIVSON, K.M., LEIPOLD, D., and ANNER, B. (1997). Endogenous natriuretic factors 7: biospecificity of a natriuretic $\gamma$-tocopherol metabolite LLU-$\alpha$. J. Exp. Pharm. Therapy **282,** 657–662.

NORRIS, S.R., SHEN, X., and DELLAPENNA, D. (1998). Complementation of the Arabidopsis pds1 mutation with the gene encoding p-hydroxyphenylpyruvate dioxygenase. Plant Physiol. **117,** 1317–1323.

OUAHCHI, K., ARITA, M., KAYDEN, H., HENTATI, F., BEN HAMIDA, M., SOKOL, R., ARAI, H., INOUE, K., MANDEL, J.L., and KOENIG, M. (1995). Ataxia with isolated vitamin E deficiency is caused by mutations in the alpha-tocopherol transfer protein. Nature Genet. **9,** 141–145.

PARKS, E.J., HYSON, D.A., SCHNEEMAN, B.O., and KAPPAGODA, C.T. (1995). Significant increase in LDL antioxidant content in coronary atherosclerosis patients consuming a low-fat, high-carbohydrate diet. Am. J. Clin. Nutr. **61,** 896 (abstr).

PETERSON, S., and SIGMAN-GRANT, M. (1997). Impact

of adopting lower-fat food choices on nutrient intake of American children. Pediatrics **100,** E4.

PETERSON, S., SIGMAN-GRANT, M., EISSENSTAT, B., and KRIS-ETHERTON, P. (1999). Impact of adopting lower-fat food choices on energy and nutrient intakes of American adults. J. Am. Diet. Assoc. **99,** 177–183.

PRINCEN, H.M., VAN POLLEL, G., VOGELEZANG, C., BUYTENHEK, R., and KOK, F.J. (1992). Supplementation with vitamin E but not beta-carotene in vivo protects low density lipoprotein from lipid peroxidation in vitro. Effect of cigarette smoking. Arterioscler. Thromb. **12,** 554–562.

PRINCEN, H.M., VAN DUYVENVOORDE, W., BUYTENHEK, R., VAN DER LAARSE, A., VAN POPPEL, G., GEVERS LEUVEN, J.A., and VAN HINSBERGH, V.W. (1995). Supplementation with low doses of vitamin E protects LDL from lipid peroxidation in men and women. Arterioscler. Thromb. Vase. Biol. **15,** 325–333.

REAVEN, P.D., HEROLD, D.A., BARNETT, J., and EDELMAN, S. (1995). Effects of vitamin E on susceptibility of low-density lipoprotein and low-density lipoprotein subfractions to oxidation and on protein glycation in NIDDM. Diabetes Care **18,** 807–816.

RIMM, E.B., STAMPFER, M.J., ASCHERIO, A., GIOVANNUCCI, E., COLDITZ, G.A., and WILLETT, W.C. (1993). Vitamin E consumption and the risk of coronary heart disease in men. N. Engl. J. Med **328,** 1450–1456.

ROUHIAINEN, P., ROUHIAINEN, H., and SALONEN, J.T. (1996). Association between low plasma vitamin E concentration and progression of early cortical lens opacities. Am. J. Epidemiol. **144,** 496–500.

SANO, M., ERNESTO, C., THOMAS, R.G., KLAUBER, M.R., SCHAFER, K., GRUNDMAN, M., WOODBURY, P., GROWDON, J., COTMAN, C.W., PFEIFFER, E., SCHNEIDER, L.S., and THAL, L.J. (1997). A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N. Engl. J. Med. **336,** 1216–1222.

SCHLAGHECK, T.G., RICCARDI, K.A., ZORICH, N.L., TORRI, S.A., DUGAN, L.D., and PETERS, J.C. (1997). Olestra dose response on fat-soluble and water-soluble nutrients in humans. J. Nutr. **127,** 1646S–1665S.

SCHULTZ, M., LEIST, M., PETRZIKA, M., GASSMANN, B., and BRIGELIUS-FLOHÉ, R. (1995). Novel urinary metabolite of alpha-tocopherol, 2,5,7,8-tetramethyl-2(2′-carboxyethyl)-6-hydroxychroman, as an indicator of an adequate vitamin E supply? Am. J. Clin. Nutr. **62(suppl),** 1527S–1534S.

SCHULTZ, M., LEIST, M., ELSNER, A., and BRIGELIUS-FLOHÉ, R. (1997). $\alpha$-Carboxyethyl-6-hydroxychroman as an urinary metabolite of vitamin E. Methods Enzymol. **282,** 297–310.

