

The Emerging Role of Vitamins as Antioxidants

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The recommended dietary allowances for vitamins are designed to estimate the levels of intake needed to prevent known deficiency states in most healthy people. Evidence is now accumulating that some vitamins may have health-promoting benefits in amounts higher than the current recommendations. The antioxidant properties of vitamins may play a role in treating or preventing a variety of disorders, including atherosclerosis, age-related cataracts and macular degeneration, and some cancers. This article reviews the possible risks and benefits of high intakes of antioxidant vitamins, including the controversy about supplementation. (Arch Fam Med. 1994;3:809-820)

It has now been about 100 years since the discovery that vitamin deficiencies were responsible for many common diseases. For example, niacin deficiency is responsible for pellagra; vitamin C (ascorbic acid) deficiency, scurvy; vitamin D deficiency, rickets (in children) and osteomalacia (in adults); and thiamine deficiency, beriberi. Relatively small amounts of these vitamins (termed micronutrients) are necessary to prevent these deficiency states; for example, 10 mg/d of vitamin C will prevent scurvy. The recommended dietary allowances (RDAs) are the result of a rigorous attempt to scientifically determine how much of each vitamin most healthy people need to consume to prevent the known and agreed on classic deficiency states.¹ There is now a growing recognition, however, that some vitamins may have important disease-preventing and health-promoting effects at intakes higher than the RDAs (**Table**). That is, the amount of a vitamin necessary for optimum health may be higher than that needed to prevent deficiency states.² The RDAs are not minimal requirements, and they do not claim to represent optimal intakes.¹ This makes their utility confusing for

the practicing clinician. The RDAs were designed for population groups; there are many conditions that require adjustments for any specific individual. In addition, the RDAs continue to include elderly persons within the category of all persons above 51 years of age, which may not be appropriate for certain vitamins and minerals.

It is difficult to find a balanced assessment of the potential antioxidant role for vitamins. Definitive and incontrovertible experimental conclusions are still lacking and may be years away. This article is designed to clarify what is currently known about the emerging role of antioxidants in health and disease in adults, particularly the role of vitamins as antioxidants, and to allow physicians to intelligently counsel adult patients who have questions about high-dose vitamin intake or may already be consuming vitamins for their antioxidant properties. This article concerns antioxidative effects and does not cover all potential positive effects of high-dose vitamin intake.

THE DAMAGING EFFECTS OF OXIDATION

Oxygen is essential for human life, and oxygen therapy has many benefits. However, like most other chemicals, it can also be

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Recommended Dietary Allowances (RDAs) for Vitamins With Antioxidant Properties in Persons 15 Years of Age and Over*

Vitamin (Supplement)	RDA	
	Men	Women
Vitamin A (retinol)†	1000 µg	800 µg
Vitamin E (tocopherol)‡	10 µg	8 µg
Vitamin C (ascorbic acid)	60 mg	60 mg

*Excludes pregnant or lactating women. There are no RDAs for β-carotene or other carotenoids. From the National Research Council.¹

†Measured as retinol equivalents (1 retinol equivalent is 1 µg of retinol or 6 µg of β-carotene [3.33 IU]).

‡Measured as α-tocopherol equivalents (1 α-tocopherol equivalent is 1 mg of d-α-tocopherol).

toxic. Environments with high levels of oxygen are known to injure the eyes (retinopathy of prematurity), lungs (adult respiratory distress syndrome, atelectasis, and bronchopulmonary dysplasia), and central nervous system (seizures).^{3,4} In addition, potentially toxic intermediate compounds are generated as oxygen is metabolized normally within the body.⁵ As electrons are added to oxygen (oxygen reduction), free radicals (possessing one or more unpaired electrons that make them very reactive to other molecules) and other unstable compounds are generated (**Figure 1**).⁶ Subcellular organelles, membranes, and various enzymes in all tissues, including the cytochrome P-450 system in the liver, can reduce oxygen and make free radicals. Highly reactive oxygen metabolites are also generated by the mitochondrial respiratory chain, by detoxification of xenobiotics by cytochromes, and during metabolism of arachidonic acid that generates prostaglandins and leukotrienes.⁷ Cigarette smoke, ozone, carbon tetrachloride, and ionizing radiation appear to be toxic in part because of free radical generation.^{8,9}

