A DOCTOR'S OVERVIEW OF FREE RADICALS AND FOUR SYNERGISTIC ANTIOXIDANTS

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As you read this, there is a raging battle going on inside your body. Unstable molecules called *free radicals* are attacking cells and tissues; meanwhile, the body is unleashing substances called *antioxidants* to ward off these attackers and repair itself.

Free Radicals

What is a free radical? Ironically, oxygen—essential to life—is the dangerous culprit. When oxygen molecules are stripped of one or more electrons in their outer orbits and are left with unpaired electrons, they become very unstable and highly reactive.

In a process called oxidation, the stripped oxygen molecules, called free radicals, aggressively attack other stable molecules and snatch away their electrons. The formerly stable molecules, after having their electrons stolen, then become free radicals themselves. In the ensuing chain reaction, the cascading numbers of free radicals may overwhelm the body's defenses and inflict lethal damage.

Free radicals have been implicated in more than 60 diseases, including coronary and blood vessel diseases, cancers, cataracts, gastrointestinal diseases, and the aging process itself. Reducing the body's exposure to free radicals can therefore potentially reduce the risk or likelihood of many health problems.

The Source of Free Radicals

The body itself normally produces free radicals as a byproduct of metabolism. Heavy exercise can produce higher quantities of free radicals. And many free radicals continually enter the body from exogenous sources such as air pollution (eg, ozone, nitrous oxide), cigarette smoke (active or passive), drugs, pesticides, contaminated or rancid foods, unsaturated fats, exposure to ionizing radiation (eg, ultraviolet light, x-rays, cosmic

rays), heavy metals (eg, mercury, cadmium, lead), alcohol, and various environmental chemicals.

Not all free radicals are villains, though. The body uses some to fight inflammation, kill invading bacteria, and even help manage the tonus of smooth muscle. But if the body is overwhelmed by excess free radicals, they may damage cell nuclei, cellular DNA, and the DNA repair process. This may result in uncontrolled cell growth that leads to malignant lesions and tumors.

Excess free radicals also contribute to coronary atherosclerosis. Low-density lipoprotein (LDL), the so-called "bad cholesterol", forms cholesteric plaques that accumulate when oxidized by free radicals. Macrophages attempting to eliminate the damaged LDL particles can't expel the cholesterol and swell up to become *foam cells*. The foam cells build up and thicken arterial walls, which narrows the arterial openings and restricts the flow of blood.

Types of Free Radicals and How They Originate

Four main types of destructive oxygen species are of interest in this article:

- hydroxyl radical ($\text{OH}^\cdot$): the most highly reactive radical
- superoxide radical ($\text{O}_2^\cdot$): oxygen that has gained 1 unpaired electron
- oxygen singlet ($^1\text{O}_2$): a non-radical reactive oxygen species
- hydrogen peroxide (H_2O_2): a non-radical reactive oxygen species

The most reactive and dangerous free radical, the *hydroxyl radical*, is many orders of magnitude more reactive than the other oxygen species. The hydroxyl radical forms from the action of hydrogen peroxide (see below).

The *superoxide radical* forms when an oxygen molecule is reduced by the addition of a single electron to an outer shell. Superoxide radicals are not particularly damaging

by themselves, but they are an intermediary source in producing hydrogen peroxide and the hydroxyl radical.

Oxygen singlets and *hydrogen peroxide* are technically not free radicals, ie, they don't have unpaired electrons, but they act as free radicals and are highly reactive themselves. Oxygen singlets are generated in a number of ways, eg, by radiation or several biological chemical reactions. Hydrogen peroxide is formed in biological systems by the reaction of two superoxide radicals. In the presence of transition metal ions (copper, iron), as found in hemoglobin, hydrogen peroxide generates and is a main source of hydroxyl radicals.

Antioxidants

Antioxidants minimize radical-caused damage by reducing the energy of the free radical, preventing the free radical from forming, or interrupting the oxidation chain reaction itself. To control the number of free radicals, the body produces enzymatic scavengers called *endogenous antioxidants*, which include superoxide dismutase (SOD), glutathione peroxidase (GSH-px), and catalase.

Even with maximum production of endogenous antioxidants, the body's defenses can sometimes be overwhelmed. That's when *exogenous antioxidants*, such as particular vitamins, minerals, and herbs may be used to assist the body. The four main exogenous antioxidants interact synergistically and may be easily remembered by the mnemonic "ACES."

A is for Vitamin A

Vitamin A, an oil-soluble vitamin, regulates and maintains many essential functions throughout our bodies, including:

- healthy skin
- vision, especially night vision
- mucous membranes
- immune system
- wound healing
- sexual functioning
- antioxidant activity

Working as a powerful antioxidant, vitamin A detoxifies certain chemicals, counters stress-related damage, and lowers the risk of cancers.

