

Symposium: Prooxidant Effects of Antioxidant Vitamins

Introduction¹

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This symposium, by five bench researchers who regularly add to existing knowledge rather than merely regurgitating prior claims, illustrates the following four aphorisms in nutritional biochemistry:

1. All vitamins have pharmacological effects and actions, some of which are either unrelated, or only indirectly related, to their vitamin action (Food and Drug Administration 1993, Herbert et al. 1994, Herbert 1994). The recent slang term *nutraceuticals* to describe those pharmaceuticals that are also nutrients misleads by conveying they are separate from, rather than a subset of, pharmaceuticals.

2. Every antioxidant, including vitamin antioxidants, is in fact a redox (reduction-oxidation) agent, protecting against free radicals in some circumstances, promoting free radical generation in others. Excessive antioxidant action can adversely affect key physiological processes (Food and Drug Administration 1993, Herbert et al. 1994, Olson, this symposium).

When present in physiological [Recommended Dietary Allowance (RDA)] amounts, as part of the balanced biochemistry of >150 redox and nonredox phytochemicals in each fruit or vegetable, they are always in both the reduced and oxidized forms. In the pharmacological (above RDA) amounts found in supplements, where they are only in the reduced form, they are unbalanced biochemistry not only lacking the over 150 balancing phytochemicals nature put in each fruit and vegetable but often promoting free radical generation. They also have many chemical actions unrelated to either vitamin or redox activity; these chemical actions also are not counterbalanced by the other phytochemicals in each fruit or vegetable (Herbert 1994, Herbert 1995).

Harms reported from pharmacological amounts of antioxidant vitamin supplements include promotion of heart disease, cancer and liver and kidney disease (Herbert 1994, 1995).

The answer to the question, "If I drink orange juice for vitamin C, why not take a vitamin C pill for the same effect?" is that the effect is entirely different.

Antioxidant vitamins as naturally present in food are balanced biochemistry, i.e., part of a mixture of redox agents partly in oxidized form and partly in reduced form, plus numerous other phytochemicals.

For truth in advertising, all supplements should be labeled, "Physiological (RDA) amounts of supplements help some people, harm others, and have no effect on most. Because of their potential for harm, pharmacological (above RDA) amounts should not be taken without the advice of a licensed health professional."

People who ingest large amounts of fruit and vegetables have high blood levels of a host of fruit and vegetable phytochemicals, including a number of anticarcinogens and a dozen redox agents, two of which are β -carotene and vitamin C. Ignoring all the confounding variables, careless epidemiologists decree that it is the β -carotene and vitamin C, rather than the mix of over 150 phytochemicals in each fruit and vegetable, that is protective against cancer (Herbert 1992).

3. The reduction of molecular oxygen to water by the addition of four electrons is the major source of energy for animal life (Farber et al. 1990). Free radicals, "the price we pay for breathing," are essential for health and life in moderation and harmful to health and life in excess.

4. Moderation in all things is the essence of sound nutrition. Too little or too much of any nutrient is harmful. More is sometimes better, sometimes worse but always more expensive. For every nutrient, every theoretical (and actual) "up" side is balanced by a theoretical (and actual) "down" side. Too little provitamin

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A (β -carotene), vitamin C, vitamin E, iron or selenium promotes cancer, so does too much (Herbert & Kasdan 1994; Herbert et al. 1995). In the Netherlands study (De Vet et al. 1994), β -carotene supplements promote cancer, and the Finnish study, published in 1994 (The Alpha-Tocopherol, β -carotene Cancer Prevention Group 1994), indicating β -carotene associated with 18% more lung cancer is a placebo.

In a double-blind, placebo-controlled trial comparing daily supplementation with β -carotene, both or placebo in Finland showed that neither promoted lung cancer. In fact, lung cancer was more frequent with β -carotene than with placebo. More heart disease deaths. Men had more hemorrhagic strokes. All-cause mortality was 10% higher among those who took β -carotene than those taking placebo.

Vitamin C supplements increase lung cancer in smokers may be because vitamin C drives nicotine out of the blood into the urine (Herbert and Subak-Sharpe 1995), causing the next cigarette (more carcinogenic) to sustain their nicotine high. Dr. Subak-Sharpe is now investigating whether vitamin C supplements also drive nicotine into the urine. Vitamin C supplements can double cardiac risk. In this symposium that the damage is produced by catalytic iron. 10% of all Americans who have heterozygous hemochromatosis, iron overload, vitamin C (taken by 43% of Americans) promotes free radical release from iron and insidiously promote heart disease and premature aging. Elsewhere (Herbert 1995, Herbert 1995a) we discuss the chemical action, to be a promoter of kidney stones (and oxalate kidney stones) as well as harms from vitamin E supplements as an inhibitor of immune activity (Herbert 1995a).