The controlled production and release of free radicals allow phagocytes to kill invading organisms and may be successfully exploited in some forms of cancer chemotherapy.³ However, free radicals from the environment or generated within the body can also cause damage.⁹ When reactive electrons are passed from mol-

ecule to molecule, a cascade of injury can result. The body has many natural defenses; but, over time or under stressful conditions, these defenses may wane or be overwhelmed. The accumulation of free radical damage can lead to injury, disease, or aging phenomena.¹⁰⁻¹⁵ For example, strenuous physical exercise can cause free radical-mediated muscle cell injury that may be prevented by antioxidant administration.^{16,17} Free radicals can react with fatty acids in cell membranes to produce lipid peroxides, which in turn inhibit cellular enzymes or decompose into other reactive metabolites.⁴ Lipid peroxidation can lead to accumulation of lipofuscin in amounts found inversely related to longevity. Free radicals also impair generation of adenosine triphosphate, damage DNA, depolymerize mucopolysaccharides, and inactivate enzymes by protein sulfhydryl oxidation.⁸ Free radicals may play a role in cancer or immune disorders and have been implicated in over 50 diseases.¹⁵

Both intracellular and extracellular protective antioxidant systems exist.^{18,19} Enzymes such as superoxide dismutase, catalase, and glutathione peroxidase are important intracellularly. Antioxidants can also be divided into those that are water soluble (nonenzymatic) (vitamin C, uric acid, bilirubin, glutathione, albumin, ferritin, transferrin, and ceruloplasmin) or lipid soluble (vitamin E [tocopherol], carotenoids [including β-carotene], and ubiquinone [coenzyme Q]). This dichotomy helps predict or explain their

different modes of action.^{4,6,8,18-21} Estrogens like estriol and estradiol-17β are naturally occurring antioxidants that may have the capacity to protect lipids from oxidation, while corticosterone and cortisone have mild prooxidant properties.^{22,23} Various foods (eg, soybeans, garlic, and tea) also have antioxidant properties.²⁴⁻²⁶

OXIDATION AND ATHEROGENESIS

Oxidative damage appears to play a significant role in atherogenesis (**Figure 2**).²⁷⁻²⁹ Oxidized low-density lipoprotein (LDL) cholesterol and probably other oxidized lipoproteins such as small, dense, LDL particles and lipoprotein (a), unlike unmodified LDL, can bypass a down-regulation protective system and become actively taken up by special scavenger receptors on monocytes and macrophages in the subendothelial space of blood vessel walls. Oxidized LDL within the vessel wall eventually leads to foam cell formation, attracting monocytes and inhibiting macrophage movement out of the vessel wall, which further induces endothelial cell damage and begins atherogenesis.^{30,31} Glycation (or glycosylation) of proteins, as occurs in diabetes mellitus, can accelerate vascular injury caused by oxidized LDL.^{32,33} Intervention directed at reducing the oxidation of LDL may modify the process of atherogenesis and lesion development.³⁴ The susceptibility of LDL to lipid oxidation in vitro is associated with the severity of atherosclerosis.³⁵ Probucol, a drug found to lower LDL cholesterol independent of the LDL receptor, also has lipophilic antioxidant activity that appears to delay lipid peroxidation and reduce atherosclerotic lesion development (independent of its effect of lowering cholesterol levels).³⁶ A recent National Institutes of Health consensus conference concluded that clinical trials of antioxidant supplementation should be encouraged based on the promising evidence now available.³⁷

The LDL particle can also carry molecules of vitamin E, β -carotene, and coenzyme Q that may counteract or delay lipid peroxidation.^{19,38} Vitamin C may intercept oxidants in the aqueous phase before they can attack and damage lipids,³⁹ and it can also modify LDL to increase its resistance to metal ion-dependent oxidation.⁴⁰ High-dose tocopherol (vitamin E) supplementation (but not beta carotene) decreases LDL susceptibility to oxidation *in vitro*.⁴¹

Considerable synergism exists among antioxidants. For example, vitamin C helps regenerate oxidized vitamin E back to its reduced (antioxidant) state.⁴² In turn, oxidized vitamin C can itself be regenerated via glutathione, using selenium as a cofactor.^{19,43} Ascorbic acid supplementa-

tion can maintain red blood cell glutathione, an important intracellular antioxidant, in its effective state.⁴⁴

Observational and epidemiologic studies strongly suggest, but do not conclusively prove, that antioxidant intake is inversely associated with cardiovascular disease and mortality.^{45,46} Population studies suggest that α -tocopherol serum levels show a stronger correlation with ischemic heart disease than either cholesterol levels or diastolic blood pressure.⁴⁵ A cohort study of 11 000 people found a substantial reduction in cardiovascular and total deaths in persons with higher intakes of vitamin C.⁴⁷ Those persons who took ascorbic acid supplements and had a reasonable dietary intake of vitamin C did better than those who just consumed vitamin C in their diet. A 12-year follow-up of the Prospective Basel (Switzerland) Study found that either low plasma carotene or vitamin C levels are associated with a significant increase in the risk for ischemic heart disease and, if both are low, cerebrovascular stroke.⁴⁸

