Vitamin E

DESCRIPTION

Vitamin E is the collective term for a family of chemical substances that are structurally and, in some cases, biologically related to the best known member of this family, alpha-tocopherol. Vitamin E is a fat-soluble vitamin and an essential nutrient for humans. However, in contrast with the other vitamins present in human nutrition, its exact biochemical role remains unknown.

Vitamin E does not appear to play roles in reproduction and lactation in humans as it does in such animals as rats, and overt deficiency states of this vitamin are rare. Deficiency states of vitamin E, however, do exist in humans, and sub-optimal nutriture of the vitamin may increase the risk of certain degenerative disorders, such as coronary heart disease, Alzheimer's disease and cancer.

Vitamin E deficiency occurs as a result of rare genetic abnormalities affecting the alpha-tocopherol transfer protein (alpha-TTP), as a result of various malabsorption syndromes and as a result of protein-energy malnutrition. Alpha-TTP is a protein found in the liver, heart, cerebellum and retina. Alpha-TTP selectively recognizes alpha-tocopherol and is believed to mediate the secretion of alpha-tocopherol taken up by the liver cells into the circulation. It may also function in delivering alpha-tocopherol to the cerebellum and retina.

Genetic defects in alpha-TTP are associated with a characteristic syndrome, ataxia with vitamin E deficiency or AVED, previously called familial isolated vitamin E (FIVE) deficiency. AVED patients suffer from neurologic symptoms that are characterized by progressive peripheral neuropathy.

Vitamin E deficiency can also be caused by genetic defects in lipoprotein synthesis. Lipoproteins containing apolipoprotein (apo-B) are necessary for absorption and transport of vitamin E. Those with homozygous hypobetalipoproteinemia have a defect in the apo-B gene and those with abetalipoproteinemia have genetic defects in the microsomal triglyceride-transfer protein. Homozygous hypobetalipoproteinemics and abetalipoproteinemics become vitamin E-deficient and develop the progressive peripheral neuropathy characteristic of vitamin E deficiency.

Fat malabsorption syndromes can result in vitamin E deficiency. Since vitamin E requires biliary and pancreatic secretions, as well as an intact and healthy intestine for its absorption, a wide range of hepatobiliary, pancreatic and intestinal disorders can lead to deficiency of the vitamin. These disorders include cholestatic hepatobiliary disease in children, cystic fibrosis, primary biliary cirrhosis, chronic pancreatitis, short bowel syndromes, Crohn's disease, celiac disease, mesenteric vascular thrombosis, blind loop syndrome, intestinal pseudo-obstruction, intestinal lymphangiectasia, Whipple's syndrome and sclerodermal bowel disease. In adults with these disorders, the development of the neurological symptoms of vitamin E deficiency takes many years. In children, the deficiency symptoms of vitamin E deficiency can be reversed by supplementation with vitamin E but only if it is provided before irreversible neurological injury occurs.

The primary syndrome of vitamin E deficiency, whether genetic or secondary to fat malabsorption syndromes or protein-calorie malnutrition, is peripheral neuropathy. This neuropathy is characterized by the degeneration of the large-caliber axons in the sensory neurons. The cardinal neuropathological changes consist of marked dying back-type degeneration of the posterior columns of the spinal cord. In addition, spinocerebellar ataxia, skeletal myopathy and pigmented retinopathy have been observed in vitamin E deficiency in humans. Vitamin E-deficiency anemia may also occur in premature infants as a result of peroxidation damage to red blood-cell membranes.

The vitamin E family of molecules can be divided into two groups, the tocopherols and the tocotrienols. Vitamin E occurs naturally in eight different forms: four tocopherols, alpha-, beta-, gamma- and delta-tocopherol and four tocotrienols, alpha-, beta, gamma- and delta-tocotrienol. All of these forms consist of a substituted hydroxylated ring system (the chromanol ring or head group) with a long phytyl side chain or tail. The phytyl tail is bonded to the chromanol ring at the 2 position of the ring. It is the hydroxyl group of the chromanol ring that confers antioxidant activity to vitamin E.

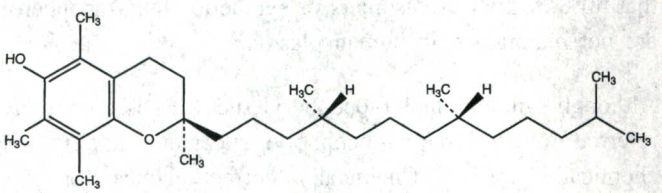
Tocopherols differ from tocotrienols in that tocopherols have three chiral centers, (at positions 2, 4' and 8') while the tocotrienols have only one chiral center (at position 2) and three double bonds in the tail. That is, tocotrienols possess polyunsaturated phytyl side chains. The chiral center of the tocotrienols is located at the point where the phytyl side chain bonds to the chromanol ring (the 2 position of the ring).

The various natural tocopherols and tocotrienols are characterized by the number of methyl groups and the pattern of methylation in the chromanol ring. Alpha-tocopherol and tocotrienol have three methyl groups, beta- and gamma-tocopherol and tocotrienol have two methyl groups and delta-tocopherol and tocotrienol have one methyl group.

Of the eight naturally occurring forms of vitamin E, it appears that only alpha-tocopherol is maintained in human plasma. This is most likely due to the fact that alpha-tocopherol transfer protein (alpha-TTP) selectively recognizes alpha-tocopherol and is believed to mediate the secretion of alpha-tocopherol taken up by the liver cells into

the circulation. This does not rule out possible important roles for the other natural forms of vitamin E. It does, however, indicate that alpha-tocopherol is probably the most important member of the vitamin E family in human physiology.

Alpha-tocopherol is commonly known as d-alpha-tocopherol. Chemically, this implies that alpha-tocopherol has only one chiral center. In fact, alpha-tocopherol has three chiral centers. Its correct name is RRR-alpha-tocopherol or 2, 5, 7, 8-tetramethyl-2R- (4'R, 8'R, 12' trimethyltridecyl)-6-chromanol. Since alpha-tocopherol has 3 chiral centers, it can have 2^3 or eight stereoisomeric forms. d-alpha-tocopherol is represented by the following chemical structure:



d-Alpha-Tocopherol

Synthetic vitamin E, which is produced by coupling trimethylhydroquinone with racemic isophytol, does contain all eight stereoisomers of alpha-tocopherol in equal amounts Synthetic alpha-tocopherol is commonly known as d1-alpha-tocopherol. This would be correct if alpha-tocopherol had only one chiral center, but since it has three, this nomenclature is incorrect. Synthetic alpha-tocopherol is correctly called *all racemic*-or *all rac*-alpha-tocopherol. It is also known as (2RS)-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol. *All rac*-alpha-tocopherol consists of four 2R-stereoisomers: RRR-alpha-tocopherol, RSR-alpha-tocopherol, RRS-alpha-tocopherol and RSS-alpha-tocopherol and four 2S-stereoisomers: SRR-alpha-tocopherol, SSR-alpha-tocopherol, SRS-alpha-tocopherol and SSS-alpha-tocopherol. 2R and 2S refer to the configuration of the phytyl tail at the point it meets the chromanol ring or the 2 position of the ring.

The only forms of alpha-tocopherol that are maintained in human plasma are the 2R-stereoisomers. The 2S-stereoisomers of alpha-tocopherol are not maintained in human plasma or tissue. Therefore, the only forms of alpha-tocopherol maintained in human plasma are the natural RRR-alpha-tocopherol and the four 2R synthetic stereoisomers.

Vitamin E is found in plants, animals and in some green, brown and blue/green algae. The richest sources of the vitamin are found in unrefined edible vegetable oil, including wheat germ, safflower, sunflower, cottonseed, canola and olive oils. In these oils, approximately 50% of the tocopherol content is in the form of alpha-tocopherol. Soybean and corn oils contain about ten times as much gamma-tocopherol as they do alpha-tocopherol. Palm, rice bran and coconut oils are rich sources of tocotrienols. Alpha-tocopherol is the major form of vitamin E in animal products and is found mainly in the fatty portion of the meat. Other foods containing vitamin E include unrefined cereal grains, fruits, nuts and vegetables.

Most of the marketed supplemental RRR-alpha-tocopherol (d-alpha-tocopherol) is derived from unrefined soy oil. Since soy oil contains mainly gamma-tocopherol, a synthetic process is necessary to convert the gamma-tocopherol to the alpha-tocopherol. Therefore, alpha-tocopherol derived from soy oil is a semi-synthetic product for which reason it is called natural-source alpha-tocopherol, rather than natural alpha-tocopherol.

D-ALPHA-TOCOPHERYL ACETATE

d-Alpha-tocopheryl acetate is the acetate ester of natural-source d-alpha-tocopherol. Its molecular weight is 472.75 daltons. It is obtained by the vacuum steam distillation and acetylation of edible vegetable oil products. It is found in nutritional supplement products either as a light brownish yellow, nearly odorless, clear viscous oil or as a water-dispersible solid substance with a melting point of 25° centigrade. The water-dispersible solid form of d-alpha-tocopheryl acetate is about 96 to 100% d-alpha-tocopheryl acetate, while the typical oil supplement is comprised of about 40-50% d-alpha-tocopheryl acetate.

d-Alpha-tocopheryl acetate is also known as RRR-alpha-tocopheryl acetate and 2R, 4', 8'R-d-alpha-tocopheryl acetate.

d-Alpha-tocopheryl acetate, in addition to being available as a nutritional supplement, is used in topical skin care products. It appears that it can diffuse into skin cells where it is converted to d-alpha-tocopherol. The acetate itself does not have antioxidant activity. d-alpha-tocopherol may protect skin against ultraviolet damage and is also a skin moisturizer. Some are hypersensitive to topical d-alpha-tocopherol and may develop dermatitis from its use.

DL-ALPHA-TOCOPHERYL ACETATE

dl-alpha-tocopheryl acetate is an all-synthetic form of alpha-tocopherol. It is produced by coupling racemic isophytol with trimethylhydroquinone to form d1-tocopherol. This product is then acetylated to produce d1-alpha-tocopheryl acetate. Since alpha-tocopherol has three chiral centers, eight stereoisomers are formed in the coupling reaction in equal amounts, four 2R-stereoisomers and four 2S-stereoisomers. 2R and 2S refer to the configuration of the phytyl tail at the point it bonds to the chromanol ring, the 2 position of the ring. The four 2R-stereoisomers are RRR-alpha tocopherol, RRS-alpha-tocopherol, RSS-alpha-tocopherol and RSR-alpha tocopherol. The four 2S-stereoisomers are SRR-alpha-

tocopherol, SSR-alpha-tocopherol, SRS-alpha-tocopherol and SSS-alpha-tocopherol.