Fully formed vitamin A is found naturally in animal food such as liver, fish oil, eggs, milk, cheese, and butter. Because the liver stores unused vitamin A, the

amount can build up to toxic levels if the intake is too great. Doses above 5,000–10,000 IU/day have been associated with liver toxicity, nausea, deep bone pain, headaches, blurred vision, hair loss, dry skin, spleen enlargement, and birth defects.

The *provitamin* beta-carotene is also an antioxidant and precursor to vitamin A. Found in dark green and yellow-orange vegetables and fruit (eg, carrots, sweet potatoes, spinach, broccoli, cantaloupe, squash, mustard greens, etc.), beta-carotene is converted by the body into vitamin A. Beta-carotene, safer and less toxic than fully-formed vitamin A, is not known to cause any serious side effects except for a few possible exceptions (see below).

Available in supplemental form, beta-carotene's usual intake is 25,000–50,000 IU/day (15–30 mg/day). Excessive intake (more than 100,000 IU/day or 60 mg/day) will sometimes impart a yellow-orange tinge to the skin.

The supplemental form of beta-carotene is usually synthetic, consisting of one molecule of *all trans beta-carotene*. The natural form of beta-carotene, as found in food, is a combination of *all trans beta-carotene* and *9-cis beta-carotene*. The two forms were originally thought to be biochemically equivalent, but some studies suggest the synthetic form may actually increase the risk of lung cancer and blood vessel disease in heavy smokers, and enhance liver toxicity in alcoholics and heavy drinkers. As a result, only the use of natural beta-carotene is recommended. And with heavy smokers and drinkers, any use of supplemental beta-carotene should be approached with caution.

The label on a beta-carotene supplement will inform the user if it's the natural form or not. The synthetic version is simply listed as beta-carotene; the natural form is identified with phrases such as "natural beta-carotene," "from an algal source," "from *D. salina*," or "from a palm source."

C is for Vitamin C

Water-soluble vitamin C is another powerful antioxidant and versatile vitamin involved in many vital biochemical processes, including:

- collagen formation
- wound healing
- liver bile formation
- alcohol and other substances detoxification
- immune system enhancement
- iron absorption

- histamine destruction
- nervous system regulation
- cataract prevention
- vitamin E recycling
- antioxidant activity

The chemical name of vitamin C, *ascorbic acid*, means “without scurvy,” a debilitating and sometimes deadly disease caused by vitamin C deficiency. Vitamin C is a necessary vitamin, but humans and some other species (primates, guinea pigs) can’t manufacture it and must rely on their diets for a continuing supply. Humans can store only about 5 grams of vitamin C, a fact that was a serious hindrance to early exploration. On long ocean voyages before the cause of scurvy was discovered meant that after 40 days or so, sailors would run out of stored vitamin C and begin showing signs of scurvy. Eventually, it was discovered that daily intake of limes (or other citrus fruits) prevented scurvy—the source of the nickname for British sailors, “limeys.”

Because it is water soluble, vitamin C functions both inside and outside cells. It prevents harmful genetic changes caused by free radicals within cell DNA and prevents chromosomal mutations in lymphocytes. As an excellent source of electrons, vitamin C can donate many electrons to free radicals, thereby neutralizing their reactivity.

Vitamin C protects LDL cholesterol from oxidative damage, reduces arterial stiffness, and lessens platelet agglutination. It helps protect against the effects of free radicals in active and passive cigarette smoke. Vitamin C indirectly contributes to lipid-related antioxidant activity by working with the body’s GHS-px to revitalize vitamin E. It stimulates liver enzymes to detoxify many environmental pollutants, such as ozone, carbon monoxide, hydrocarbons, pesticides, lead and other heavy metals. It also prevents the formation of carcinogenic nitrosamines from nitrates found in many foods.

Natural sources of vitamin C include citrus fruits, papaya, cantaloupe, chile peppers, tomatoes, broccoli, and other fruits and vegetables.

Most people can tolerate high doses of vitamin C, but some may develop diarrhea, kidney stones, or liver problems. Vitamin C increases iron absorption, so people with iron overload diseases (hemochromatosis, hemosiderosis) should avoid taking it. Vitamin C also tends to deplete essential copper stores, but they can be replaced by taking multivitamin and mineral supplements containing copper. The chewable form of vitamin

C should be avoided because its acidity can dissolve tooth enamel.

The recommended dietary allowance (RDA) for vitamin C for non-smoking adult women is 75 mg/day and 90 mg/day for adult men. RDA for women and men who smoke is higher at 110 mg/day and 125 mg/day, respectively. The optimal intake of vitamin C is somewhat controversial; some scientists and doctors feel that 200 mg/day is adequate because the body can’t absorb any more than that, while others recommend 500–1,000 mg/day or even megadoses of 3–4 g/day.