In an 8-year follow-up of 80 000 women in the Nurses' Health Study, those in the top fifth of the cohort with respect to vitamin E intake (averaging 200 IU/d, mostly consumed as a supplement) had a relative risk for major coronary artery disease of 0.66 after adjusting for age and smoking, compared with those in the lowest fifth (consuming about 3 IU/d).⁴⁹ As expected, there was little apparent benefit to the short-term use of tocopherol, but those who took supplements for more than 2 years had a relative risk of 0.59. Although not statistically significant, there were trends

toward a reduction in risk for mortality from cardiovascular causes and ischemic stroke, as well as decreased risk for coronary artery surgery and overall mortality.

An evaluation involving almost 40 000 men in the Health Professionals Follow-up Study after 5 years found a lower risk for coronary disease among men with higher vitamin E intakes.⁵⁰ Those consuming more than 60 IU/d of vitamin E had a relative risk of 0.64 compared with those consuming less than 7.5 IU/d. Compared with men who did not take tocopherol supplements, men who took at least 100 IU/d for at least 2 years had a relative risk of coronary disease of 0.63. Without supplements, the top quintile of the cohort consumed only 8 IU/d of vitamin E. Carotene intake was inversely associated with the risk for coronary heart disease in current or former smokers but not among those who had never smoked. A high intake of vitamin C was not associated with a lower risk for coronary disease in either this study or the Nurses' Health Study.⁴⁹

Among 333 physicians participating in the Physicians' Health Study who had evidence of coronary artery disease (chronic stable angina or coronary revascularization or stroke), preliminary analysis has found that the group taking beta carotene supplements (50 mg every other day) had 40% fewer coronary events than the control group.^{46,51,52}

While antioxidants appear to be protective against cardiovascular disease, prooxidants likely increase the risk. The best example is iron. Iron is intimately associated with aerobic metabolism. It is necessary in the transport, storage, and use of oxygen, as well as being an essential part of oxidases, oxygenases, and antioxidant enzymes.⁵³ However, it also has the ability to generate oxidants (Figure 1), and therefore the body tries to sequester iron in poorly reactive forms (eg, transferrin, hemosiderin, and ferritin). The exact role of iron in coro-

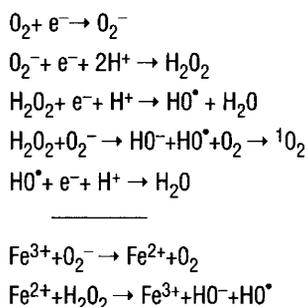


Figure 1. Mechanisms for generation of free radicals and reactive oxidative by-products in normal metabolism. Superoxide ion (O_2^-) and hydroxyl radical (HO^\bullet) are reactive free radicals. Hydrogen peroxide (H_2O_2) can readily cross cell membranes and mediate oxidative damage. Molecular oxygen (O_2) can decompose to singlet oxygen (1O_2), another reactive compound. Iron also plays a significant role as an oxidizing agent. Raised dot indicates unpaired electron; e^- , electron transfer; H^+ , hydrogen ion; H_2O , water; Fe^{2+} , ferrous iron; and Fe^{3+} , ferric iron. Further discussion can be found in Stogner and Payne,⁴ 1992.

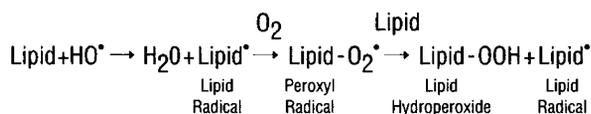


Figure 2. Mechanism of lipid peroxidation. The hydroxyl radical (HO^\bullet) can initiate lipid oxidation, which creates intermediate metabolites that cause an autocatalytic chain reaction of lipid peroxidation (lipid-OOH), resulting in membrane damage and, eventually, cell death. O_2 indicates oxygen; H_2O , water; and raised dot, unpaired electron. Further discussion can be found in Marzatico and Cafe,¹⁵ 1993.