The 2R-stereoisomers are the only forms of alpha-tocopherol that are maintained in human plasma and tissue. The activity of natural or natural-source alpha-tocopherol (RRR alpha-tocopherol), on an equal weight basis, is at least twice as high as synthetic alpha-tocopherol. This is mainly because half of the stereoisomers of synthetic alpha-tocopherol are not maintained in human plasma and are, therefore, not bioavailable.

Although synthetic alpha-tocopheryl acetate is commonly referred to as dl-alpha-tocopheryl acetate, this is not chemically correct. Chemically correct names are *all-racemic-* or *all-rac*-alpha-tocopheryl acetate and 2, 5, 7, 8-tetramethyl-2RS-(4'RS, 8'RS, 12' trimethyldecyl)- 6-chromanol hydrogen acetate.

D-ALPHA-TOCOPHEROL SUCCINATE

d-Alpha-tocopherol succinate is the succinate ester of natural-source d-alpha-tocopherol. It is a white to off-white crystalline powder with a molecular weight of 530.79 daltons. d-Alpha-tocopherol succinate is obtained by the vacuum steam distillation and succinylation of edible vegetable oil. It is insoluble in water, but is water-dispersible.

d-Alpha-tocopheryl succinate is also known as RRR-alpha-tocopheryl succinate and 2R, 4', 8'R-alpha-tocopheryl succinate. It is sometimes called "dry" vitamin E, referring to its solid nature.

Some cell culture studies show that d-alpha-tocopheryl succinate can enter into cells as the intact ester and is then hydrolyzed intracellularly to d-alpha-tocopherol. Most ingested d-alpha-tocopheryl succinate is hydrolyzed to d-alpha-tocopherol prior to absorption from the lumen of the small intestine into enterocytes. A small percentage of ingested d-alpha-tocopheryl succinate may enter enterocytes as the ester and is subsequently hydrolyzed to d-alpha-tocopherol within the enterocytes. d-Alpha-tocopheryl succinate itself has no antioxidant activity.

DL-ALPHA-TOCOPHERYL SUCCINATE

dl-Alpha-tocopheryl succinate is an all-synthetic form of alpha-tocopherol. It is produced by coupling racemic isophytol with trimethylhydroquinone to form dl-tocopherol. The dl-tocopherol product is then succinylated to dl-alpha-tocopheryl succinate. Since alpha-tocopherol has three chiral centers, eight stereoisomers are formed in the coupling reaction in equal amounts, four 2R-stereoisomers and four 2S-stereoisomers. 2R and 2S refer to the configuration of the phytyl tail at the point it bonds to the chromanol ring, the 2 position of the ring. The four 2R- stereoisomers are RRR-alpha-tocopherol, RRS-alpha-tocopherol, RSS-alpha-tocopherol and RSR-alpha-tocopherol. The four 2S-stereoisomers: SRR-alpha-tocopherol, SSR-alpha-tocopherol, SRS-alpha-tocopherol and SSS-alpha-tocopherol. dl-Alpha-tocopheryl succinate is not a commercial product. The major reason for its lack of commercial availability is that it does not crystallize well but forms a paste. However, it is available for research purposes.

The 2R-stereoisomers are the only forms of alpha-tocopherol that are maintained in human plasma and tissue. The activity of natural or natural-source alpha-tocopherol (RRR-alpha-tocopherol), on an equal weight basis, is at least twice as high as synthetic alpha-tocopherol. This is due to the fact that 50% of the stereoisomers of synthetic alpha-tocopherol are not maintained in human plasma.

Although synthetic alpha-tocopheryl succinate is commonly referred to as dl-alpha-tocopheryl succinate, this is not chemically correct. Chemically correct names for this substance are *all-racemic-* or *all-rac*-alpha-tocopheryl succinate and 2, 5, 7, 8-tetramethyl-2RS- (4' RS, 8'RS, 12'trimethyldecyl)-6-chromanol hydrogen succinate.

MIXED TOCOPHEROLS

Mixed tocopherols consist of mixtures of the natural tocopherol homologues: d-alpha-tocopherol, d-beta-tocopherol, d-gamma-tocopherol and d-delta-tocopherol. These tocopherols are present in their unesterified forms. Mixed tocopherols are obtained by the vacuum steam distillation of edible vegetable oil products.

There are two types of mixed tocopherol products available for nutritional supplementation: high-alpha-mixed-tocopherols and low-alpha-mixed-tocopherols. High-alpha-mixed-tocopherols contain mainly d-alpha-tocopherol with much smaller amounts of beta-, gamma- and delta-tocopherol. Low-alpha-mixed-tocopherols typically contain gamma-tocopherol as the major tocopherol homologue. High-alpha-mixed-tocopherols are labeled to indicate the milligrams of d-alpha-tocopherol present, as well as the milligrams of total tocopherols present. Low-alpha-mixed-tocopherols are usually labeled to indicate the total amount of tocopherols and sometimes tocotrienols-present, as well as the amounts of gamma-, beta- and delta-tocopherols. Mixed tocopherols occur as brownish-red to red, clear viscous oils.

ACTIONS AND PHARMACOLOGY

ACTIONS

Vitamin E has antioxidant activity. It may also have antiatherogenic, antithrombotic, anticoagulant, neuroprotective, antiproliferative, immunomodulatory, cell membrane-stabilizing and antiviral actions.

MECHANISM OF ACTION

All forms of vitamin E possess antioxidant activity. However, the only forms maintained in human plasma and tissue are the 2R-alpha forms, including the natural RRR-alpha-tocopherol, commonly known as d-alpha-tocopherol. Vitamin E is the principal antioxidant of the lipid domains of the body, such as cellular membranes. It is a chain-breaking antioxidant that prevents the propagation of free radical activities. It is a peroxyl radical scavenger and especially protects the polyunsaturated fatty acids (PUFAs) within membrane phospholipids and in plasma lipoproteins (LDL) against oxidation. The hydroxyl group of the chromanol ring reacts with an organic peroxyl radical to form the corresponding organic hydroperoxide and the tocopheroxyl radical. The tocopheroxyl radical is the pro-oxidant form of vitamin E and is thought to be regenerated to the antioxidant form by a network of other antioxidants, including vitamin C and glutathione.

The relative antioxidant activity of the tocopherols with regard to peroxyl radical scavenging is alpha > beta > gamma > delta. The order is similar among the tocotrienols. Interestingly, this order also parallels the relative order of their biological activities as determined by the classical rat fetal gestation-resorption assay.

This is the case, though, only for the natural tocopherols. All eight stereoisomers of the synthetic *all rac*-alpha-tocopherol, commonly known as dl-alpha-tocopherol, have equivalent peroxyl radical scavenging activity but different activities in the rat fetal resorption assay. And, alpha-tocotrienol has about one-third the activity of alpha-tocopherol in this assay but is a better peroxyl radical scavenger than alpha-tocopherol.

It can be concluded that antioxidant activity of vitamin E is not sufficient to explain the vitamin's biological activity. Recently, it has been demonstrated that vitamin E has activity against reactive nitrogen species (peroxyl radicals are reactive oxygen species). In this regard, gamma-tocopherol inhibits peroxynitrite-induced lipid peroxidation more effectively than alpha-tocopherol (see Gamma-Tocopherol).

Several mechanisms have been proposed to account for vitamin E's possible anti-atherogenic activity. Oxidation of LDL is believed to be a key early step in atherogenesis. It is thought that oxidation of LDL triggers a number of events which lead to the formation of atherosclerotic plaque. These events include uptake of oxidized (ox) LDL by monocytes leading to foam cell formation, promotion of apoptosis by oxLDL, induction of endothelial-cell damage and stimulation of cytokine and growth factor release from cells in the artery wall. LDL contains alpha-tocopherol and smaller amounts of gamma-tocopherol. Alpha-tocopherol inhibits the oxidation of LDL and the accumulation of oxLDL in the arterial wall. It, as well as gamma-tocopherol, also appears to reduce oxLDL-induced apoptosis in human endothelial cells.

A non-antioxidative mechanism of vitamin E is its inhibition of protein kinase C (PKC) activity. PKC is involved in smooth muscle cell proliferation, and, consequently, inhibition of PKC results in inhibition of smooth muscle cell proliferation. Smooth muscle cell proliferation is involved in atherogenesis. PKC inhibition by alpha-tocopherol is, in part, attributable to its attenuating effect on the generation of membrane-derived diacylglycerol, a lipid that facilitates PKC translocation thus increasing its activity. Mitogen-activated protein kinase (MAPK) is also involved in smooth muscle proliferation, and both alpha-tocopherol and gamma-tocopherol inhibit this activity.

Vitamin E enrichment of endothelial cells in culture downregulates the expression of intracellular cell adhesion molecule(ICAM)-1 and vascular cell adhesion molecule(VCAM)-1, both induced by exposure to oxLDL, thereby decreasing the adhesion of blood-cell components to the endothelium. Vitamin E also upregulates the expression of cytosolic phospholipase A_2 and cyclooxygenase (COX)-1. The enhanced expression of these two rate-limiting enzymes in the arachidonic acid cascade appears to explain the observation that vitamin E, in a dose-dependent fashion, enhances the release of prostacyclin, a vasodilating factor and inhibitor of platelet aggregation in humans.

Vitamin E appears to inhibit platelet adhesion, aggregation and platelet release reactions. Enhancing the release of prostacyclin may play a role in these effects. Also, it is known that platelet aggregation is mediated by a common mechanism that involves the binding of fibrinogen to the glycoprotein IIb/IIIa (GPIIb/ IIIa) complex of platelets. GPIIb/IIIa is the major membrane receptor protein that is central to the role of the platelet aggregation response. Glycoprotein IIb (GPIIb) is the alpha-subunit of this platelet membrane protein. It has been shown in tissue culture that alpha-tocopherol downregulates, in a dose-dependent manner, GPIIb promoter activity. This could result in reduction of GPIIb protein expression and decreased platelet aggregation.

Vitamin E has also been found in culture to decrease plasma production of thrombin, a protein which binds to platelets and induces aggregation. A metabolite of vitamin E called vitamin E quinone or alpha-tocopheryl quinone (TQ) is a potent anticoagulant. This metabolite inhibits vitamin K-dependent carboxylase, which is a major enzyme in the coagulation cascade.

A number of mechanisms are proposed to account for the possible neuroprotective effects of high doses of vitamin E.