SHEPPARD, A.J., PENNINGTON, J.A.T., and WEIHRAUCH, J.L. (1993). Analysis and distribution of vitamin E in vegetable oils and foods. In *Vitamin E in Health and Disease.* L. Packer and J. Fuchs, eds. (Marcel Dekker, Inc., New York, NY) pp. 9–31.

SHINTANI, D., and DELLAPENNA, D. (1998). Elevating the vitamin E content of plants through metabolic engineering. Science **282,** 2098–2100.

SOKOL, R.J. (1993). Vitamin E deficiency and neurological disorders. In *Vitamin E in Health and Disease.* L. Packer, and J. Fuchs, eds. (Marcel Dekker, Inc., New York, NY) pp. 815–849.

STAMPFER, M.J., HENNEKENS, C., MANSON, J.E., COLDITZ, G.A., ROSNER, B., and WILLETT, W.C. (1993). Vitamin E consumption and risk of coronary disease in women. N. Engl. J. Med. **328,** 1444–1449.

STEPHEN, A.M., SIEBER, G.M., GERSTER, Y.A., and MORGAN, D.R. (1995). Intake of carbohydrate and its components-international comparisons, trends over time, and effects of changing to low-fat diets. Am. J. Clin. Nutr. **62,** 851S–867S.

STEPHENS, N.G., PARSONS, A., SCHOFIELD, P.M., KELLY, F., CHEESEMAN, K., and MITCHINSON, M.J. (1996). Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). Lancet **347,** 781–786.

SWINBURN, B.A., WOOLLARD, G.A., CHANG, E.C., and WILSON, M.R. (1999). Effects of reduced-fat diets consumed ad libitum on intake of nutrients, particularly antioxidant vitamins. J. Am. Diet. Assoc. **99,** 1400–1405.

TIJBURG, L.B., HADDEMAN, E., KIVITS, G.A., WESTSTRATE, J.A., and BRINK, E.J. (1997). Dietary linoleic acid at high and reduced dietary fat level decreases the faecal excretion of vitamin E in young rats. Br. J. Nutr. **77,** 327–336.

TINKER, L.F., PARKS, E.J., BEHR, S.R., SCHNEEMAN, B.O., and DAVIS, P.A. (1999). (*n*-3) fatty acid supplementation in moderately hypertriglyceridemic adults changes postprandial lipid and apolipoprotein B responses to a standardized test meal. J. Nutr. **129,** 1126–1134.

TRABER, M.G. (1999). Vitamin E. In *Modern Nutrition in Health and Disease.* M.E. Shils, J.A. Olson, M. Shike, and A.C. Ross, eds. (Williams & Wilkins, Baltimore) pp. 347–362.

TRABER, M.G., RUDEL, L.L., BURTON, G.W., HUGHES, L., INGOLD, K.U., and KAYDEN, H.J. (1990a). Nascent VLDL from liver perfusions of cynomolgus monkeys are preferentially enriched in *RRR*-compared with *SRR*-$\alpha$ tocopherol: studies using deuterated tocopherols. J. Lipid Res. **31,** 687–694.

TRABER, M.G., SOKOL, R.J., BURTON, G.W., INGOLD, K.U., PAPAS, A.M., HUFFAKER, J.E., and KAYDEN, H.J. (1990b). Impaired ability of patients with familial isolated vitamin E deficiency to incorporate $\alpha$-tocopherol into lipoproteins secreted by the liver. J. Clin. Invest. **85,** 397–407.

TRABER, M.G., BURTON, G.W., HUGHES, L., INGOLD, K.U., HIDAKA, H., MALLOY, M., KANE, J., HYAMS, J., and KAYDEN, H.J. (1992). Discrimination between forms of vitamin E by humans with and without genetic abnormalities of lipoprotein metabolism. J. Lipid Res. **33,** 1171–1182.

TRABER, M.G., SOKOL, R.J., KOHLSCHÜTTER, A., YOKOTA, T., MULLER, D.P.R., DUFOUR, R., and KAYDEN, H.J. (1993). Impaired discrimination between stereoisomers of $\alpha$-tocopherol in patients with

familial isolated vitamin E deficiency. J. Lipid Res. **34,** 201–210.

TRABER, M.G., RADER, D., ACUFF, R., RAMAKRISHNAN, R., BREWER, H.B., and KAYDEN, H.J. (1998). Vitamin E dose response studies in humans using deuterated *RRR*-$\alpha$-tocopherol. Am. J. Clin. Nutr. **68,** 847–853.