nary heart disease remains controversial. However, ferritin levels do reflect the body's iron load, and a high ferritin level has been found to be associated with an increased relative risk for myocardial infarction.⁵⁴ A recent analysis of the ongoing Health Professionals Follow-up Study found that heme iron intake, but not total iron intake, was associated with an increased serum level of ferritin as well as increased incidence of fatal coronary disease and nonfatal myocardial infarction.^{55,56} One reason that women are protected from cardiovascular disease until after menopause may be their low iron stores resulting from menstruation.⁵⁷

AGE-ASSOCIATED EYE DISEASE

The prevalence of cataract formation in the lens of the eye increases with age. Senile cataract is found in over 45% of persons above 75 years of age^{58,59} and may be associated with markedly decreased vision and quality of life. Cataract removal is also one of the most commonly performed surgical procedures in the United States. Oxidation may cause or be associated with cortical and nuclear cataract, possibly owing to the formation of free radicals from the hydrogen peroxide present in aqueous humor, near-ultraviolet radiation, and/or glucose oxidation in diabetes mellitus.^{58,60,61}

Glutathione and vitamin C are present in the lens of the eye, as are the antioxidant enzymes glutathione peroxidase, catalase, and superoxide dismutase.⁶² Animal studies suggest an age-related decline in ascorbate levels in the lens. Levels of ascorbic acid are low or absent in cataractous lenses.⁶³ There is a statistical association between supplementary ascorbic acid and tocopherol intake over the previous 5 years and decreased risk for senile cataract of 2½ times.⁶⁴ Persons who consume more than 300 mg/d of ascorbic acid or 400 IU/d of tocopherol have about one third the risk of developing cataracts.⁵⁹ Persons who consumed less than 125 mg/d of

ascorbic acid over the previous year have a fourfold greater probability of having any cataract and an 11 times greater risk for having a posterior subcapsular cataract than those who consumed more than 490 mg/d of ascorbic acid.⁶⁵ Low serum concentrations of α -tocopherol and β -carotene are also associated with an increased incidence of senile cataract.⁶⁶ Similar associations have been found with vitamin A,⁶⁷ carotenoids,^{65,67} and multivitamins^{68,69} and consumption of fewer than 3½ servings of fruits and vegetables daily.⁶⁵

Not all studies find the same associations. An analysis of the Nurses' Health Study⁶⁷ found that long-term multivitamin intake was not protective against cataracts, but long-term vitamin C intake (>10 years) was, perhaps because multivitamins contain relatively low levels of vitamin C. Since spinach consumption, but not carrot intake, was associated with a lower relative risk, carotenoids other than β -carotene may be more protective.

A study of patients with neovascular age-related macular degeneration found that persons with higher carotenoid levels had one half to one third the risk of macular degeneration compared with control patients.⁷⁰ While no statistically significant protective effect was found for vitamins C or E or selenium individually, an antioxidant index combining all micronutrients showed significant reductions in risk with increasing levels of the index. In addition, persons with age-related macular degeneration have much lower levels of several antioxidant enzymes in their cells compared with age-matched controls.⁷¹

On the other hand, increased levels of copper and iron, reported in aging lenses and cataracts, may oxidize ascorbate and produce metabolites that induce cataract formation. Therefore, under certain conditions, the antioxidant-prooxidant balance can tip, and ascorbate may increase protein modifications that produce cataracts.⁶³

CARCINOGENESIS

Free radicals and oxidant damage appear to play a major role in some forms of cancer.⁷² Epidemiologic studies have generally shown a protective effect of consumption of fruits and vegetables, foods rich in vitamin C and β -carotene, on many kinds of cancers.^{2,73,74} To what degree the antioxidant properties of vitamins are specifically responsible for these effects is unclear. For example, ascorbate, unrelated to its antioxidant capabilities, may inhibit stomach cancer by reducing levels of nitrous acid and inhibiting the formation of carcinogenic N-nitroso compounds in the gastrointestinal tract. Because carotenoids, folic acid, vitamin C, soluble and insoluble fiber, and various phytochemicals are frequently in the same foods, it is difficult to document which dietary factor is most responsible or how synergetic the interactions are.^{75,76} In addition, persons who consume this type of diet may have other lifestyle behaviors that also lower their risk.⁷⁷