Oxidative stress is thought to be a factor in the pathogenesis of many disorders of the nervous system. Since the nervous system is rich in lipids and since vitamin E is the principal lipid antioxidant, the vitamin has become attractive as a possible preventive, as well as therapeutic agent, for nervous system disorders. Also, the primary syndrome of overt deficiency of this vitamin is peripheral neuropathy.

Vitamin E may play a special role in the cerebellum because concentrations of the vitamin are the lowest in this part of the brain, and the vitamin is more quickly depleted in the cerebellum than in other parts of the brain during vitamin E deficiency. Electrophysiologic investigations in vitamin E-deficient humans show signs of a distal "dying-back" axonal neuropathy, especially in the posterior columns and the gracile and cuneate nuclei.

Vitamin E may also be involved in signal-transduction. Vitamin E may play a number of roles associated with neuronal cell membranes and other lipids in the nervous system. However, a specific and unique mechanism of action of the vitamin in the nervous system has not been elucidated.

Several animal and human studies have shown that vitamin E can improve the immune response in aged animals and humans. *In vitro*, alpha-tocopherol increases mitogenic response of T lymphocytes from aged mice. The mechanism of this response by vitamin E is not well understood. It has been suggested that vitamin E itself may have mitogenic activity independent of its antioxidant activity. All four homologues of tocopherol, alpha-, beta-, gamma- and delta-tocopherol, were found to enhance both spontaneous and mitogen-stimulated lymphocyte proliferation in mouse splenocytes in culture.

Alpha-tocopherol was reported to have potent activity against human immunodeficiency virus (HIV)-1. Oxidative stress is thought to contribute to HIV-1 pathogenesis, as well as to the pathogenesis of other viral infections. The anti-HIV-1 activity may be due, in part, to alpha-tocopherol's antioxidant activity. Vitamin E also affects membrane integrity and fluidity. HIV-1 is a membraned virus. Altering membrane fluidity of HIV-1 may interfere with its ability to bind to cell-receptor sites, thus decreasing its infectivity. It is unclear, however, how much vitamin E would bind to HIV-1 if administered *in vivo*, since vitamin E can bind to several different sites including alpha-tocopherol transfer protein (alpha-TTP) and LDL.

In conclusion, oxidative stress appears to play a major role in the pathogenesis of many chronic degenerative disorders, and, as the principal lipophilic antioxidant in the body, vitamin E may play a significant role in the prevention, as well as treatment of these disorders. Vitamin E may also have roles independent of its antioxidant action. The action and mechanisms of action of this vitamin are a work in progress.

PHARMACOKINETICS

The precise rate of vitamin E absorption is not known with certainty. The absorption of this vitamin is typically low and variable. The absorption of one form of vitamin E, d-alpha-tocopheryl polyethylene glycol 1000 succinate or vitamin E TPGS, is different (see d-Alpha-Tocopheryl Polyethylene Glycol 1000 Succinate).

Reported rates of absorption of vitamin E following intake with food have varied from as high as 51% to 86% to as low as 21% to 29%. It is likely the higher values are an overestimation and that the lower numbers represent a truer picture. Absorption is significantly lower on an empty stomach and may be somewhat higher with the esterified acetate and succinate delivery forms of vitamin E. However, some studies show that the free and esterified tocopherols have similar absorption efficiency. All forms of vitamin E, including all of the tocopherol and tocotrienol homologues, are absorbed in a similar manner.

Vitamin E is absorbed from the lumen of the small intestine into the enterocytes by passive diffusion. Prior to its absorption, vitamin E is emulsified together with dietary lipids. Bile acids and salts secreted by the liver aid in the emulsification process. Lipolysis and emulsification of the formed lipid droplets lead to the spontaneous formation of mixed micelles. Esterified forms of vitamin E, alpha-tocopheryl acetate and succinate, undergo hydrolysis via esterases secreted by the pancreas. The micelles containing vitamin E are absorbed at the brush border of the intestinal mucosa in the enterocytes. There is some recent evidence that the Niemann-Pick C1-like 1 (NPC1L1) transporter may help mediate the uptake of alpha-tocopherol. Vitamin E is secreted by the enterocytes into the lymphatics in the form of chylomicrons. The chylomicrons contain the various forms of vitamin E, including alpha-, beta-, gamma-, and delta-tocopherol, alpha-, beta-, gamma- and delta-tocotrienol and, if consumed either in supplement form or in fortified foods, all eight stereoisomers of *all rac*-alpha-tocopherol (dl-alpha-tocopherol).

Chylomicrons undergo metabolism in the circulation via lipoprotein lipase to form chylomicron remnants. During this process, some vitamin E, including all the above-cited forms, is transferred to various tissues, such as adipose tissue, muscle and possibly the brain. Lipoprotein lipase appears to be required for the transfer of vitamin E to these tissues. Chylomicron remnants can transfer tocopherols to high density lipoproteins (HDL), which, in turn, can transfer tocopherols to LDL and very low density lipoproteins (VLDL). Chylomicron remnants can also acquire apolipo-

protein E (apoE), which directs them to the liver for metabolism. The remnants are taken up by the liver, which, in turn, secretes vitamin E in VLDLs.

The secretion by the liver of vitamin E in VLDLs is, arguably, the most important singular event in the biochemistry of vitamin E. The only forms of the vitamin secreted by the liver are the natural RRR-alpha-tocopherol and the four 2R forms of synthetic tocopherol. The four 2S synthetic forms of *all rac*-alpha-tocopherol are not secreted by the liver in VLDLs, and only very small amounts of the other tocopherol and tocotrienol homologues are secreted. It is this step that discriminates between all the various forms of vitamin E; the reason for this is that hepatic alpha-tocopheryl transfer protein (alpha-TTP) is selective for the binding of RRR-alpha-tocopherol and the 2R forms of alpha-tocopherol. The secretion of RRR-alpha-tocopherol in VLDLs by the liver is also the mechanism that maintains the plasma concentration of vitamin E. Following secretion of VLDL in the circulation, lipoprotein lipase and triglyceride lipase convert VLDL to LDL. Alpha-tocopherol is transported in the plasma mainly in LDL and also in HDL. Alpha-tocopherol is distributed to the central nervous system (CNS) via LDL. Newly absorbed vitamin E slowly accumulates in the CNS. Sebaceous gland secretion is a major route of vitamin E delivery to the skin.

Alpha-tocopherol can be oxided to the tocopheroxyl radical, which is the pro-oxidant form of this molecule. Reduction back to the antioxidant form is thought to take place with the help of such reducing agents as vitamin C and glutathione. Alpha-tocopherol, vitamin C, glutathione and alpha-lipoic acid are major components of the so-called antioxidant network. Metabolites of alpha-tocopherol include alpha-tocopheryl quinone, alpha-tocopheryl hydroquinone and 2, 5, 7, 8-tetramethyl-2- (2^9 -carboxyethyl)-6-hydroxychroman (alpha-CEHC). A gamma-tocopherol metabolite is 2, 7, 8-trimethyl-2- (2^9-carboxyethyl)-6-hydroxychroman (gamma-CEHC).

Fecal excretion is the major route of excretion of oral vitamin E. Fecal excretion of the vitamin includes non-absorbed vitamin E, as well as vitamin E forms not utilized. For example, the forms not secreted by the liver, such as the 2S alpha-tocopherol forms and the beta-, gamma- and delta-tocopherol homologues, are excreted via the biliary route.

Vitamin E metabolites, such as alpha-CEHC and gamma-CEHC, are excreted via the urinary route. About three times as much *all rac*-alpha-tocopherol, compared with RRR-alpha-tocopherol, is excreted as alpha-CEHC. Alpha-CEHC is the major urinary metabolite of alpha-tocopherol.

INDICATIONS AND USAGE

Vitamin E is a widely recognized fat soluble vitamin essential for human health and notable for some of its antioxidant properties. Claims that it is an effective treatment for established cardiovascular disease continue to be controversial and unsettled. The evidence for prevention of cardiovascular disease is somewhat better. It may have anticancer effects and favorable immunomodulating activity. The evidence that vitamin E has meaningful neuroprotective effects is equivocal. There is the suggestion of limited vitamin E benefit in some patients with asthma and rheumatoid arthritis. It may be protective to some extent against some forms of air pollution and other toxins. It may be of some benefit in some eye disorders, in some forms of diabetes and in premenstrual syndrome. It may help protect against ultraviolet irradiation. Claims that it boosts male fertility, sexual prowess and exercise performance and that it reverses skin aging are poorly supported. It may have some benefit in muscle cramps. There is very preliminary evidence that it might be helpful in treating non-alcoholic steatohepatitis (NASH).

RESEARCH SUMMARY

The results of a very large number of studies, including *in vitro* and animal studies, epidemiological and intervention trials, support a role for vitamin E in the prevention of cardiovascular disease. Recently, however, some large intervention trials have raised some doubts about that role; concurrently, controversy has erupted over the design of these trials. The situation, in some ways, parallels that of the conflicting evidence related to beta-carotene's possible role in preventing lung cancer. (See Beta-Carotene.) Vitamin E has been shown to inhibit the oxidation of LDL-cholesterol in various *in vitro*, animal and human experiments. Other *in vitro*, animal and some human studies demonstrate that vitamin E also acts on coagulation, platelet aggregation and endothelial relaxation, among other factors, in ways that may reduce cardiovascular risk.

In one study of hyperlipidemic rabbits, supplemental vitamin E significantly reduced oxidation of LDL-cholesterol and surface area of atherosclerotic lesions. In male monkeys, 108 IUs of vitamin E daily decreased progression (and produced some regression) of atherosclerosis over a three-year study period. Rabbits on high cholesterol diets given supplemental vitamin E or beta-carotene exhibited aortas with normal endothelial function, compared with controls receiving only the high-cholesterol diet. A number of animal studies have consistently shown that supplemental vitamin E can reduce formation of atheromas by 25% to 50%.

In humans supplemented with vitamin E, their LDL-cholesterol was subsequently shown to contain elevated amounts of

the vitamin. Concurrently, increased oxidation resistance was measured in these LDL samples.

Many epidemiological studies have associated low-vitamin E status with significantly increased risk of cardiovascular disease. Angina sufferers, in some case-control studies, were found to have lower vitamin E levels than controls. In a much larger case-control study, results were obtained suggesting that higher concentrations of vitamin E in adipose tissue indirectly helped protect against myocardial infarction through vitamin E's favorable effects on beta-carotene.