Dr. Joel L. Schwartz discusses his work at the National Institute of Dental Research on antioxidant vitamins.

The subject of the above four symposium papers is deranged cell replication, as are most chronic diseases (Herbert 1993). Whether a genetic predisposition to disease or suppressed is due to environmental factors, including what we avoid eating (Herbert and Simopoulos et al. 1993).

Dr. Herbert's paper "Supplements do not reduce cancer risk," which concluded this Sym-

posium, discussed the balance of helpful and harmful actions the carotenoids can have, depending on circumstances and on the mix of carotenoids in any given diet.

The report (Blot et al. 1993) of 29,584 vegetarian Chinese with a high frequency of esophageal cancer has been represented by supplement promoters as evidence that antioxidant supplements protect against cancer. This is hype, not fact. The China study showed the following three things, none of which are new: 1) Vegetarianism did not protect the Chinese against cancer. 2) Nutrient deficiencies promote the development of some cancers. 3) Correcting those nutrient deficiencies reduces the frequency of those cancers (Herbert 1992).

It has been known for many years that nutrient deficiencies promote cancers. The Plummer-Vinson syndrome, due to iron deficiency, has been known for more than half a century to promote the development of esophageal cancer (Wynder et al. 1957). The China study subjects were deficient (i.e., below minimal daily vitamin requirements to sustain normal metabolism) in so-called antioxidant vitamins A, β -carotene and E. Supplements containing β -carotene and vitamin E, by raising intakes above the minimum daily requirement, eliminated the deficiencies that promoted the cancers, thereby reducing the frequency of those cancers (Herbert, 1992).

Interestingly, in the China study, vitamin C supplements were worthless against cancer, just as they (and β -carotene) proved worthless against heart disease (Jialal and Grundy 1993, Steinberg 1993).

Our own group (Ran et al. 1993) reported that, in the area in China with the highest frequency of the trio of folic acid deficiency (caused by cooking the nutrients out of food), vitamin B-12 deficiency (caused by vegetarianism) and esophageal carcinoma, we could reverse toward normal precancerous esophageal dysplasia by either improving the diets (by less prolonged cooking of food plus adding a few ounces of animal protein three to four times a week), or keeping the bad diet and administering supplements of vitamin B-12 and folic acid. Those people whose esophageal dysplasia cells were not yet morphologically committed to be cancer cells reversed to normal; those whose cells were committed did not.

In this symposium, Mariette Gerber presents work from her INSERM-CRLC group in Montpellier, France. They studied 269 hospital-based controls and 146 patients with prostatic, ovarian, endometrial, colorectal or lung carcinomas. They found that vitamin E plasma concentrations increased and malondialdehyde (MDA) plasma concentrations decreased in proportion to growing tumor size and node invasion. This suggested that, although vitamin E may have decreased lipid peroxidation (suggested by the drop in MDA levels), it may simultaneously have increased growth and spread of cancer.

In this symposium, James A. Olson, a past president of AIN and one of the world's leading researchers on vitamin A and the many carotenoids, discusses the bal-

ance of helpful and harmful actions the carotenoids can have, depending on circumstances and on the mix of carotenoids in any given diet.

Olson's paper follows (Herbert et al. 1991), suggesting that vitamin E promotes cancer of the cervix. Published in 1994 (The Alpha-Tocopherol, β -carotene Cancer Prevention Study Group 1994), β -carotene supplements are associated with 18% more lung cancer in smokers than placebo.

This randomized, double-blind, placebo-controlled primary prevention trial with 29,133 male smokers in Finland showed that vitamin E prevented lung cancer. Lung cancer rates were 18% higher among those taking vitamin E than placebo, and there were no deaths from lung cancer. Although they did have a 10% higher cause mortality was 8% higher among those taking β -carotene than among those taking placebo.

One reason vitamin E promotes cancer and mortality in smokers is that vitamin C supplements drive iron into the urine (Herbert and Subak-Sharpe 1995) causing smokers to reach for the next cigarette (more carcinogenic) to sustain their nicotine high. Dr. Subak-Sharpe is now investigating whether vitamin C supplements also drive nicotine into the urine. Vitamin C supplements can double cardiac risk. In this symposium that the damage is produced by catalytic iron. 10% of all Americans who have heterozygous hemochromatosis, iron overload, vitamin C (taken by 43% of Americans) promotes free radical release from iron and insidiously promote heart disease and premature aging. Elsewhere (Herbert 1995, Herbert 1995a) we discuss the chemical action, to be a promoter of kidney stones (and oxalate kidney stones) as well as harms from vitamin E supplements as an inhibitor of immune activity (Herbert 1995a).