β -Carotene and/or preformed vitamin A intake have been most strongly associated with a decreased risk for lung cancer and upper gastrointestinal tract cancers.^{75,78-81} The association is less consistent with prostate and breast cancer.⁸²⁻⁸⁵ A 12-year follow-up of almost 3000 men in Basel revealed a significant inverse relationship between carotene levels on entering the study and subsequent cancer, particularly lung and stomach cancers.^{48,80} A prospective study of nearly 90 000 female registered nurses found that large intakes of vitamin C or E did not protect women from breast cancer, but a low intake of all forms of vitamin A (<6630 IU/d) was associated with an increased risk for the disease.⁸⁵ Women who consumed little vitamin A from food, but who took at least 10 000 IU from supplements, had about half the risk of women who did not take supplements. On the other hand, an analysis combin-

ing the data of 12 case-control studies of diet and breast cancer found a significant inverse association between vitamin C intake and breast cancer.⁸⁶ There is also an inverse relationship between vegetable consumption and the risk for breast cancer.⁴⁹

Antioxidant vitamin and mineral supplementation over a 6-year period (beta carotene, 50 mg; tocopherol, 30 mg; and selenium sulfide, 50 µg) in 15 000 people in ru-

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ral China, which has one of the world's highest rates of upper gastrointestinal tract cancer, was associated with a reduction in total mortality, primarily owing to a decrease in stomach cancer.⁸⁷ The incidence of heart disease in this population is minuscule. Vitamin C has also been associated with a decreased risk for many gastrointestinal tract cancers, breast cancer, and lung cancer.^{73,86}

In a study of 209 individuals who were followed up for an average of 18 months after removal of adenomatous polyps and randomized to receive antioxidant vitamins (axerophthol palmitate, equivalent to 30 000 IU/d of vitamin A activity; ascorbic acid, 1 g/d; and *dl*- α -tocopherol, 70 mg/d), 20 g/d of lactulose, or nothing, percentages of recurrences of adenomas were 5.7% for the vitamin group, 14.7% for the lactulose group, and 35.9% for the untreated group.^{88,89}

Not all studies are uniformly positive. Some studies have reported a relationship between vitamin E status alone and certain cancers, although this has not been uniform.^{79,90,91} For example, an inverse association has been found be-

tween vitamin E status and lung cancer occurrence in nonsmokers but not among smokers.⁹² Results from one recent case-control study examining dietary factors and lung cancer in nonsmokers suggest that dietary β -carotene (but not retinol), raw (not processed) fruits and vegetables, and tocopherol supplements are significantly associated with risk reduction.⁹³

A randomized, double-blind, placebo-controlled primary prevention trial of white male smokers (aged 50 to 69 years) undergoing analysis following 5 to 8 years of supplementation found *no* protective effect of 20 mg/d of beta carotene and 50 IU/d of α -tocopherol. This study was surprising in that it showed a higher incidence of lung cancer and ischemic heart disease among men who received beta carotene but fewer cases of prostate cancer in those who received α -tocopherol.⁹⁴ Other long-term prospective studies are now in progress to look at vitamin chemoprevention (including natural and synthetic analogues) in cancer.⁹⁵⁻⁹⁷

VITAMIN TOXICITY

It should be expected, because diseases can have multifactorial causes, that some vitamin intervention studies have ambiguous results or have not shown a positive influence. Indeed, some animal and human studies have even shown a disease-enhancing, prooxidant effect for some vitamins under some conditions.^{63,94,98} This should temper unbridled enthusiasm but is usually ignored by proponents of vitamin supplementation. Vitamins do have known toxicity. Of all the antioxidant vitamins, vitamin A is easily the most dangerous. Hypervitaminosis A can occur both acutely and after long-term ingestion. Acute toxic effects present as headaches, drowsi-

ness, irritability, dizziness, nausea, vomiting, and diarrhea. Elderly people with normal kidney and liver functions may tolerate a daily dose of 50 000 retinol equivalents (RE) for up to 6 months, while younger adults have taken 300 000 RE/d (as retinyl palmitate) for 12 months with few adverse effects.⁹⁹ However, toxic effects have been seen in intakes of as little as 15 000 RE/d.¹⁰⁰ Chronic toxic effects may classically, and nonspecifically, present as desquamation and redness of the skin and mucous membranes, disturbed hair growth, loss of appetite, fatigue, irritability, thyroid suppression, cerebrospinal fluid pressure elevation (producing symptoms similar to those of pseudotumor cerebri), and elevation of liver enzyme levels. Toxic effects increase in the presence of renal failure and preexisting hepatic dysfunction and decrease in the presence of excess levels of vitamin E. Hypercalcemia and a negative calcium balance similar to that seen with hypervitaminosis D may occur, but excess retinol levels affect the organic bone matrix, whereas excess vitamin D levels cause dissolution of the mineral matrix.¹⁰⁰⁻¹⁰²

Toxic effects of vitamin E may present as diarrhea or fatigue, but even huge intakes are usually well tolerated.^{103,104} The major potential side effect may be that vitamin E can potentiate warfarin sodium (Coumadin) and increase the risk for bleeding in persons receiving this anticoagulant. Under certain circumstances, vitamin E has been found to promote skin tumorigenesis in animal studies.¹⁰⁵ Therefore, prolonged topical exposure to antioxidants like vitamin E should be discouraged until more is known.