Among prospective cohort studies examining the possible role of vitamin E in cardiovascular disease, The Nurses' Health Study has yielded some significant findings. In a cohort of 87,000 of these nurses, all free of cardiovascular disease at baseline, there was a 34% reduction in coronary heart disease risk among those women in the highest versus the lowest quintile of vitamin E intake after adjustment for age, smoking and other relevant variables. Dietary intake alone did not show this significant inverse relationship, but total intake (diet plus supplementation) did. The nurses were followed for eight years. In nurses in the highest quintile of vitamin E intake from supplementation extending for at least two years, risk reduction was even greater: 46%. Similar risk reduction was seen in a large cohort of men free of heart disease at baseline (the Health Professionals Follow-Up Study). Almost all of the benefit was restricted to those men who took daily supplements of vitamin E in doses of 100 IUs or greater for at least two years.

Several other smaller cohort studies have similarly reported significant evidence of vitamin E's protective role in cardiovascular disease. High dietary intake alone (without supplementation) has also been associated with significantly reduced risk in some of these studies.

A number of other studies have correlated blood levels of vitamin E with risk of cardiovascular disease. In many, but not all, of these, high levels of the vitamin have correlated with reduced risk. Additionally, there are angiography and ultrasound studies that provide some further evidence that vitamin E helps protect the arteries.

Some small clinical intervention trials have found supplemental vitamin E to be beneficial in some with intermittent claudication and angina. More recently, however, the large Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) study of 29,000 Finnish male smokers failed to find any overall significant cardiovascular benefit from low dose (50 milligrams daily) vitamin E (synthetic). However, a subsequent analysis showed some slight benefit from vitamin E among those smokers who had no history of myocardial infarction. After a median follow-up of 6.1 years, there was an observed 4% reduction in primary major coronary events in this subset. Vitamin E decreased the incidence of fatal coronary heart disease by 8%. These findings were statistically non-significant. There was also a significant increase in fatal hemorrhagic stroke in the vitamin E group, although use of the vitamin was associated with a reduction in ischemic stroke, and, overall, there was no statistically significant difference in stroke between those taking the vitamin and those not taking it.

This study has been criticized for using doses of vitamin E significantly lower than those generally shown to have positive preventive effects. Additionally this study involved subjects who had been smoking, in many cases, for decades and thus, some argued, posed a far greater challenge for antioxidant therapy.

Much was made, by some, of the small but statistically significant increase in hemorrhagic stroke associated with vitamin E supplementation in this study. Others, however, have pointed out that some other long-term studies, using considerably higher doses of vitamin E, found no increased risk. There was a statistically non-significant reduction in risk of ischemic stroke in the vitamin E-supplemented subjects in the Nurses' Health Study. There was also a statistically non-significant reduction in cerebrovascular mortality in the vitamin E-supplemented group in the large interventive Linxian China study. And there was a statistically non-significant reduction in total stroke incidence among those receiving vitamin E in the recently concluded GISSI-Prevenzione trial.

In the Cambridge Heart Antioxidant Study (CHAOS), 2002 subjects with cardiovascular disease confirmed by angiography were given 400-800 IUs of natural source vitamin E daily or placebo. A significant 77% reduction in risk of nonfatal myocardial infarction was reported after 510 days of vitamin E administration. There was, however, no effect on cardiovascular death or total mortality.

There was, in fact, a small statistically non-significant increase in cardiovascular death in the vitamin E group. This was a group with serious cardiovascular disease at baseline, and there were considerably more deaths in the early stages of the study, at a point when vitamin E had been used for a relatively short period of time, than at later stages. Thus, there was little concern that the vitamin itself was contributing to an increase in death. Additionally, a recent further analysis has shown that most of these deaths occurred in subjects who were non-compliant with the vitamin E regimen.

The study's reliability has been questioned by some due to purported design flaws, small size and short duration. Defenders of the study, however, say that its results are all the more dramatic, given that the subjects who benefited

were already beset with advanced cardiovascular disease. Moreover, the benefit came in relatively short order. This suggested, they said, that the vitamin might be affecting more than just lipid oxidation in these subjects.

One reviewer, commenting on this possibility, has noted that in subgroup analyses of the Cholesterol Lowering Atherosclerosis Study (CLAS), vitamin E supplementation, in doses greater than 100 IUs daily, was shown to reduce the rate of angiographic progression of mild-to-moderate lesions over a two-year period. On the other hand, some critics of the CHAOS trial said the reported results were improbable in so short a study period, and they concluded that the results occurred by chance alone rather than owing to any real vitamin E effect.

In the Linxian China study, supplemental beta-carotene (15 milligrams daily), synthetic vitamin E (30 IUs daily) and selenium (50 micrograms daily) significantly protected against total mortality and total cancer (which was the primary focus of the study) and non-significantly protected against cerebrovascular disease. The vitamin E dose used in this study was even smaller than that used in the ATBC study. In both cases, synthetic alpha-tocopherol was used.

In the GISSI-Prevenzione trial, 11,324 Italian survivors of myocardial infarction were given 300 milligrams of synthetic vitamin E daily or a mixture of n-3 polyunsaturated fatty acids (PUFA) in a combination of docosahexaenoate (DHA) and eicosapentaenoate (EPA), or both the vitamin E and the n-3 PUFA combination, or neither. The primary end points were nonfatal myocardial infarction, stroke and death. Comparing each treatment against no treatment, the n-3 PUFA combination achieved a statistically significant 15% reduction in primary endpoint risk, while vitamin E achieved a statistically non-significant 11% reduction in the same risks. Vitamin E produced a non-significant reduction in risk of stroke, while the n-3 PUFA combination non-significantly increased risk of stroke.

The GISSI researchers noted that "a possible beneficial effect of vitamin E" was suggested "in the secondary analyses of the individual components of cardiovascular death of the combined endpoints, for which the increasing benefit (from 20% for all cardiovascular deaths to 35% for sudden death) is similar to the picture for n-3 PUFA. The absence of a difference in the rate of non-fatal cardiovascular events between vitamin E and the control group is also similar to the findings related to n-3 PUFA." They added: "The significant decrease of cardiovascular deaths . . . cannot be easily dismissed."

The multi-center GISSI study has been criticized by some for not being placebo-controlled and for dispensing with independent monitors at each participating center. One reviewer noted that synthetic vitamin E was used in this study, reducing the potency of the 300 milligram daily doses, he said, to the equivalent of 150 milligrams of natural-source vitamin E. The greater potency of natural-source vitamin E is widely recognized, and some studies have indicated that natural-source alpha-tocopherol is at least twice as bioavailable as synthetic vitamin E.

Some other researchers said the GISSI trial made too little of the reduction in deaths apparently attributable to vitamin E. Two researchers stated that "cardiovascular mortality was significantly reduced by vitamin E in GISSI, and the effect on overall survival showed a very favorable trend." Others argued that a longer follow-up period was needed. The GISSI trial lasted for 3.5 years.

One of the CHAOS researchers commented on the GISSI trial: "Whether patients who have an MI despite a lifetime of Mediterranean diet and are subsequently treated with a statin would be expected to benefit from vitamin E is not clear, especially since many of the complications of MI depend more on the state of the myocardium than of the coronary arteries." Since the Mediterranean diet is generally higher in vitamin E than the English diet consumed in the CHAOS study, this researcher suggested that the English subjects might be more responsive to vitamin E supplementation.

In this same commentary, the CHAOS researcher observed that investigators in that trial have reported that the English patients had a 3.5-fold increased frequency for a polymorphism in the gene for endothelial nitric oxide synthase (eNOS). Vascular endothelial function is reduced in such individuals, and he speculated that vitamin E may thus have worked in these subjects through an avenue other than the inhibition of LDL-cholesterol oxidation. Conceivably this might help explain the more rapid activity of vitamin E seen in the CHAOS study and might explain why some other populations (with possibly lower frequency of the eNOS gene) are less responsive. More research is needed to clarify these issues.

Recently, results of the Heart Outcomes Prevention Evaluation (HOPE) study were released. This study of 2,545 women and 6,996 men 55 years and older with cardiovascular disease or diabetes tested 400 IUs of natural-source vitamin E against placebo (it also tested the angiotensin-converting-enzyme inhibitor ramipril against placebo) and found no significant protective effect for vitamin E with respect to either primary or secondary endpoints: myocardial infarction, stroke and death from cardiovascular causes, unstable angina, congestive heart failure, revascularization or amputation, death from any cause, complications of diabetes and cancer. Neither did it find any adverse vitamin E effects. Subjects were supplemented for a mean of 4.5 years.

If there was an inconsistency in this study it was that, in contrast with the previous large intervention trials, it appeared to consistently show virtually no vitamin E activity, positive or negative.

The HOPE researchers hypothesized that this lack of activity could be due, in part, to the moderate duration of the trial, to the characteristics of the population studied and/or to the fact that vitamin E was used by itself without some of the co-factors found in some other studies to potentiate its effects. They noted that some trials in which vitamin E is used with some other antioxidants are now in progress. Clearly, these and other studies may be needed before vitamin E's role in various populations with various forms and stages of cardiovascular disease can be adequately evaluated. Some do not expect antioxidants to have notable effects in established disease and say their real strength is in preventing disease in healthy populations.

Unfortunately, in the years since these controversial studies were published, subjected to multiple analyses and, in some cases, modified by the original authors, still more controversy—and very little clarity—has accrued with respect to vitamin E's possible role as a cardioprotectant or interventive in cardiovascular disease. The HOPE study, for example, was extended to the so-called HOPE-TOO trial, the TOO standing for The Ongoing Outcomes. HOPE-TOO looked at long-term vitamin E (400 IU daily) on cardiovascular events and cancer. The subjects, as in the HOPE trial, had cardiovascular disease and/or diabetes mellitus. Again, no benefit was seen and, in fact, the authors noted that vitamin E, in these patients, might be associated with increased risk for heart failure. The authors concluded that "vitamin E supplements should not be used in patients with vascular disease or diabetes mellitus." The study was again criticized by some who pointed out that many of the participants in the original study did not agree to continue in the extended study, that all were suffering from disease and were often on multiple medications and that the observation related to increased heart failure risk could have been due to chance. Indeed, the authors conceded that the latter finding "cannot be confirmed at this time by other trials." That said, the trial nonetheless provided some evidence that vitamin E is not likely to have significant efficacy in treating established cardiovascular disease, at least in the dose tested. It does not address the issue of prevention.

