

# The NUTRITION REPORTER™

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## British Researchers: High-Dose Vitamin E Supplements Reduce Risk of Heart Attack

In one of the most dramatic studies ever conducted on vitamin E, a team of researchers at Cambridge University found that supplements reduced the risk of non-fatal heart attacks by 77 percent. The benefits were clearly noticeable after taking the vitamin for just one year.

The double-blind, placebo-controlled study involved 2,002 patients, with an average age of 61, over 18 months. Angiography, a type of heart x-ray, confirmed that all of the patients had coronary atherosclerosis.

About half of the patients received either 400 IU or 800 IU of the natural form of the vitamin, d-alpha tocopherol, each day. The other half received dummy capsules. On average, blood levels of vitamin E rose by 49 percent among those taking 400 IU and by 88 percent among those taking 800 IU daily.

Patients taking vitamin E were one-fourth as likely to suffer a non-fatal heart attack, according to an article by Nigel G. Stephens, MRCP, and his colleagues in *Lancet* (March 23, 1996;347:781-6).

The findings were even more remarkable considering that the vitamin E group was generally at a high risk for "cardiovascular events." More than 37 percent had been diagnosed with serious coronary heart disease or already had triple-bypass surgery, and 24 percent had moderate or severe left ventricular dysfunction.

The researchers focused on non-fatal cases of myocardial infarction, or heart attack, because of the ability to precisely diagnose heart attacks through electrocardiography, cardiac enzyme measurements, and hospital records.

During the study, 23 of the placebo patients and 27 of the vitamin E patients died. Although deaths were slightly higher among people taking vitamin E, the researchers noted that the difference was not statistically significant and that most of the deaths occurred early in the study, before the vitamin E provided maximum benefits.

The researchers thought the vitamin E worked primarily by preventing free radical oxidative damage to cholesterol, considered a primary cause of coronary heart disease. But the study did not prove it.

"The study could not directly address the mechanism by which alpha-tocopherol reduces the risk of myocardial infarction," they wrote. "The extent of the

risk reduction suggests that the benefit may be due to more than one mechanism, such as alpha-tocopherol-mediated reductions in platelet adhesion and aggregation, inhibition of vitamin-K-dependent clotting factors...and oxidised-LDL-mediated stimulation of endothelin production and inhibition of nitric oxide production. However, we believe that inhibition of oxidation is likely to exert its main effects by modification of plaque enlargement or plaque rupture."

According to the researchers, the benefits from vitamin E were greater than those from aspirin or cholesterol-lowering drugs.

The use of vitamin E in the treatment of heart disease—which was often considered controversial—dates back to the mid-1930s, when Evan Shute, MD, of Canada became the first physician to use the vitamin therapeutically in people. □

## Do Free Radicals Play a Role in "Mad Cow" Disease?

It seems almost too incredible to be true, but free radicals and oxidative stress may be factors in the recent outbreak of "mad cow disease" and Creutzfeldt-Jacob disease in England, two deadly neurological diseases.

According to laboratory experiments, antioxidants—particularly vitamin E and N-acetyl-cysteine—may slow brain damage characteristic of these diseases.

In March, the British government's health secretary acknowledged that bovine spongiform encephalopathy (BSE, mad cow disease) in cattle was probably the cause of the recent wave of Creutzfeldt-Jacob disease in people. Within days, beef consumption plummeted, and nation after nation banned the importation of British beef.

BSE, which has been infecting large numbers of British cattle and dairy cows since the 1980s, is caused by the abnormal behavior of proteins called prions, which are neither viruses nor bacteria. The disease carves holes in the brains of animals, causing progressive and irreversible neurological degeneration. Prions also cause scrapie, a similar neurological disease in sheep, and researchers believe that the disease-causing prions were transmitted to cattle when they were fed the remains of

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butchered sheep as a high-protein supplement.

Since then, Creutzfeldt-Jacob disease, a rare neurological disease that affects people, has increased in incidence in England. Historically, Creutzfeldt-Jacob disease has struck people in their 60s. But the new strain is affecting people in their 20s, with a particularly high cluster among English dairy farmers. Although there's no definitive evidence that eating BSE-tainted meat causes Creutzfeldt-Jacob disease, the link is suspected.