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Dr. Herbert's paper "Supplements do not reduce cancer risk," which concluded this Sym-

posium, updated and strengthened the work of her Centers for Disease Control group, published in 1993 (Kim et al. 1993), indicating that mortality among Americans who take supplements is identical to that of those who never take them. This suggests that supplements help some, harm others and have no effect on most, so the bottom line is a wash. Caring for her new baby precluded her making the deadline to publish her symposium paper in this issue of THE JOURNAL.

This Symposium also illustrates the following three nutrition science axioms, all detailed at length in the books *The Vitamin Pushers* (Barrett and Herbert 1994) and *Total Nutrition* (Herbert and Subak-Sharpe 1995): 1) What is true about nutrition is not magic, and what is magic about nutrition is not true. 2) Science is not about what one believes, but about what the evidence says. 3) Nutrition is a science and not a religion.

Finally, this Symposium illustrates three therapy axioms (Herbert 1986). These are as follows: 1) No therapy is effective until it has been objectively, reproducibly and reliably demonstrated to be more effective than a suggestion, a placebo or doing nothing. 2) No therapy is safe until it has been objectively, reproducibly and reliably demonstrated to be as safe as doing nothing. 3) If there is any question with respect to safety, before using a product, it must be objectively, reproducibly and reliably demonstrated that the potential for benefit exceeds the potential for harm.

The ubiquitous Hoffmann LaRoche advertising blanketing the lay and professional literature claiming that "The safety of antioxidant vitamins E, C and beta carotene is well established" (verbatim quote) is a deception for profit.

The ads deceive by omission of adverse facts. This is the most pernicious of the tactics of vitamin pushers because it makes it impossible for the reader, even if a health professional, to recognize that he or she is being deceived (Barrett and Herbert 1994, Herbert 1987, Herbert 1995).

The core of sound nutrition is three basic words (moderation, variety and balance), five basic food groups, seven dietary guidelines (the new moderately updated U.S. government guidelines are due out at the end of 1995) and the modifications thereof for age group, sex, genetic variations and so forth. Selling megadoses of antioxidant vitamins to fight cancer, enhance the immune system and retard aging, with representations that the products have been demonstrated to do so and also have been demonstrated to be safe is yet another multibillion dollar alternative medicine fraud (Barrett and Herbert 1994). The term alternative medicine cloaks many frauds, because the term conceals that there are three kinds of alternatives: genuine, questionable and fraudulent (Barrett and Herbert 1994, Herbert 1986).

American diets average 120% of the RDA for vitamin A, β -carotene and vitamin C (Herbert and Subak-Sharpe 1995). Nonexperimentally produced dietary vi-

tamin E deficiency has never been reported in the United States (Herbert and Subak-Sharpe 1995). The research reported in this Symposium confirms the logic of the 10th Recommended Dietary Allowance Committee authors (Hodges and Olson 1987, Olson 1987) in lowering the RDA for vitamins A and C and rejects the logic of the 10th RDA Subcommittee editors (Subcommittee 1989) to not only have a high vitamin C RDA of 60 mg but to raise it to 100 mg for smokers.

Note added in proof. On January 19, 1996, Gina Kolata reported in The New York Times ("Studies find beta-carotene, used by millions, doesn't forestall cancer or heart disease," p. A16) that Dr. Richard Klausner, Director of the National Cancer Institute (NCI), called a press conference to announce that:

1) *The Physicians' Health Study, funded by NCI, involving 22,071 physicians who were randomly assigned to take 50 mg of β -carotene or a dummy pill every other day, had ended on December 31, 1995, after 12 years, with the conclusion that β -carotene supplements did not protect against cancer or heart disease. The director of the study, Dr. Charles Hennekens of Harvard University, was quoted as saying, "There is absolutely no benefit" in β -carotene supplements, and that finding is "the biggest disappointment of my career."*

2) *The Beta-Carotene and Retinol Efficacy Trial (CARET), funded by NCI, tested 30 mg β -carotene plus 25,000 I.U. vitamin A daily vs. placebo in 18,314 smokers or asbestos workers at high risk for lung cancer. The study was halted on January 10, 1996, 21 months ahead of schedule, when study director Dr. Gilbert S. Omenn of the University of Washington in Seattle concluded that the vitamins might be harmful because the rate of lung cancer was 28% higher among the supplement-takers than the placebo group, and the rate of death from heart disease was 17% higher.*

3) *Dr. Klausner concluded that Dr. Victor Herbert was right (Herbert, 1986a) that "no matter how compelling and exciting a hypothesis is, we don't know whether it works without clinical trials."*

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