About the same time that the HOPE-TOO results were published, another group published a meta-analysis suggesting that dosages of vitamin E 400 IU or greater daily may increase all-cause mortality "and should be avoided." This meta-analysis involved 19 clinical trials, nine of them with vitamin E alone and 10 with vitamin E in combination with other vitamins and minerals. Considerable criticism of this meta-analysis ensued, emanating from individual researchers and from some major research groups around the world. One critic noted that 12 clinical trials that were among those with the lowest reported deaths were excluded from the meta-analysis. Others said that the inconsistent use of the various vitamin E isoforms, as well as the large variability in patient conditions, dosages, trial designs and end-point analyses, were so significant that comparisons became "difficult and fallacious." The combination of vitamin E with various other substances also presented difficulties in terms of drawing meaningful conclusions. The authors of the DATATOP trial took exception to the analysis of their data included in the meta-analysis. In the DATATOP trial, 800 patients with early Parkinson's disease were randomly administered 2,000 IU of vitamin E daily or seligilene (399 received vitamin E). This study used the highest dose of vitamin E of any of the studies included in the meta-analysis and might thus have been expected to provide the best evidence of increased mortality if such an effect was real. The DATATOP authors stated that the authors of the meta-analysis did not adequately analyze their data and that, in fact, "after adjustment for age and sex in a logistic regression, there was no excess mortality in the group assigned to vitamin E." They further concluded: "We found no evidence of increased mortality in DATATOP related to 2.6 years of high-dosage vitamin E exposure through 13 years of observation." Researchers at another university center called the increased mortality finding an artifact of a flawed analytical design and added: "We also question the applicability of the data to the general population." They pointed out that most of the subjects included in the meta-analysis were suffering from cardiovascular disease. They also stated they were "surprised by the lack of emphasis on the benefits of reduction of all-cause mortality by doses of vitamin E below 400 IU, an effect that reached statistical significance if vitamin E alone was considered." These critics pointed to their own double-blind, placebo-controlled study of vitamin E supplementation (200 IU daily for one year) in patients in nursing homes. No difference was noted in this study in all-cause mortality between controls and experimentals. Benefit was observed in the vitamin E group in terms of significantly reduced group-acquired upper respiratory tract infections, particularly the common cold, a significant health problem in the aging population. Numerous other criticisms were mounted by other researchers.

Mixed results continue to accumulate. One research group recently reported that, in contrast with some other clinical trials that failed to find a vitamin E benefit in cardiovascular disease, they found benefit in subgroups with increased oxidative stress, specifically in individuals with both type 2 diabetes mellitus and the haptoglobin 2-2 genotype. Myocardial infarction, stroke and cardiovascular death were signifi-

cantly reduced in vitamin E-supplemented (400 IU daily) subjects compared with controls in this prospective double-blinded trial. In another recent study, vitamin E supplementation was judged to have beneficial effects on endothelial complications in type 2 diabetes mellitus patients who underwent coronary artery bypass graft. Also, recently, researchers using data from the ATBC cohort study concluded that higher circulating concentrations of alpha-tocopherol within the normal range are associated with significantly lower total and cause-specific mortality in older male smokers. In the HDL Atherosclerosis Treatment Study (HATS), subjects with low HDL-cholesterol levels benefited from treatment with simvastatin and niacin. Angiographically confirmed stenosis regressed in the simvastatin-niacin group but progressed in a group given simvastatin-niacin along with a combination of antioxidants that included vitamin E, suggesting that the antioxidant combination might actually attenuate the benefits of simvastatin and niacin in coronary disease. If this is true it may provide a clue as to why some antioxidants may not be of benefit in established cardiovascular disease. In a recent review of the vitamin E literature, however, a study is cited in which transplant-associated atherosclerosis was prevented by supplementation with combined vitamin E and C. In this double-blind prospective trial, 40 patients (0-2 years after cardiac transplant) were randomly assigned vitamin C (500 mg) plus vitamin E (400 IU) or placebo. After one year of treatment, disease progression was significantly inhibited in the vitamin group but not in the placebo group. Various other clinical studies conducted in recent years have demonstrated both positive and negative effects of vitamin E on atherosclerotic progression. Some of these have used vitamin E alone and others have used vitamin E in combination with other antioxidants without consistent results.

Some review authors have tried to address the hypothesis that vitamin E may be useful as a preventive but not as an interventive in cardiovascular disease. They found some evidence of adverse interactions between vitamin E and other substances used to treat disease that might explain an adverse vitamin E effect, particularly in severe disease states requiring significant medication. Their conclusion may be the most persuasive based on current knowledge: "In summary, the often neutral outcome of secondary prevention studies suggests that vitamin E supplementation is not an effective therapy against pre-existing cardiovascular disease, but rather may play a preventive role as evidenced in the more positive outcome seen in primary prevention and epidemiologic studies."

Another useful conclusion may have been drawn by the authors of the recent study, using the ATBC cohort data, in which they reported that higher serum concentrations of vitamin E are associated with lower total and cause-specific mortality in older male smokers. "Because supplemental vitamin E has not been shown to reduce mortality in randomized trials, efforts to improve vitamin E status through dietary means (e.g., through increased consumption of foods rich in vitamin E, including nuts, seeds, whole grains and dark-green leafy vegetables) may be warranted." Though part of this statement is contradicted by other studies (some randomized trials *have* shown reduced mortality, as discussed above), the dietary recommendation may be well-founded.

Though it has long been assumed that vitamin E's starring role would be in heart disease, it may turn out to have as big a part to play in preventing and treating some cancers. The same study that dealt a blow to claims that beta-carotene supplementation prevents lung cancer raised hopes that vitamin E might effectively help prevent prostate cancer. In the ATBC study of Finnish smokers, low-dose synthetic vitamin E (50 milligrams daily) reduced the incidence of prostate cancer by a significant 32% and prostate cancer deaths by a significant 41%. This unexpected result was sufficiently impressive that the National Cancer Institute continues to follow up via the ongoing Selenium and Vitamin E Cancer Prevention Trial (SELECT), the largest ever prostate cancer prevention trial.

Reduction in prostate cancer incidence became evident in the ATBC study within two years of beginning supplementation. Some believe there is the suggestion in this and other research that vitamin E blocks the progression of latent prostate cancer, particularly important, if verified, because latent prostate cancer cannot be detected clinically, and many deaths occur because of this. There is often little or no warning of the transition from latent to aggressive disease. A lesser reduction in colon cancer associated with vitamin E supplementation was also seen in this study.

In the Linxian China study, another randomized long-term intervention study, administration of synthetic vitamin E, in combination with selenium and beta-carotene, resulted in a significant reduction in total mortality and total cancer incidence. Only this combination of nutrients, among four regimens tested, was effective with respect to these end-points. The combination was particularly protective against esophageal and stomach cancers. This was the only regimen tested that included vitamin E. Dosage was low—30 IUs daily.

In a recent further analysis of data from the ATBC study, researchers found that "higher serum alpha-tocopherol status is associated with reduced lung cancer risk; this relationship appears stronger among younger persons and among those with less cumulative smoke exposure. These findings

suggest that high levels of alpha-tocopherol, if present during the early critical stages of tumorigenesis, may inhibit lung cancer development." Those in the highest versus the lowest quintile of serum vitamin E concentrations had a 19% reduction in incidence of lung cancer in this study. The researchers further noted that "There was a stronger inverse association among younger men .... And possibly among men receiving supplementation."

Did vitamin E supplementation, then, help protect against lung cancer? The conclusion in the original study report was that it did not. Secondary analyses of the ATBC trial, however, suggested that study subjects who supplemented with vitamin E for the longest periods of time experienced a 10-15% reduction in lung cancer risk in this cohort of smokers. Supplementation was low-dose (50 milligrams daily of synthetic alpha-tocopherol).

In the serum vitamin E analysis, the researchers further concluded that there was "synergism between usual intake and the controlled intervention." Those who had higher pre-trial serum levels of vitamin E did better than those with lower pre-trial serum levels, and still better results were seen in those with higher pre-trial serum levels who also received vitamin E supplements during the trial. Thus there is the suggestion that epidemiology may coincide here with intervention.

The researchers concluded that "while it is tempting, based on the present data, to speculate that the administration of greater quantities of alpha-tocopherol might have produced a substantial reduction in lung cancer incidence in the ATBC study, only future studies, and controlled trials in particular, can shed light on this question."

Numerous epidemiological studies have associated higher vitamin E status with reduced cancer, including lung, colorectal, prostate, colon, stomach, reproductive organs, upper gastrointestinal tract, bladder, breast, cervix, mouth, pharynx and thyroid cancer. Reduced serum vitamin E levels are also associated with a higher incidence of lymphoma and leukemia in some populations. Not all epidemiological studies have shown an inverse relationship between vitamin E status and cancer risk, but the majority have.

Vitamin E has shown significant activity against various cancers *in vitro* and in experimental animal models of carcinogenesis. In a review of animal work, results overall strongly indicated that vitamin E significantly reduced the incidence of a variety of cancers. Vitamin E has shown significant anti-cancer activity in these experiments when used alone and when used in combination with vitamin C and/or selenium, among other antioxidant companions. Mammary tumors have been significantly inhibited in rat experiments using vitamin E and selenium. Chemically induced skin cancers in mice were inhibited with vitamin E and beta-carotene.

In one intervention trial, neither beta-carotene, vitamin C, nor vitamin E reduced the incidence of colorectal adenoma recurrence in subjects who had undergone removal of colorectal adenoma prior to entering this study. Supplementation continued for four years. Critics of the study said far longer supplementation would be required to have any impact on this problem.

Vitamin E (400 IUs twice daily for 24 weeks) achieved clinical improvement (disappearance of at least 50% of lesions) in 20 of 43 patients with oral leukoplakia. In a randomized, double blind, placebo-controlled study, a topical preparation of vitamin E completely resolved the oral lesions of subjects with chemotherapy-induced mucositis.

The HOPE-TOO trial, discussed earlier, did not find evidence of reduced cancer in the patients it studied with vascular disease and/or diabetes mellitus. In a further amplification of the ATBC cancer findings, researchers have reported that participants in that study who had higher concentrations of the major vitamin E fractions had significantly lower prostate cancer risk. This association held both before supplementation was given and afterwards (when the effect was accentuated). The authors of a recent mini-review of the vitamin E cancer data concluded that different vitamin E isomers and analogs have different anticancer potencies and activities. Their findings persuaded them that more research is needed and warranted to determine which of these substances, either singly or in various combinations, are most likely to serve as possible adjuvant chemotherapeutic agents in a variety of cancers. They believe that alpha-tocopherol itself may not be capable of effective tumor cell apoptosis (in contrast with some of the other isomers and analogs) but that it might still be effective, primarily through its antioxidative properties.