Vitamin C can increase the absorption of iron, and supplementation should not be recommended in persons at risk of iron overload (eg, persons with thalassemia or hemochromatosis) without close supervision. It is possible that, in the presence of appropriate levels of copper

or iron, vitamin C may act as a prooxidant⁶³; whether this finding is clinically significant is unknown. However, in general, ascorbic acid supplementation causes no problems, even in older persons.^{106,107} Vitamin C may also affect results of fecal occult blood tests as well as some urinary and blood glucose tests. Abruptly discontinuing high vitamin C intake may make some persons deficient, but this result is probably rare.^{106,108} There are few acute toxic effects of high-dose vitamin C ingestion; occasionally diarrhea can occur.

VITAMIN A AND CAROTENE

Most total vitamin A intake in the United States comes from liver, carrots, eggs, vegetable-based soups, whole-milk products, and fortified food products.¹⁰⁹ While vitamin A intake decreases with age, hypovitaminosis A in adults is uncommon, even in the very old. There is evidence that vitamin E and C status declines in many older individuals, while retinol status usually does not.^{110,111}

Vitamin A may refer to two different groups of substances. One is retinol, or preformed vitamin A, found in dairy products and animal and fish meats. Similar forms include synthetic vitamin A analogues such as all-*trans*-retinoic acid and 13-*cis*-retinoic acid, which can be converted to retinol within the body. Vitamin A is necessary for maintaining the integrity of epithelial tissues (skin, cornea, gastrointestinal tract, lungs, urinary tract, etc). It is also required for proper retinal function, immune function, and growth.¹¹²

Vitamin A activity in foods is currently expressed as RE; 1 RE is defined as 1 μg of all-*trans*-retinol and roughly estimated to be equivalent to 6 μg of all-*trans*- β -carotene or 12 μg of other provitamin A carotenoids.^{1,113} International units are often used for both vitamin A and the carotenoids and are frequently

confusing and inaccurate. One RE equals 3.33 IU (or IU_a) of preformed vitamin A (retinol) and 10 IU (or IU_c) of provitamin A carotenoids. Despite this, food composition tables often assume that 1 IU_a equals 1 IU_c. Therefore, consumers and physicians should use food composition tables only as rough guides to approximate vitamin A and carotenoid quantities in specific foods.

Using the retinol equivalent to determine the antioxidant activity of foods is also misleading, since retinol is generally not an antioxidant. The current RDA is 1000 μg RE in men and 800 μg RE in women (Table). However, it has been proposed that the RDA for vitamin A is too high and should be reduced to 700 and 600 μg RE for men and women, respectively.^{113,114} Except at the extreme ranges, retinol levels correlate poorly with vitamin A status and are affected by many non-nutritional diseases. Hepatic levels of vitamin A appear unchanged in adults up to advanced age. Retinol absorption increases with age in some animals, but it is not known whether the absorption rate in humans changes with age.

Preformed vitamin A enters the intestinal cell by a carrier-mediated mechanism. In contrast, carotenoids are passively absorbed. Vitamin A is transported via the lymphatics to the liver and stored as the retinyl ester. From the liver, which contains 95% of the body's vitamin A stores, it can be released as retinol bound to retinol-binding protein and prealbumin and transported to various tissues.¹¹⁵

The other form of vitamin A is carotene (provitamin A), found primarily in plants, especially carrots and dark green leafy vegetables. The color intensity of a fruit or vegetable, however, does not reliably indicate its provitamin A content.¹ β -Carotene usually makes up the largest fraction of provitamin A in foods. Carotene is also found in yellow animal fat and dairy products. Of the approximately 500 or so ca-

rotenoids, only 50 to 60 are known to be precursors of vitamin A, but many more may act as antioxidants.¹¹³ It is difficult to interpret tables of carotenoid contents of foods since neither REs nor β -carotene content may fully reflect the significant biologic antioxidant activity. In fact, γ -carotene is a better antioxidant than β -carotene.¹¹⁶ There are no RDAs for the carotenoids. Because of their many conjugated double bonds, carotenoids can act as antioxidants by quenching the unpaired electrons of free radicals and diverting free radical damage to themselves rather than other molecules (like LDL cholesterol). β -Carotene and other carotenoids like lycopenes may be protective of the body independent of any provitamin A role.¹¹⁷ β -Carotene can be converted to retinoic acid without being converted into retinol. This retinoid effect may promote cell differentiation by binding to and turning on genes. β -Carotene may also improve cell-cell communication.