TRELFALL, D.R., and WHISTANCE, G.R. (1971). *Aspects of Terpenoid Chemistry and Biochemistry*. T.W. Goodwin, ed. (Academic Press, London) pp. 357–404.

TRIBBLE, D.L. (1999). Antioxidant consumption and risk of coronary heart disease: emphasis on vitamin C, vitamin E, and beta-carotene: a statement for healthcare professionals from the American Heart Association. Circulation **99,** 591–595.

WECHTER, W.J., KANTOCI, D., MURRAY, E.D.J., D'AMICO, D.C., JUNG, M.E., and WANG, W.-H. (1996). A new endogenous natriuretic factor: LLU-alpha. Proc. Natl. Acad. Sci. USA **93,** 6002–6007.

WINKLHOFER-ROOB, B.M., VAN'T HOF, M.A., and SHMERLING, D.H. (1997). Reference values for plasma concentrations of vitamin E and A and carotenoids in a Swiss population from infancy to adulthood, adjusted for seasonal influences. Clin. Chem. **43,** 146–153.

Address reprint requests to:
*Dr. Elizabeth J. Parks*
*Department of Food Science and Nutrition*
*University of Minnesota, Twin Cities*
*St. Paul, MN 55108-6099*

*E-mail:* ejparks@tc.umn.edu

Received for publication January 15, 2000; accepted May 8, 2000.

**This article has been cited by:**


1. Francesca Mangialasche, Weili Xu, Miia Kivipelto, Emanuela Costanzi, Sara Ercolani, Martina Pigliautile, Roberta Cecchetti, Mauro Baglioni, Andrew Simmons, Hilkka Soininen, Magda Tsolaki, Iwona Kloszewska, Bruno Vellas, Simon Lovestone, Patrizia Mecocci. 2012. Tocopherols and tocotrienols plasma levels are associated with cognitive impairment. *Neurobiology of Aging* **33**:10, 2282-2290. [CrossRef]
2. S.V. Rama Rao, M.V.L.N. Raju, A.K. Panda, N.S. Poonam, G. Shyam Sunder. 2011. Effect of dietary # -tocopherol concentration on performance and some immune responses in broiler chickens fed on diets containing oils from different sources. *British Poultry Science* **52**:1, 97-105. [CrossRef]
3. P. Pavana, S. Sethupathy, S. Manoharan. 2007. Antihyperglycemic and antilipidperoxidative effects ofTephrosia purpurea seed extract in streptozotocin induced diabetic rats. *Indian Journal of Clinical Biochemistry* **22**:1, 77-83. [CrossRef]
4. Teresa Montiel, Ricardo Quiroz-Baez, Lourdes Massieu, Clorinda Arias. 2006. Role of oxidative stress on #-amyloid neurotoxicity elicited during impairment of energy metabolism in the hippocampus: Protection by antioxidants. *Experimental Neurology* **200**:2, 496-508. [CrossRef]
5. Barry Halliwell. 2006. Oxidative stress and neurodegeneration: where are we now?. *Journal of Neurochemistry* **97**:6, 1634-1658. [CrossRef]
6. Luc J. Teppema, Raymonda R. Romberg, Albert Dahan. 2005. Antioxidants Reverse Reduction of the Human Hypoxic Ventilatory Response by Subanesthetic Isoflurane. *Anesthesiology* **102**:4, 747-753. [CrossRef]
7. Orhan Aydemir, Serdal Çelebi, Turgut Y#lmaz, Hayrettin Yekeler, A. #ahap Kükner. 2004. Protective Effects of Vitamin E Forms (Alpha-tocopherol, Gamma-tocopherol and d-alpha-tocopherol Polyethylene Glycol 1000 Succinate) on Retinal Edema During Ischemia–reperfusion Injury in the Guinea Pig Retina. *International Ophthalmology* **25**:5-6, 283-289. [CrossRef]
8. C. Villaverde, L. Cortinas, A. C. Barroeta, S. M. Martin-Orue, M. D. Baucells. 2004. Relationship between dietary unsaturation and vitamin E in poultry. *Journal of Animal Physiology and Animal Nutrition* **88**:3-4, 143-149. [CrossRef]
9. F RUPEREZ. 2004. Direct liquid chromatography method for retinol, $alpha;- and $gamma;-tocopherols in rat plasma. *Journal of Chromatography B* **800**:1-2, 225-230. [CrossRef]