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Good Studies, Bad Studies — Making Sense of What They Mean

Two more studies again questioned the value of beta-carotene supplements, and one of them also gave a lukewarm endorsement to vitamin E. But the researchers also acknowledged the limitations of their research, the value of dietary beta-carotene, and the potential benefits from high-doses of vitamin E.

Confusing? It can be. Furthermore, a prominent researcher recently questioned the validity of clinical studies like these. (See the following article.)

In the first study, E. Robert Greenberg, MD, of the Dartmouth Medical School and the Norris Cotton Cancer Center, Lebanon, N.H., studied whether beta-carotene supplements might lower the incidence of non-melanoma skin cancer among 1,720 older men and women. All of the subjects had at one time been diagnosed with and treated for skin cancer.

The men and women, with an average age of 63, were given either 50 mg of synthetic beta-carotene or a placebo daily for 4.3 years. People taking the beta-carotene had a 10-fold increase in blood levels of beta-carotene. But, according to Greenberg, after 10 years of follow-up, the beta-carotene produced no clear benefit in terms of reduced skin cancer, cardiovascular disease, or death in general, according to his article in the *Journal of the American Medical Association* (March 6, 1996;275:699-708)

There was, however, some good news. Unlike the recent and unpublished CARET study, the researchers found no harm from the beta-carotene supplements. (See the February supplement to THE NUTRITION REPORTER.)

More importantly, people who had the highest blood levels of beta-carotene at the beginning of the study were 40 percent less likely to develop cardiovascular disease or die during the study period. According to Greenberg, those initial high beta-carotene levels suggest that the people were already eating foods rich in this nutrient and other carotenes—and probably had been all their lives.

"One cannot firmly conclude from these data that beta-carotene supplementation is entirely without benefit," Greenberg observed. "It is possible, for example, that a benefit of beta-carotene requires a longer duration of supplementation and follow-up."

In the second study, Janne M. Rapola, MD, of the National Public Health Institute, Finland, investigated whether supplements of 20 mg of synthetic beta-carotene or 50 IU of synthetic vitamin E would decrease the incidence of angina pectoris among 22,269 male smokers.

Of the 1,983 men who eventually developed angina, a type of heart pain, two trends emerged, according to an article in the *Journal of the American Medical Association* (March 6, 1996;275:693-8). First, men taking the beta-carotene had a 6 percent increased risk of developing angina, although the researchers acknowledged that this increase was of "borderline statistical significance." Second, the vitamin E resulted in a "minor" 9 percent decrease in angina.

The researchers acknowledged that 50 IU of vitamin E may be too low, since recent clinical studies have found that 800-1,200 IU are necessary to reduce or prevent the oxidation of cholesterol. In addition, population-based studies by Meir Stampfer, MD, and Eric Rimm, DSc, of the Harvard School of Public Health found that a minimum of 100 IU daily was needed to decrease the risk of coronary heart disease. □

What's Wrong with How Clinical Studies are Done?

Gladys Block, PhD, an epidemiologist at the University of California, Berkeley, has long urged people to eat a diet rich in antioxidants to reduce their risk of disease. But, recognizing that relatively few Americans eat nutritious diets, Block has also recommended the use of vitamin supplements.

Now, in a thoughtful essay, she argues that clinical studies on one or two nutrients are not the best way to judge the benefits of vitamin supplements. The reason, she writes, is that nutrients fundamentally work as a team.

"If anything is well established in biochemistry, it is that nutrients interact with one another...Probably, no single agent exists that is completely sufficient; rather, nutrients act optimally in conjunction with other agents," Block explained in the *American Journal of Clinical Nutrition* (Dec 1995;62 suppl:1517S-20S). "Furthermore, it is possible, even probable, that the effective amount of an agent is different for different conditions. For example, a

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dose or an agent that is ineffective at preventing lung cancer may be effective at preventing cataracts."

Block also pointed out that medical/nutritional studies over the past 10 years have tended to focus on beta-carotene at the expense of other nutrients. "What about the hundreds or thousands of other components in foods and herbs?" she asked.