Only about 15% of β -carotene is absorbed by the body, and only 20% of that absorbed is ultimately converted to retinol. Therefore, except for reversible carotenoderma, an orange-yellow skin discoloration most prominent in palms and soles but not sclera, which may be seen with an ingestion of 30 mg/d of β -carotene,¹¹⁸ side effects of β -carotene ingestion are rare. Most of the β -carotene in the blood is associated with LDL cholesterol and stored primarily in fat rather than in the liver.

VITAMIN C

The current RDA for vitamin C in adults is 60 mg (Table). It has been argued that this amount could be safely reduced.¹¹⁹ In contrast, body pools are saturated at 100 to 150 mg/d in men and 80 to 100 mg/d in women, suggesting to some that the RDA should be higher.¹²⁰ The RDA for vitamin C was not formulated with respect to its antioxidant properties.

POTENTIAL ROLES FOR ANTIOXIDANTS

ANTIOXIDANTS AND CENTRAL NERVOUS SYSTEM INJURY

The brain may be particularly vulnerable to oxidative stressors because of its limited capacity for regeneration, high concentrations of polyunsaturated fatty acids and iron, and a relative deficiency in antioxidant protective mechanisms.¹⁵ It has been postulated that some neurodegenerative disorders, such as Parkinson's disease, may be slowed by the use of antioxidants.¹⁴¹⁻¹⁴⁴ However, a multicenter study of *l*-deprenyl (selegiline hydrochloride, an inhibitor of monoamine oxidase B that decreases hydrogen peroxidase production during brain monoamine catabolism) and vitamin E did not find that oral vitamin E at high doses (2000 IU/d) slowed functional decline or clinically improved patients with Parkinson's disease.¹⁴⁵

However, a familial variant of amyotrophic lateral sclerosis is linked to defective synthesis of the endogenous antioxidant, superoxide dismutase, suggesting that this chronic neurodegenerative disease may be related to the production of reactive oxidant metabolites in the brain.¹⁴⁶ In addition, high doses of vitamin E (1600 IU/d) may be useful in treating tardive dyskinesia.¹⁴⁷

Acute central nervous system injury can be exacerbated by oxygen radical formation from arachidonic acid, catecholamine and hemoglobin oxidation, leaking mitochondria, and infiltrating neutrophils.^{15,148,149} These free radicals, in turn,

can initiate peroxidation of neuronal, glial, and vascular cell membranes and myelin, catalyzed by the presence of iron. There is a strong correlation between the ability to inhibit central nervous system tissue peroxidation and neurologic recovery. The steroid methylprednisolone has antioxidant efficacy independent of its glucocorticoid action and, when administered in high amounts, has improved recovery after spinal cord injury. Novel 21-aminosteroids now being developed have antioxidant activity surpassing methylprednisolone and have been shown to be quite effective in animal models of brain and spinal cord injury.

REPERFUSION INJURY

Postischemic tissue injury results from the additive effects of both the ischemia and subsequent reperfusion. The reperfusion that follows tissue ischemia (eg, heart or bowel infarction or organ transplantation) generates large quantities of toxic oxygen metabolites, such as superoxide anion (Figure 1), from activated inflammatory cells, xanthine oxidase, heme protein, and disrupted mitochondria. This overwhelms antioxidant defense mechanisms, paradoxically producing further injury (including capillary permeability and endothelial cell lysis).^{5,150-153} The prostaglandin synthesis and the autoxidation of catecholamines accompanying reperfusion may also generate free radicals. Studies are in progress to examine whether tissue injury can be moderated by preventing free radical generation, directly scavenging free radicals, or preventing increased tissue damage by neutrophils.^{5,7,8}

Vitamin C deficiency is common in general malnutrition and many frail, elderly populations.¹²¹⁻¹²³ The pharmacokinetics of vitamin C do not appear to change with age, although higher intakes of ascorbic acid are needed in older men than older women to attain the same plasma concentrations, probably owing to higher renal tubular reabsorption in women.

Tables from the US Department of Agriculture provide L-ascorbate content only; biologically active dehydroascorbate present in foods may provide an unrecognized additional vitamin C source.¹ Vegetables and fruits contain the highest concentrations of vitamin C; meats, fish, poultry, eggs, and dairy products contain some; and grains contain none. In the United States, most ascorbate is supplied by citrus fruits, potatoes, and other vegetables.¹ Vitamin C is eas-

ily destroyed by heat and oxygen or lost in cooking water.