E is for Vitamin E

The fat-soluble vitamin E is a vitamin and antioxidant with a variety of protective functions, including:

- anticoagulation
- vitamin K utilization
- cataract risk reduction
- coronary arterial disease risk reduction
- atherosclerosis inhibition
- LDL oxidation inhibition
- antioxidant activity

Vitamin E is yet another powerful antioxidant that protects fat-soluble constituents of the body, e.g., cell membranes and LDL cholesterol, from the damaging effects of free radicals. It affects the body’s ability to process glucose, controls inflammation, regulates blood cell and connective tissue growth, and controls genetic aspects of cell division.

Vitamin E is found naturally in wheat germ oil, nuts and seeds, whole grains, vegetable oils, peanuts, egg yolks, and butter. Because the usual range of recommended doses for maximum antioxidant activity (100–800 IU/day) can’t be obtained from eating food, supplemental forms must be used.

Not all vitamin E supplements are created equal, however. The natural forms of vitamin E derived from vegetable oils are designated with a “d,” as in *d*-alpha tocopherol or *d*-alpha tocopheryl. The synthetic versions—derived from petroleum or turpentine—are designated with a “dl,” as in *dl*-alpha tocopherol or *dl*-alpha tocopheryl. Many experts advise using the natural form because it’s more active than the synthetic version and is better absorbed by the body.

The RDA for vitamin E is only 15 mg/day (22 IU/day), but the most commonly recommended supplemental amount is 400–800 IU/day. However, some researchers

TABLE 1
RECOMMENDED SUPPLEMENTAL THERAPEUTIC DAILY DOSES

AGE	5–12	13–21	22–50	50+	HEAVY EXERCISER OR >200 LBS
VITAMIN A (SUPPLEMENTAL FORM NOT RECOMMENDED)					
BETA-CAROTENE					
MALE	10,000 IU	25,000 IU	25,000 IU	50,000 IU	50,000 IU
FEMALE	10,000 IU	25,000 IU	25,000 IU	50,000 IU	50,000 IU
VITAMIN C					
MALE	500 MG	1,000 MG	1,500 MG	2,000 MG	3,000 MG
FEMALE	500 MG	500 MG	1,000 MG	1,000 MG	2,000 MG
VITAMIN E					
MALE	200 IU	400 IU	400 IU	600 IU	1,200 IU
FEMALE	200 IU	400 IU	400 IU	600 IU	1,200 IU
SELENIUM					
MALE	50 µg	50 µg	50 µg	50 µg	100 µg
FEMALE	50 µg	50 µg	50 µg	50 µg	100 µg

(ADAPTED FROM A TABLE IN DR. KENNETH COOPER'S ANTIOXIDANT REVOLUTION)

suggest amounts of 100–200 IU/day, feeling there is no further benefit beyond those amounts. Vitamin E toxicity is very rare and the National Academy of Sciences has established a daily tolerable upper limit of 1,500 IU of natural vitamin E or 1,100 IU of synthetic vitamin E.

Use of vitamin E may increase plasma lipids, and at very high daily levels (over 3,200 IU) may cause a variety of side effects, including diarrhea, headaches, hypertension, fatigue, hypoglycemia, and lowered thyroid hormone levels. Certain medications may also interact with vitamin E, especially anticoagulants (vitamin E is also an anticoagulant).

S is for Selenium

The mineral selenium activates GHS-px, an enzyme that helps protect the body from various forms of cancer, including those affecting the intestines, rectum, breasts, ovaries, prostate, lungs, pancreas, skin, kidney, bladder, and blood (some types of leukemia) by converting reactive peroxides into harmless water. Selenium activates thyroid hormones and, as an essential element for a healthy immune system, has been shown to stimulate white blood cells. Selenium also interacts synergistically with vitamins A, C, and E.

Selenium deficiencies may be associated with coronary disease, rheumatoid arthritis, and other diseases. Gross deficiencies of selenium are somewhat rare, but selenium can be deficient in some diets because of poor food selection or lack of selenium in certain soils. Interestingly, the states with the lowest levels of selenium in the soil (Washington, Oregon, California, Florida, and

the north-central and northeast states) have correspondingly higher levels of breast cancer.

Selenium is required only in trace amounts (20 µg/day for children; 55 µg/day for women; 70 µg/day for men). Its safe at typical supplemental levels (50–200 µg/day), but too much selenium can be harmful (the National Academy of Sciences recommends a maximum of 400 µg/day). At levels exceeding 900 µg/day, selenium toxicity is associated with loss of fingernails, hair loss, skin rash, neuropathy, nausea, vomiting, diarrhea, and fatigue.

Selenium is found naturally in Brazil nuts, yeast, seafood, and seeds and grains grown in soil containing selenium.

Table 1 lists recommended supplemental therapeutic daily doses for the nutrients described in this paper.

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