The disease process appears to involve microglia, a type of brain and nervous system cell that normally collects metabolic waste products from nerve tissues, according to Hans A. Kretzschmar, PhD, and his colleagues at the University of Gottingen, Germany. In recent studies, Kretzschmar found that killing microglia outright stopped the damage to brain cells, suggesting that microglia play a pivotal role in prion diseases.

So Kretzschmar focused on the behavior of microglia. In an experiment described in the journal *Nature* (March 28, 1996; 380:345-347), he determined that prion-stimulated microglia release large amounts of free radicals, particularly superoxide radicals and nitric oxide, which destroy normal brain cells. Another experiment by Kretzschmar showed that vitamin E and N-acetylcysteine block this damage.

"Oxidative stress is involved in this mechanism," Kretzschmar and his colleagues wrote. "Microglia are also activated in murine [mouse] scrapie and there is evidence that microglia are stimulated by beta-amyloid [an undesirable brain protein] to produce neurotoxic agents. Microglia appear to be an important mediator of neuronal death in degenerative diseases of the brain."

Kretzschmar's findings are consistent with a growing body of research showing that free radical damage may cause other brain diseases, including Alzheimer's and Parkinson's diseases (Harman D, *Age*, 1995;18:97-119). In addition, the body's immune response to bacterial and viral infections releases large numbers of free radicals (Hickman P, et al., *British Journal of Surgery*, 1994;81:790-8)

It's conceivable that susceptibility to Creutzfeldt-Jacob disease is aggravated by accumulating free radical, or oxidative, stresses. While there's no evidence vitamin E can cure BSE or Creutzfeldt-Jacob disease, Kretzschmar's research points to a potential role of antioxidant therapy in slowing the disease's progression. □

## Acetaminophen, Antioxidants, and Liver Damage

Physicians have long known that high doses of acetaminophen, a common pain-relieving drug, can cause liver damage and kidney failure. But recent pharmaceutical advertising has conveyed these risks to the general public.

The mechanism? Acetaminophen may injure the liver and kidneys by depressing the body's production of its own antioxidants, including glutathione, glutathione peroxidase, and catalase.

Researchers at the University of Buenos Aires fed mice large doses of acetaminophen, then measured changes in their antioxidant production. Glutathione levels decreased by 83 percent, reaching their lowest point one hour after acetaminophen injection, and glutathione peroxidase levels decreased by 40-53 percent within 15 minutes. Catalase levels decreased by 15 percent, but not superoxide dismutase.

The decrease in antioxidants, and a concurrent increase in free radicals, would contribute to cell injury. "Our results indicate the occurrence of oxidative stress as a possible mechanism for acetaminophen-induced hepatotoxicity," wrote Silvia L. Arnaiz, PhD, in *Free Radical Biology & Medicine* (1995;19:303-10). □

## Vitamin B12 Seems to Help Vaccinations Work Better

If you're one of those folks who's had a vaccination but still got sick, it might be worthwhile getting your vitamin B12 levels checked.

The reason, according to a recent study, is that low vitamin B12 levels stymie the body's production of protective antibodies after a shot—that is, the ability of a shot "to take."

Farid T. Fata, MD, Barry C. Herzlich, MD, and their colleagues at the Mamonides Medical Center, New York, gave pneumonia (*Streptococcus pneumoniae*) vaccinations to 15 elderly patients with low B12 blood levels and to 15 comparable patients with normal B12 levels.

"Patients with low vitamin B12 levels had impaired antibody response to pneumococcal vaccine," the researchers wrote in *Annals of Internal Medicine* (Feb 1996;124:299-304).

The problem may be widespread. According to Fata and Herzlich, 15 percent of the elderly have low vitamin B12 blood levels. In most cases, the B12 deficiency is not recognizable by traditional blood or neurological signs, but can be identified by measuring for methylmalonic acid, a more sensitive indicator of B12 status.

Furthermore, 30 percent of elderly patients develop atrophic gastritis, a stomach condition that interferes with B12 absorption.

"Our findings suggest that a low serum vitamin B12 level is associated with impaired humoral immunity in elderly immunocompetent adults...Further studies are needed to determine whether vitamin B12 treatment can enhance the synthesis of specific immunoglobulins and improve the clinical efficacy of the pneumococcal vaccine in patients with low vitamin B12 levels." □

## Strict Vegetarians Eat Lots of Antioxidants

Although vegetarians are more likely than meat eaters to be deficient in vitamins B12 and D, they do have substantially higher blood levels of antioxidant nutrients. That's the finding of a study that compared 21 vegans eating a strict, uncooked "living food diet" with people who ate broader diets, including meat.