High plasma vitamin E levels have been associated with greater resistance to infection in some, but not all, epidemiological studies. Some of these have shown a stronger protective effect in the elderly. *In vitro* and animal studies have demonstrated that vitamin E can enhance some immune functions. In animals, there is evidence that supplemental vitamin E increased resistance to a number of pathogens including *Escherichia coli* and *Pneumoccocus pneumonia* type I. Influenza viral lung titers were significantly reduced in elderly mice supplemented with vitamin E, compared with unsupplemented controls who were also infected and who consumed normal amounts of vitamin E in their diets. A number of immunologic studies have tested vitamin E alone and in combination with other nutrients in humans. The number of CD4 and CD8 T cells were high and lymphocyte

proliferative response to mitogen was significantly enhanced in elderly subjects given supplemental vitamins A, E and C for four weeks, compared with those given placebo. In some other human studies, supplementation with vitamin E alone or in combination with vitamin C, beta-carotene and some other nutrients has favorably affected T-cell counts, lymphocyte response, levels of interleukin-2 and natural killer cell activity.

One reviewer of the vitamin E literature concluded: "Evidence from animal and human studies indicates that vitamin E plays an important role in the maintenance of the immune system. Even a marginal vitamin E deficiency impairs the immune response, while supplementation with higher than recommended dietary levels of vitamin E enhances humoral and cell-mediated immunity."

In one double-blind, placebo-controlled study, 88 healthy elderly subjects were randomized to receive 60, 200 or 800 milligrams of synthetic vitamin E daily or placebo for 235 days. The objective was to determine the effects, if any, of these varying doses of vitamin E on various measures of cell-mediated immunity. Some older healthy people have been shown to have an impaired ability to produce an effective delayed-type hypersensitivity skin response (DTH), which, in turn, has been associated with greater mortality. Decreased DTH appears to be indicative of diminished capacity to deal with infectious and neoplastic challenges and prolonged illness.

Subjects receiving 200 milligrams of vitamin E daily in this study had a significant 65% increase in DTH and a six-fold increase in antibody titer to hepatitis B, compared with subjects receiving placebo. Subjects receiving the 200 milligram dose also had significant increases in antibody titer to tetanus vaccine, compared with controls. Supplementation did not affect antibody titer to diphtheria, immunoglobulin levels or levels of T and B cells. Nor was there any observed effect on antibody levels.

The 60 milligram dose did not produce statistically significant results in some of the parameters measured. The 200 milligram dose generally produced better results than the 800 milligram dose. Thus the researchers concluded that there may be a threshold level for vitamin E's observed immunostimulatory effects and that the 200 milligram dose, pending possible different findings in future research, appears to be the optimal dose for healthy elderly individuals seeking to preserve immune function. Very high doses of vitamin E have been associated with adverse effects on immunity in some studies. Subjects given 1,600 milligrams of vitamin E daily for one week, for example, were shown to have diminished polymorphonuclear leukocyte bactericidal activity.

Finally, with respect to immunity, there have been some reports that vitamin E may be helpful in some with HIV-disease. In a study of 311 HIV-infected individuals followed over a period of nine years, those with the highest blood levels of vitamin E were 34% less likely than those with low levels to progress to fully-developed AIDS. The higher vitamin E status was also associated in this study with higher T helper lymphocyte counts.

In another study, there was the suggestion that low vitamin E status might be associated with elevated immunoglobulin E (IgE) levels and consequent increased inflammation in HIV-infected individuals. This inflammation is postulated to increase HIV replication.

And in an animal model of AIDS, vitamin E supplementation reportedly helped restore some T cell functions and reduced production of inflammation-promoting interleukin-6 and tumor necrosis factor.

Results of an additional study showed that vitamin E, in combination with erythropoietin and interleukin-3, increased survival and weight of fetuses in pregnant rats administered AZT. Thus it has been suggested that vitamin E might help protect against some of the toxic effects of AZT and similar drugs. Research continues.

As for autoimmune disorders, here too there is epidemiological evidence linking low vitamin E status with a higher incidence of rheumatoid arthritis. In one small interventive trial, 1,200 IUs of vitamin E daily reportedly reduced pain in rheumatoid arthritis patients but not inflammation, compared with subjects receiving placebo. Other studies have also reported significant pain reduction.

Vitamin E has been used with benefit in some with asthma. Lung function measures were significantly improved in one double-blind, placebo-controlled study of asthmatic volunteers exposed to ozone and sulfur dioxide who received 400 IUs of vitamin E and 500 milligrams of vitamin C daily for five weeks.

Various animal and human experiments have demonstrated that supplemental vitamin E can protect against some of the toxic effects of cigarette smoke and smog. In a recent study of Dutch bicyclists, 100 milligrams of vitamin E and 500 milligrams of vitamin C daily for 15 weeks significantly protected measures of lung function against effects of ozone, compared with controls receiving placebo.

Vitamin E (50 milligrams daily) did not have any effect on the recurrence or incidence of chronic obstructive bronchopulmonary diseases in the ATBC study of Finnish smokers. Higher dietary intake of vitamin E, however, was associated in this study with lower incidence of chronic bronchitis and dyspnea.

Supplemental vitamin E has shown some positive activity in neurological disorders. In a well-designed double-blind, multicenter, placebo-controlled study, 2,000 IUs of synthetic vitamin E daily, alone or in combination with the drug selegiline (10 milligrams daily), were administered to subjects with moderate Alzheimer's disease over a two-year period. Primary endpoints were death, severe dementia, loss of ability to perform everyday tasks and need of institutionalization. Those receiving vitamin E alone had a 53% reduction in risk of reaching any of these endpoints, while those on selegiline had a 43% reduction in risk, and those taking both vitamin E and selegiline had a 31% reduction. There was an increase of 230 days in the time it took on vitamin E to reach a primary endpoint, compared to those on placebo. Partly because of this study, the American Psychiatric Association updated its treatment guidelines for Alzheimer's disease. Those guidelines include the use of vitamin E in newly diagnosed, mildly impaired and moderately impaired victims of this disease and some other diseases that also cause dementia.

Unfortunately, a follow-up to the study cited above did not yield similarly positive effects. In this study, subjects with risk for progression to Alzheimer's were randomly assigned to receive 2,000 IU vitamin E daily or the drug donepezil or placebo for three years. The donepezil showed some small effect, which was abolished after the first year. Vitamin E was no better than placebo in inhibiting the onset of cognitive impairment. In another trial, 160 patients with Alzheimer's got no benefit from 5,000 IU of vitamin E daily based on cognitive measures taken after 18 months of follow-up.

In another trial, selegiline but not vitamin E was shown to significantly delay the need for levodopa in patients with Parkinson's disease (a benefit that was not sustained during follow-up).

Results have been mixed with respect to vitamin E's effects on tardive dyskinesia. In one study, the vitamin significantly out-scored placebo at 400-800 IUs daily. In a more recent randomized, multicenter, placebo-controlled study, vitamin E (1,600 IUs daily) showed no effect in the treatment of tardive dyskinesia over a two-year supplementation period.

In a study of 3,385 elderly men, age 71 to 93 years, use of either vitamin E or vitamin C supplements, ascertained by questionnaire, was significantly associated with better cognitive test performance and protection against vascular dementia.

Pre-treatment and post-treatment with vitamin E enhanced neurologic recovery after experimental spinal cord compression injury in cats. Four weeks post-injury, treated cats recovered 72% of pre-injury function, compared with 20% recovery in untreated controls.

Epidemiological associations have been made between high blood levels of vitamin E and reduced incidence of cataract. In a study of 764 elderly subjects, those taking vitamin E supplements had a 50% reduced risk that their cataracts would progress over a 4-5 year period. Multivitamin use was associated with a 33% reduction in the same risk. Vitamin E supplementation has prevented cataract development and significantly inhibited its progression in several animal models.

Results of a population-based study of 2,584 French subjects recently showed that high plasma vitamin E levels are associated with decreased risk of late age-related macular degeneration (AMD). The risk of late AMD was reduced by 82% in those individuals in the highest vitamin E quintile compared with the lowest quintile. There was also a lesser but still significant reduction in risk of early signs of AMD associated with high vitamin E status. The study adjusted for smoking and factors related to cardiovascular disease including diabetes, all of which are associated with increased AMD risk. No association was found between reduced risk of AMD and plasma retinol, ascorbic acid levels or with red blood cell glutathione values.

The controlled, clinical intervention trial that could demonstrate supplemental vitamin E's possible benefit in the treatment of AMD has yet to be conducted, but, as several researchers have noted, such a study is clearly warranted.

Through its possible cardiovascular-protective effects, vitamin E is hypothesized by some to be beneficial in some cases of diabetes. Additionally, in animal studies, vitamin E has exerted various effects in the kidneys, eyes and nerves that may be helpful in combating some of the damage of diabetes. Vitamin E did not show any benefit with respect to incidence of complications of diabetes in the HOPE study previously discussed. Some said the follow-up was of insufficient duration to show and any effect.

A recent report indicated serum vitamin E concentrations at baseline, in a case-control study nested within a 21-year follow-up study, were inversely associated with insulin-dependent diabetes mellitus incidence 4-14 years later. Risk was diminished 85% among those with the highest vitamin E status versus those with the lowest. This reduced risk persisted after adjustment for serum cholesterol levels.

Recently, researchers reported that supplemental oral vitamin E normalized retinal hemodynamic abnormalities and improved renal function in type 1 diabetic patients of short disease duration. This was a randomized, double-blind,

placebo-controlled crossover trial of eight months duration. Vitamin E dose was 1,800 IUs daily.

In another recent double-blind, placebo-controlled study 1,600 IUs of vitamin E daily did not improve postulated receptor-specific vascular endothelial dysfunction in subjects with type 2 diabetes mellitus. Vitamin E has, however, been shown to prevent and reverse some of the vascular complications of diabetes in *in vitro*, animal and human studies. Vitamin E has demonstrated an ability to inhibit hyperglycemia-induced activation of protein kinase C (PKC) and to also inhibit diacylglycerol (DAG) levels. Both PKC and DAG have been implicated in diabetic complications, and inhibition of PKC has reversed some of the vascular dysfunctions in retina, kidney and cardiovascular systems caused by hyperglycemia or diabetes.

In a recent pilot study, vitamin E treatment (300 mg daily for six months) resulted in a reduction in biochemical markers and oxidative stress associated with nonalcoholic steatohepatitis. A subsequent study similarly suggested a possible role for vitamin E in the treatment of this disease.