Other common problems with clinical studies are that they have generally been conducted on people with precancerous conditions or people at high risk of disease, such as smokers. These people tend to be older, when disease processes may be well underway and preventive strategies may be too late. In addition, the studies are often of short duration.

"Thus, administration of a single agent at a single dose by itself for a short time late in life does not tell us about the potential value of a diet rich in antioxidants throughout life," Block wrote.

What's the answer if it's not clinical trials? Block suggested that researchers rely on a combination of epidemiological, animal, and in vitro studies. "Even in particle physics, where experimentation is central, the approach is not randomization but observation and prediction," she explained.

"What is sufficient, because it is necessary, is the use of our brains to synthesize all the available evidence," Block concluded. □

Free Radicals Underscore Alzheimer's Disease

Free radical damage may speed the aging of brain cells and the development of Alzheimer's disease, whereas antioxidant nutrients may prevent or slow down the disease's progression. That's the conclusion of Denham Harman, MD, PhD, of the University of Nebraska College of Medicine, in a review of Alzheimer's research.

According to Harman, who conceived the free radical theory of aging in 1954, the characteristics of late- and early-onset of Alzheimer's disease are identical. Late-onset Alzheimer's tends to occur after age 60, whereas early-onset Alzheimer's generally occurs before age 60 and is generally inherited.

The body uses free radicals to mark unneeded cellular components, which are subsequently broken down, eliminated, or recycled. However, this "cellular recycling system" becomes less efficient with age, and free radical damage accumulates.

Alzheimer's patients suffer higher than normal levels of free radical reactions and have lower than normal levels of nutritional antioxidants, such as vitamin E and beta-carotene, according to Harman's article in *Age* (1995;18:97-119). These free radicals damage deoxyribonucleic acid (DNA), which contains the body's genetic blueprint. They also decrease the production of cellular energy.

"The hypothesis that increased free radical reaction levels in brain neurons causes Alzheimer's disease, as well as the similar disorder observed in Down's syndrome and dementia pugilistica [senility caused by an injury to the head], is suggestive of measures to prevent and treat," Harman wrote.

One possible approach to the prevention of Alzheimer's, suggested Harman, might be to increase dietary antioxidant consumption among pregnant and breastfeeding women. Doing this might create an antioxidant reserve of sort, which would minimize early and cumulative free radical damage and give newborns an antioxidant head start in life. □

Environmental Stresses Increase Antioxidant Needs

Extreme heat, cold, and living at a high altitude may increase the need for antioxidants. That's the conclusion of Eldon W. Askew, PhD, of the University of Utah and the U.S. Army Research Institute of Environmental Medicine.

Askew reviewed how these "environmental stresses" impact energy production and increase free radical production. For example, in a hot environment, energy expenditures might increase by about 10 percent, and in a cold environment by as much as 250 percent. As the body's energy expenditures increase to adapt to the temperature extremes, more free radicals are produced.

The thinner air at higher altitudes appears to interfere with the synthesis of adenosine triphosphate (ATP), which is essential for energy production. Lower levels of ATP also interfere with the body's production of glutathione, an important antioxidant.

"Oxidative stress is high in all three outdoor environments [heat, cold, high altitude], and men and women working in these environments may benefit from supplemental dietary antioxidant nutrients to reduce lipid peroxidation and protein and DNA damage due to the increased production of reactive oxygen species," he wrote in the *American Journal of Clinical Nutrition* (March 1995;61 suppl:631S-7S). □

Lycopene a Potent Cancer Inhibitor in Experiments

Two recent studies explored the potential value of lycopene, the red carotenoid found in tomatoes, in preventing cancer.

In laboratory experiments, Joseph Levy, PhD, and

his colleagues at the Ben-Gurion University, Israel, found that lycopene inhibited the growth of endometrial, breast, and lung cancers. The lycopene inhibited the cancer growth in just 24 hours, and it was substantially more potent than alpha-carotene or beta-carotene. Four times more alpha-carotene and 10 times more beta-carotene were needed to achieve the same result, according to Levy's article in *Nutrition and Cancer* (1995;24:257-66).

The findings were consistent with studies showing that patients with bladder and prostate cancer tended to have low blood levels of the nutrient, according to Levy.