Bioavailability of vitamin C is inversely related to the amount as well as the form ingested. Sustained-release capsules allow higher absorption than standard pills.¹²⁴ Smoking lowers vitamin C levels, and smokers require a higher intake to achieve plasma levels comparable with those of nonsmokers,¹²⁰ perhaps because of increased metabolism. Absorption does not appear to change with age.^{124,125}

VITAMIN E

Vitamin E is the generic term for a group of chemicals (tocopherols and tocotrienols) originally discovered to affect reproduction in the rat.¹²⁶ It was given the letter E to follow vitamin D and the name tocopherol from the Greek word *tokos*, for child-

birth, and *pherin*, to bring forth.¹²⁶ α -Tocopherol is considered the most active compound, but other forms of tocopherols may also have significant biologic functions. The RDA for vitamin E is 10 mg (natural α -tocopherol equivalents) for men and 8 mg for women (Table). Although the synthetic form of α -tocopherol has 74% of the activity of naturally occurring vitamin E,¹ both the natural and synthetic forms provide equal antioxidant protection to LDL.¹⁰⁴ International units are still frequently used; 1 mg of natural α -tocopherol (one α -tocopherol equivalent) equals about 1.1 to 1.5 IU, while 1 mg of synthetic α -tocopherol equals 1 IU.¹ β -Tocopherol has one half of the activity of natural α -tocopherol; γ -tocopherol has one tenth of the activity.¹

Large losses of tocopherols can occur during processing, storage,

and preparation of food. The richest sources in the American diet are common vegetable oils and products made from them (eg, margarine and shortening).¹ Western diets contain much more γ -tocopherol than α -tocopherol, but α -tocopherol appears to be much better absorbed and accounts for most of the total serum vitamin E concentration.¹²⁷ Meats, fish, animal fats, fruits, and vegetables have little vitamin E.

Vitamin E decreases platelet adhesion, which does not depend on its antioxidant properties and may be protective in thromboembolic disease.¹²⁸ It also enhances cell-mediated immunity in healthy elderly persons,^{129,130} and antioxidants may retard some of the age-related changes in the immune system.¹³⁰ The role of vitamin E in intermittent claudication syndromes remains unclear.¹³¹

Clinical vitamin E deficiency syndromes are not well recognized in adults, although peripheral neuropathy, hand myopathy, and cardiomyopathy may occur in association with severe fat malabsorption.^{127,132}

TO SUPPLEMENT OR NOT?

The RDAs were developed to prevent classic vitamin deficiencies and deliberately do not reflect other possible health-promoting benefits of vitamins. Therefore, they cannot be used as a gold standard regarding vitamin use to optimize health. The Second National Health and Nutrition Examination Survey of about 12 000 adults found that 17% had eaten no vegetables and 41% no fruit on the date of the survey; only one fourth had eaten a fruit or vegetable rich in vitamin A or C; and only 10% consumed the recommended five daily servings of fruits and vegetables.¹³³ On the other hand, many vegetarians and nonvegetarians consume nutritional supplements with few adverse consequences.⁷⁷

While the data so far support the association of antioxidant consumption with positive health benefits, many questions remain un-

answered, particularly about supplementation.^{37,134-137} For skeptics, increasing consumption of fruits and vegetables and decreasing saturated fat intake¹³⁸ (and perhaps partially hydrogenated fat intake as well¹³⁹) would be the most conservative approach. However, experienced clinicians know the difficulty of changing people's eating habits. Therefore, this approach is also likely to be the least acceptable or possible or successful for many high-risk individuals.¹⁴⁰ Recent surveys in the media have suggested that people are increasingly reversing previously healthy diets and lifestyles. For clinicians who consider nutritional supplementation a reasonable additional intervention, risk factors for diseases most likely to respond to antioxidants, as well as potential toxic effects, should be explored with each patient to tailor supplements appropriately and reinforce the importance of other risk factor interventions (eg, exercise, fat reduction, weight control, and reduction of environmental toxin exposures such as alcohol and tobacco use). There are many intervention studies in progress that will continue to clarify new roles for all vitamins—not just those with antioxidant properties—and the most appropriate uses for supplementation. Physicians, dietitians, and other health care professionals need to continually reinforce the importance of good nutrition in health promotion and to use nutritional interventions appropriately in high-risk patients.

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