Preliminary research has indicated that supplemental vitamin E might be helpful in some with premenstrual syndrome (PMS). In a double-blind, placebo-controlled trial, vitamin E (in doses of 150, 300 or 600 IUs daily administered for two months) significantly outperformed placebo. It reportedly significantly improved three of four classes of PMS symptoms. A subsequent double-blind, placebo-controlled study found significant improvement in some affective and physical symptoms of PMS in subjects treated with 400 IUs of vitamin E daily for three menstrual cycles. The same research group conducted both of these studies in the 1980s. They need follow-up.

There is evidence from *in vitro* and animal studies that both oral and topically applied vitamin E can help protect against UV light-induced skin changes and protect against skin cancer. In animals and humans, studies have shown that UV irradiation diminishes both skin and plasma levels of various nutrients, including vitamin E.

In one experiment, the UVB irradiation that is considered to be the most carcinogenic suppressed immune functions in the skin of mice. This suppression was blocked with vitamin E. *In vitro*, vitamin E has also blocked some of the immune-suppressing effects UVA radiation has on human cells. Topically applied vitamin E prevented UVB-induced skin tumors in an animal model.

Some studies in humans have demonstrated that topical vitamin E can protect skin against photo-damage and subsequent wrinkling. In one placebo-controlled study, topically applied vitamin E, more than placebo, reportedly reduced eyelid wrinkling over a four-week period. And, in another human study, a patented cream containing, among other things, vitamin E and C, reportedly produced significant improvement in wrinkling. An oral preparation of vitamin E and C had no effect. Placebos were used. Treatment continued for 18 months. More rigorous follow-up studies are required before vitamin E's ability, if any, to reverse photo-damage is established.

In a recent double-blind study, vitamin E ointment did not improve the cosmetic appearance of surgical scars. Application of topical vitamin E was associated with contact dermatitis in 33% of the subjects.

It has been claimed that supplemental vitamin E increases male sexual performance and enhances male fertility. There is no evidence that supplemental vitamin E has any effect on sexual performance in either males of females. An Israeli research group has reported that 200 milligrams of oral vitamin E daily for one month apparently helped two men overcome their long-term infertility. Both had very high levels of lipid peroxidation as measured by elevated levels of malondialdehyde prior to beginning vitamin E supplementation. Within one month of starting vitamin E supplementation, the malondialdehyde levels dropped significantly. Both men were able to impregnate their wives.

A combination of vitamin E and selenium seemed to improve sperm motility and morphology in one group of men. Similar results were obtained in a second study, this one using 600 IUs of vitamin E daily. It is possible that these changes might enhance male fertility, but that endpoint was not investigated in these studies.

More recently, a more rigorous randomized placebo-controlled, double-blind study found no improvement in semen parameters in infertile men supplemented with 1,000 milligrams of vitamin C and 800 milligrams of vitamin E for 56 days. Semen parameters studied included semen volume, sperm concentration and motility, sperm count and viability.

Also poorly supported are claims that vitamin E can enhance exercise/athletic performance. There is some evidence that supplemental vitamin E can reduce some measures of oxidative stress in some exercisers but no evidence that it enhances performance.

Notable relief from persistent nocturnal cramps of legs and feet was seen in 82% of 125 subjects taking 300 IUs or less of vitamin E daily.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Vitamin E is contraindicated in those with known hypersensitivity to any component of a vitamin E-containing product.

PRECAUTIONS

Those on warfarin should be cautious in using high doses of vitamin E (i.e., doses greater than 100 milligrams daily of d-alpha-tocopherol or 200 milligrams daily of dl-alpha-tocopherol), and if they do use such doses, they should have their INRs monitored and their warfarin dose appropriately adjusted if indicated. Likewise, those with vitamin K deficiencies, such as those with liver failure, should be cautious in using high doses of vitamin E. Vitamin E should be used with extreme caution in those with any lesions that have a propensity to bleed (e.g., bleeding peptic ulcers), those with a history of hemorrhagic stroke and those with inherited bleeding disorders (e.g., hemophilia).

Supplemental doses of vitamin E higher than RDA amounts should be avoided by pregnant women and nursing mothers.

High dose vitamin E supplementation should be stopped about one month before surgical procedures and may be resumed following recovery from the procedure. Use of supplemental vitamin E in low birth weight premature infants must be undertaken with extreme caution and only by trained medical personnel.

ADVERSE REACTIONS

The risk of adverse reactions to vitamin E supplementation (in doses up to one gram daily of alpha-tocopherol) generally appears to be very low. A large randomized trial, the Alpha-Tocopherol Beta Carotene (ATBC) Cancer Prevention Study, the subjects of which were Finnish male smokers, reported that subjects consuming 50 milligrams daily of dl-alpha-tocopherol for 6 years had a 50% increase in mortality from hemorrhagic stroke. The numbers were 66 versus 44 strokes in the supplemented versus the control groups. This result was statistically significant. Interestingly, an increase in hemorrhagic stroke has not been observed in other large, long-term studies using much higher doses of the vitamin. The overall stroke rate between the two groups was not statistically significant in the ATBC study. In their most recent report (April, 2000) on vitamin E, the National Research Council comments "The unexpected finding in the ATBC study was considered preliminary and provocative, but not convincing until it can be corroborated or refuted in further large-scale clinical trials."

Adverse reactions reported for vitamin E supplementation include fatigue, breast soreness, emotional disturbances, thrombophlebitis, retinuria, gastrointestinal disturbances, altered serum lipid levels and thyroid problems. These adverse reactions were rare and none of these has been reported in controlled studies. An increased incidence of necrotizing enterocolitis has been reported in premature, very-low birth weight infants receiving 200 milligrams daily of alpha-tocopheryl acetate.

The meta-analysis discussed earlier suggested that vitamin E at 400 IU daily and above may increase all-cause mortality. There was also much criticism of this meta-analysis.

INTERACTIONS

DRUGS

Amiodarone: Alpha-tocopherol may ameliorate some of the adverse side effects of this drug. This is based on the results of cell culture studies.

Anticonvulsants such as phenobarbital, phenytoin and carbamazepine: Anticonvulsants may lower plasma vitamin E levels.

Antiplatelet drugs such as aspirin, dipyridamole, eptifibatide, clopidogrel, ticlopidine HCl, tirofiban and abciximab: High doses of vitamin E may potentiate the effects of these antiplatelet drugs.

Cholestyramine: may decrease vitamin E absorption.

Colestipol: may decrease vitamin E absorption.

Cyclosporin: Based on cell culture studies, alpha-tocopherol may help to ameliorate the renal side effects of cyclosporin.

Ezetimibe: may inhibit the intestinal absorption of alpha-tocopherol.

Isoniazid: may decrease vitamin E absorption.

Mineral oil: may decrease vitamin E absorption.

Multidrug-resistance (MDR) modifying agents: Based on cell culture studies, alpha-tocopherol is reported to antagonize the multidrug-resistance (MDR)-modifying activity of the chemosensitizing agents cyclosporin A, verapamil, clofazimine, GF120918 and B669 to both doxorubicin and vinblastine.

Neomycin: may impair utilization of vitamin E.

Orlistat: inhibits vitamin E absorption. Absorption of a vitamin E acetate supplement was inhibited by approximately 60% by orlistat.

Sucralfate: interferes with vitamin E absorption.

Warfarin: Vitamin E may enhance anticoagulant response. Monitor INRs and appropriately adjust dose of warfarin if necessary.

Zidovudine: Vitamin E may ameliorate myelosuppressive side effects of zidovudine.

NUTRITIONAL SUPPLEMENTS

Beta-carotene: Some studies have suggested that oral supplements of beta-carotene may cause a decrease in serum levels of alpha-tocopherol. However, more recent and much larger and longer studies have demonstrated that supplemen-

tation with beta-carotene does not alter serum concentrations of vitamin E.

Desiccated ox bile: Desiccated ox bile may increase the absorption of vitamin E.

Dietary fiber: Dietary fiber supplementation may decrease the antioxidative effect of a supplement containing alpha-tocopherol and carotenoids.

Iron: Most iron supplements contain the ferrous form of iron. This cation can oxidize unesterified vitamin E to its pro-oxidant form if taken concomitantly. This does not occur with esterified vitamin E (alpha-tocopheryl acetate and succinate).

Medium–chain triglycerides: Medium-chain triglycerides, if taken concomitantly with vitamin E, may enhance its absorption.

Phytosterols and phytostanols, including beta-sitosterol and beta-sitostanol: Phytosterols and phytostanols may lower plasma vitamin E levels.

Plant phenolic compounds and flavonoids: These substances may participate in redox cycling reactions and help maintain levels of reduced vitamin E.

Polyunsaturated fatty acids (PUFAs): Supplementary PUFAs, including alpha-linolenic acid (in flaxseed oil and perilla oil), gamma-linolenic acid (in borage oil, blackcurrant oil, evening primrose oil), docosahexaenoic acid, eicosapentaenoic acid and conjugated linoleic acid may increase vitamin E requirements. In most cases this can be satisfied by supplemental use of either at least 15 milligrams daily of d-alpha-tocopherol or 30 milligrams daily of d1-alpha-tocopherol.

Selenium: Selenium may function synergistically with vitamin E.

Vitamin C: Vitamin C may spare vitamin E. It, along with other antioxidants, such as glutathione, alpha-lipoic acid and coenzyme Q_{10}, are thought to be involved in a so-called antioxidant network which helps to regenerate reduced alpha-tocopherol from the tocopheroxyl radical.

FOOD

Dietary polyunsaturated fat: High polyunsaturated fatty acid intakes should be accompanied by increased vitamin E intakes to prevent their oxidation.

Olestra: The fat substitute olestra inhibits the absorption of vitamin E, as well as the other fat-soluble vitamins A, D and K, carotenoids and flavonoids. Vitamins A, D, E (alpha-tocopherol) and K are added to olestra to partly compensate for this.

HERBS

Some herbs, including garlic and ginkgo, possess antithrombotic activity. High doses of vitamin E used at the same time as these herbs may enhance their antithrombotic activity.

OVERDOSAGE

There are no reports of overdosage with vitamin E in any form.

DOSAGE AND ADMINISTRATION

There are several forms of vitamin E available commercially. These are available as nutritional supplements or in functional and fortified foods. The following table lists these forms and their common names.