Levy and his colleagues noted that lycopene is the most efficient quencher of single-oxygen free radicals, which can damage deoxyribonucleic acid. In addition, lycopene and other carotenoids are involved in cellular communication and may help tell cells to stop malignant growth.

In a separate study, a team of Japanese researchers reported that lycopene "significantly suppressed" the growth of breast tumors in mice. "All results show that lycopene could be promising as a chemopreventive agent for mammary and other types of tumours," the researchers wrote in *Anticancer Research* (July-Aug 1995;15:1173-8). □

Vitamin E Succinate Inhibits Tumor Growth in vitro

A common type of vitamn E supplement, known as vitamin E succinate, has been shown in animal experiments and cell-culture studies to inhibit the growth of various types of cancer. This trait appears unique to the succinate form of vitamin E.

Two recent studies found that vitamin E succinate stopped the proliferation of several types of human prostate cancer cells and a type of retovirus-induced cancer in birds. These particular studies were conducted with samples of cells, not in people or animals.

According to articles in *Nutrition and Cancer* (Israel K, et al.;24:161-9 and Simmons-Menchaca M, et al.;24:171-85), the vitamin E succinate appears to regulate "transforming growth factor-beta," which plays a role in cell proliferation and differentiation. □

Onions May Prevent Stomach Cancer

If you have a family risk of stomach cancer, increasing your intake of onions may improve your odds against the disease. That's the finding of Dutch researchers in a recent epidemiological study.

Elisabeth Dorant, PhD, and her colleagues at the University of Limburg, compared the dietary histories of 139 people diagnosed with stomach cancer with those who did not develop the condition. She found that the more onions people ate, the less likely they were to develop stomach cancer. Similar trends did not exist for other allium-family foods, such as garlic and leek, according to an article in *Gastroenterology* (Jan 1996;110: 12-20).

Dorant analyzed whether people ate less than 1/4 onion daily, 1/4-1/2, more than 1/2, or none at all. She conducted similar analyses for garlic and leek. The risk of developing stomach cancer decreased only as onion consumption increased.

Onions are high in the flavonoid quercetin and in glutathione. The food's sulfur-containing nutrients have been established as anticarcinogens in other research. □

Asthma and Antioxidants

Free radicals and oxidative stress may overwhelm the body's natural defenses and lead to asthmatic reactions, according to a recent review of the relevant medical literature. The solution, suggests Lawrence S. Greene, PhD, is to shore up the body's antioxidant defenses.

"Uncompensated oxidant stress in the respiratory system, due to low cellular reducing capacity, is associated with increased asthma risk," Greene wrote in the *Journal of the American College of Nutrition* (Aug 1995,14:317-24). Reducing capacity refers to the body's ability to quench free radicals or recycle antioxidants by adding electrons.

Greene, with the University of Massachusetts, Boston, cited studies showing that asthma and wheezing affects 5 to 10 percent of American children. British studies have shown that asthma may affect almost 20 percent of inner-city children in London.

Asthma, which has a strong allergic component, may be partly triggered or aggravated by excessive free radicals. For example, inflammatory reactions generate large numbers of free radicals.

Large intake of dietary iron may increase the production of hydoxyl free radicals, which would dramatically increase oxidative stress. In addition, the metal lead interferes with the body's production of glutathione and other antioxidants. Both metals would aggravate asthma in people prone to the condition.

Low dietary intake of vitamins C and E, vitamin B2 (riboflavin), and selenium reduce the efficiency of the body's antioxidant defense systems. Greene noted that vitamin C helps break down histamine, which promotes allergic responses. In addition, vitamin E has successfully been used to treat reactive airway disease.

In addition, he cited several studies showing a strong link between low blood levels of selenium and asthma. Selenium is essential for the body's production of a specific glutathione antioxidant, glutathione peroxidase. □

Quick Reviews of Recent Research

• Citrus flavonoids and health

Hesperidin, one of the principal flavonoids found in citrus fruit, significantly increased levels of high-density lipoprotein, the so-called "good" cholesterol. It also lowered total cholesterol, low-density lipoprotein, and triglyceride levels in laboratory rats with normal and elevated blood fat levels. A previous study by the same researchers showed that hesperidin possessed significant anti-inflammatory and analgesic effects.