Vitamin E Forms

Correct Name	*Common Name*
RRR-alpha-tocopherol	d-alpha-tocopherol
RRR-alpha-tocopheryl acetate	d-alpha-tocopheryl acetate
RRR-alpha-tocopheryl succinate	d-alpha-tocopheryl succinate
all-rac-alpha-tocopherol	dL-alpha-tocopherol
all-rac-alpha-tocopheryl acetate	dl-alpha-tocopheryl acetate
all-rac-alpha-tocopheryl succinate	d1-alpha-tocopheryl succinate (Available for research purposes only)
gamma-tocopherol	gamma-tocopherol
mixed tocopherols	mixed tocopherols
RRR-alpha-tocopheryl polyethylene glycol 1000 succinate	TPGS
all-rac-alpha-tocopheryl nicotinate	dL-alpha-tocopheryl nicotinate
mixed tocotrienols	mixed tocotrienols

For the purpose of defining dietary reference intakes (RDI) for vitamin E, the National Research Council, in its most recent report, restricted vitamin E activity to only one of the homologues of the tocopherol family, *RRR*-alpha-tocopherol. Therefore, the term alpha-tocopherol, when referring to vitamin E activity, includes only the naturally occurring form, *RRR*-alpha-tocopherol, commonly, but incorrectly, called d-alpha-tocopherol, and four out of the eight forms of synthetic alpha-tocopherol, *all-rac*-alpha-tocopherol, commonly, but incorrectly, known as d1-alpha-tocopherol. The four included forms are the 2*R* structures: *RRR*-, *RSR*-, *RRS*- and *RSS*-alpha-tocopherol. *RRR*-alpha-tocopherol, natural alpha-tocopherol (called "natural-source" alpha-tocopherol when sold commercially), has approximately twice the availability of the *all-rac* (synthetic) alpha-tocopherol and is

probably the better form for supplementation. Natural-source vitamin E supplements are called natural source rather than natural, since *RRR*-alpha-tocopherol is produced from natural gamma-tocopherol via a synthetic step.

The new RDA for alpha-tocopherol for both men and women is 15 milligrams a day. This is for natural or natural-source alpha-tocopherol (*RRR*-alpha-tocopherol). Since only four out of the eight stereoisomers of the *all-rac*-alpha-tocopherol have vitamin E activity, 30 milligrams daily of *all-rac*-alpha-tocopherol are needed to supply the RDA for the vitamin.

To estimate milligrams of 2*R*-alpha-tocopherol in a vitamin E supplement labeled in internationals units, multiply the dose by 0.45 mg/IU if the supplement is *all-rac*-alpha-tocopherol (synthetic) or by 0.67 mg/IU if the supplement is *RRR*-alpha-tocopherol (natural or natural source). Natural and natural source forms, include d-alpha-tocopherol, d-alpha-tocopheryl acetate and d-alpha-tocopheryl succinate. Synthetic forms, include d1-alpha-tocopherol, dl-alpha-tocopheryl acetate and dl-alpha-tocopheryl succinate. The same conversion factor (0.67 mg/IU) is used for all forms of natural and natural source vitamin E (alpha-tocopherol, d-alpha-tocopheryl acetate and d-alpha-tocopheryl succinate), and the same conversion factor (0.45 mg/IU) is used for all forms of *all-rac*-alpha-tocopherol (dl-alpha-tocopherol, dl-alpha-tocopheryl acetate and dl-alpha-tocopheryl succinate). One will note that the term *RRR*-alpha-tocopherol is used in this section interchangeably with d-alpha-tocopherol, and the term *all-rac*-alpha-tocopherol is used interchangeably with dl-alpha-tocopherol. The reason for this is because the incorrect terms d-alpha-tocopherol and dl-alpha-tocopherol are still the more commonly used terms. One day they won't be.

Regarding doses, vitamin E-deficiency conditions need to be managed by medical personnel.

Recommended doses for supplementation range from 100 to 400 IU daily. Supplemental vitamin E is best taken with meals.

The average intake of *RRR*-alpha-tocopherol derived from various dietary surveys ranges from about 7.5 to 10.3 milligrams daily for men and 5.4 to 7.3 milligrams daily for women. It is believed that these intake estimates may be low due to underreporting of fat and caloric intake and uncertainties about the particular fats or oils consumed. It is thought that an average daily intake of about 15 milligrams may be closer to reality, but this is not clear. The principal vitamin E form in the American diet is gamma-tocopherol. Vitamin E is present in fortified foods as the *all-rac* form.

The Food and Nutrition Board of the National Academy of Sciences has recently issued its report on dietary reference intakes (RDI) for vitamin E, as well as for some other antioxidant nutrients. In establishing the Recommended Dietary Allowance (RDA) for vitamin E, only *RRR*-alpha-tocopherol was taken into account. Other naturally occurring forms of vitamin E (beta-, gamma-, and delta-tocopherol and alpha-, beta-, gamma- and delta-tocotrienols) were not considered to meet the vitamin E requirement since they are not converted to alpha-tocopherol in humans and have significantly lower binding affinities to the alpha-tocopherol transfer protein. For establishing RDAs of vitamin E, alpha-tocopherol is defined as the natural *RRR*-alpha-tocopherol and the 2*R*-stereoisomers of synthetic vitamin E (found in supplements and fortified foods), *RRR*-, *RSR*-, *RRS*-, and *RSS*-alpha-tocopherols. The 2S-stereoisomers are excluded by this definition. All forms of supplemental vitamin E are included in calculating the Tolerable Upper Intake Level (UL).

The new RDA for vitamin E (again, defined as only *RRR*-alpha-tocopherol) for both men and women is 15 milligrams daily. To convert *RRR*-alpha-tocopherol from milligrams to International Units (IU), the conversion factor is 1.49. Therefore, 15 milligrams of *RRR*-alpha-tocopherol is equal to 22.4 IU. The UL for vitamin E is 1,000 milligrams or 1,490 IU/day expressed as *RRR*-alpha-tocopherol.

The following summarizes the DRIs for various age groups and conditions:

	Adequate Intake (AI)	
Infants		
0-6 months	4 mg/day	0.6 mg/kg
7-12 months	5 mg/day	0.6 mg/kg

	Recommended Daily Allowance (RDA)
Children	
1-3 years	6 mg/day
4-8 years	7 mg/day
Boys	
9-13 years	11 mg/day
14-18 years	15 mg/day
Girls	
9-13 years	11 mg/day
14-18 years	15 mg/day
Men	
19-30 years	15 mg/day
31-50 years	15 mg/day
51-70 years	15 mg/day
Older than 70 years	15 mg/day

Women	
19-30 years	15 mg/day
31-50 years	15 mg/day
51-70 years	15 mg/day
Older than 70 years	15 mg/day
Pregnancy	
14-18 years	15 mg/day
19-30 years	15 mg/day
31-50 years	15 mg/day
Lactation	
14-18 years	19 mg/day
19-30 years	19 mg/day
31-50 years	19 mg/day

The DV (Daily Value) for vitamin E, which is used for determining percentage of nutrient daily values on nutritional supplement and food labels, is 30 IU (International Units). This is based on the U.S. RDA for vitamin E.

The following summarizes the Tolerable Upper Intake Level (UL) for various age groups and conditions:

Children	(UL)
1-3 years	200 mg/day
4-8 years	300 mg/day
9-13 years	600 mg/day
Adolescents	
14-18 years	800 mg/day
Adults	
19 years and older	1,000 mg/day
Pregnancy	
14-18 years	800 mg/day
19 years and older	1,000 mg/day
Lactation	
14-18 years	800 mg/day
19 years and older	1,000 mg/day

D-ALPHA-TOCOPHEROL

d-Alpha-tocopherol is available as a stand-alone supplement and in the form of mixed tocopherols. d-Alpha-tocopherol is unesterified and thus much more susceptible to oxidation. It should be stored in a tightly closed, opaque bottle and in a cool, dry place. Typical doses for supplementation range from 100 to 400 IU daily. d-Alpha-tocopherol is also available for cosmetic application as an antioxidant and moisturizer. Some are hypersensitive to topical d-alpha-tocopherol and may develop dermatitis from its use. To convert from International Units (IU) of d-alpha-tocopherol to milligrams, multiply by 0.67. To convert from milligrams of d-alpha-tocopherol to IU, multiply by 1.49.

D-ALPHA-TOCOPHERYL ACETATE

d-Alpha-tocopheryl acetate is available as a stand-alone supplement and in multivitamin preparations. Since the acetate group protects the hydroxyl group of the chromanol ring against oxidation, it is a more stable form than d-alpha-tocopherol, the free or unesterified form.

Typical doses for supplementation range from 100 to 400 IU daily (as d-alpha-tocopherol). To convert from International Units (IU) of d-alpha-tocopheryl acetate to milligrams, multiply by 0.67. To convert milligrams of d-alpha-tocopheryl acetate to IU, multiply by 1.49.

DL-ALPHA-TOCOPHERYL ACETATE

dl-Alpha-tocopheryl acetate is available as a stand-alone supplement and in combination products. Typical doses for supplementation range from 100 to 400 IU daily (as alpha-tocopherol). To convert from International Units (IU) of d1-alpha-tocopheryl acetate to milligrams, multiply by 0.45.

D-ALPHA-TOCOPHERYL SUCCINATE

d-Alpha-tocopheryl succinate is available as a stand-alone supplement and in combination vitamin preparations. Since the succinate group protects the hydroxyl group of the chromanol ring against oxidation, it is a more stable form than d-alpha-tocopherol, the free or unesterified form.

Typical doses for supplementation range from 100 to 400 IU daily (as d-alpha-tocopherol). To convert from International Units (IU) of d-alpha-tocopheryl succinate to milligrams, multiply by 0.67. To convert milligrams of d-alpha-tocopheryl succinate to IU, multiply by 1.49.

D1-ALPHA-TOCOPHERYL SUCCINATE

d1-Alpha-tocopheryl succinate is not available as a nutritional supplement. The reason for this is that it does not crystallize well but forms a paste. However, it is available for research purposes.

MIXED TOCOPHEROLS

Typical doses for supplementation of high-alpha-mixed-tocopherols range from 50 to 250 milligrams daily, determined as d-alpha-tocopherol. Typical doses for supplementation of low-alpha-mixed-tocopherols are around 200 milligrams daily, determined as d-gamma-tocopherol.

Since the tocopherols are present in their unesterified forms, forms which are much more susceptible to oxidation than esterified forms, mixed tocopherols should be stored in a tightly closed, opaque bottle and in a cool, dry place.

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Vitamin E Phosphate

DESCRIPTION

Vitamin E phosphate is the phosphate ester of d-alpha-tocopherol. It was one of the first vitamin E derivatives studied, in the 1940s, but it garnered little attention until recently, when it entered the dietary supplement marketplace as one of the available forms of vitamin E (See Vitamin E).