Monforte MT, et al., *Farmaco*, Sept 1995;50:595-9.

• Antioxidants protect endothelial cells

Oxidized low-density lipoprotein (LDL) is toxic to the endothelial cells that line blood vessel walls. A combination of vitamins C and E and the flavonoid rutin prevented the oxidation of LDL and its toxicity to endothelial cells.

Negre-Salvayre A, et al., *Biological Trace Element Research*, Jan-Mar 1995;47:81-91.

• Flavonoids as antioxidants

Green tea flavonoids (primarily epicatechin-3-gallate), tangeretin from citrus, and other flavonoids inhibited the oxidation of liver cells. The green tea flavonoids were the most potent.

Obermeier MT, et al., *Xenobiotica*, June 1995;25:575-84.

• Citrus flavonoids and leukemia

Some anti-cancer drugs are designed to induce apoptosis (cell death) in tumor cells; however, most of these drugs are also toxic to normal cells. In a cell-culture study, researchers found that tangeretin, one of the flavonoids found in citrus fruit, causes apoptosis in leukemia cells, but does not harm normal cells.

Hirano T, et al., *British Journal of Cancer*, 1995;72:1380-8.

• Chromium and Type II diabetes

In a double-blind study, 30 men and women with non-insulin-dependent diabetes received either 200 mcg of chromium picolinate or a placebo daily for two months. The patients benefited from an average 17.4 percent decrease in blood triglyceride levels. There were no differences in cholesterol or glucose levels.

Lee NA and Reasner CA, *Diabetes Care*, Dec 1994;17: 1449-52.

• Antioxidants and heart disease risk

Researchers in India measured levels of vitamins A, C, and E and beta-carotene in a group of elderly people. They found that low levels of these nutrients were significantly related to the risk of coronary artery disease (CAD). Lipid peroxides were higher in patients with heart disease, diabetes, as well as those who smoked tobacco. "These findings suggest that some elderly Indian populations with high rates of CAD can benefit from eating foods rich in antioxidant vitamins A, C, E, and beta-carotene."

Singh RB, et al., *American Journal of Cardiology*, 1995;76:1233-1238.

• Vitamin B2 deficiency aids cancer

Aflatoxin is a well-known carcinogen. In a study using rats, researchers found that a diet deficient in vitamin B2 (riboflavin) increased damage to deoxyribonucleic acid (DNA) from aflatoxin and another carcinogen. Supplementation with vitamin B2 reduced DNA damage to normal levels.

Webster RP, *Cancer Letters*, Jan 1996;948:129-35.

• Juice and antioxidants

Researchers placed 15 male smokers on a diet high in polyunsaturated fats, which readily oxidize and damage low-density lipoprotein. Drinking orange juice (containing vitamin C) or carrot juice (containing beta-carotene) partly prevented the oxidation of low-density lipoprotein.

Abbey M, et al., *Journal of the American Dietetic Association*, June 1995;95:671-5.

• Flavonoids as antioxidants

Researchers investigated the relative antioxidant properties of several water-soluble polyphenolic flavonoids. The most effective flavonoids of those tested, in the order of effectiveness, were epicatechin gallate, epigallocatechin gallate, and epigallocatechin. These flavonoids are found in numerous foods, including grapes and green tea.

Salah N, et al., *Archives of Biochemistry & Biophysics*, Oct 1, 1995;322:339-46.

• Vitamins and surgery

Fifty-one patients with chronic arterial occlusive disease were operated on to restore blood flow to the legs and reduce edema. Twenty-four of the patients received a multivitamin containing vitamins E, C, and A and the B-complex. These people benefited from lower production of free radicals and less swelling after blood flow was restored, compared with 27 patients who did not receive the vitamins.

Rable H, et al., *World Journal of Surgery*, Sep/Oct 1995; 19:738-44.

• Vitamin E and radiation protection

Vitamin E supplementation can reduce radiation injury to the intestines, according to animal experiments. This finding could benefit patients receiving radiation therapy.

Felemovicius I, *Annals of Surgery*, Oct 1995;222:504-10.

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