Anna-Liisa Rauma, PhD, of the University of Kuopio, Finland, looked at the subjects' intake of foods containing vitamins C and E, beta-carotene, zinc/copper-dependent superoxide dismutase, and selenium-dependent glutathione peroxidase. The vegans ate more fruits, berries, root crops, and nuts than did the omnivores.

"Based on dietary records, the vegans had significantly higher intakes of beta-carotene, vitamin E, vitamin C, and copper, and a significantly lower intake of selenium than the omnivorous control subjects," Rauma and her colleagues wrote in the *American Journal of Clinical Nutrition* (Dec 1995;62:1221-7). "The calculated dietary antioxidant intakes by the vegans, expressed as percentages of the US recommended dietary allowances, were as follows: 305% of vitamin C, 247% of vitamin A, 313% of vitamin E, 92% of zinc, 120% of copper, and 49% of selenium."

The differences in antioxidant intake remained steady, even among vegans and omnivores who also took vitamin supplements. □

## Does Ginseng Owe Its Reputation to Antioxidants?

Few herbs can match the folklore of ginseng (*Panax ginseng*). Indeed, its scientific name is derived from the word that means panacea, or cure-all. Ginseng root has been used for more than 4,000 years in China as a general tonic, for enhancing the immune system, fighting cancer, and increasing virility.

Such wide-ranging claims have led to its quick dismissal by Western-trained physicians, but new research suggests that ginseng's benefits may be related in part to its ability to quench dangerous free radicals.

Daxian Zhang, PhD, led a team of Japanese and Chinese researchers who recently investigated the antioxidant properties of ginseng. They looked specifically at some of the free radical byproducts created during the oxidation of fats, called lipid peroxidation. Zhang also studied whether ginseng might quench hydroxyl radicals, which are considered the most destructive of all free radicals.

Zhang determined free radical damage to lipids by measuring thiobarbituric acid-reactive substances (TBARS), an indicator of lipid peroxidation, in cells. Ginseng inhibited the production of TBARS—and did so

for three hours. The relatively long antioxidant effect suggested that "ginseng extract might be active not only at the initiation of the radical chain reaction but also at the propagation stage," Zhang wrote in *Free Radical Biology & Medicine* (Jan 1996;20:145-50).

The actual mechanism, according to Zhang, may be that ginseng directly neutralizes hydroxyl radicals and sequesters iron, a nutrient that can generate free radicals. "This may partially explain the wide range of pharmacological actions of ginseng," he wrote.

In another recent study, researchers at the Korean Cancer Center Hospital, Seoul, investigated the potential value of ginseng in preventing cancer. In all, they looked at almost 4,000 patients.

It's not clear why, but people taking "white ginseng" extract or powder were far less likely to develop cancer than those who consumed fresh ginseng, ginseng juice, or ginseng tea. "There was a decrease in risk with the rising frequency and duration of ginseng intake, showing a dose-response relationship," the researchers wrote in *Cancer Epidemiology, Biomarkers & Prevention* (June 1995;4:401-8).

Ginseng was most protective against cancers of the mouth, pharynx, colon, liver, pancreas, larynx, lung, and ovaries. It was not protective against breast, uterine, cervix, urinary tract, or thyroid cancers. □

## CoQ10 May Reduce Muscle Injury in Strenuous Exercise

Coenzyme Q10 (CoQ10) might help prevent muscle-cell injury during endurance exercise, and it may also protect against cell damage caused by electric fields. CoQ10, a vitamin-like nutrient, is required for energy production in cells. It also functions as an antioxidant.

Muscle cell injury from exercise is often related to changes in the mitochondria, which are the energy-producing organelles in cells. So researchers at the Kobe Gakuin University, Japan, cultured cells from the femoral muscles of rats, then exposed the cells to electric fields.

After exposure to the electric fields, levels of adenosine triphosphate (ATP), which stores energy, decreased. Supplemental CoQ10, essential for normal ATP production, protected the cells, whereas supplemental vitamin E failed to provide protection.

The cell injury appeared related to excess calcium in the cell—essentially in the wrong place at the wrong time—because a lack of ATP prevented the calcium from being pumped out of the cell. "Supplementation with CoQ10 during endurance exercise may be useful for preventing skeletal muscle cell injury," wrote Tadashi Okamoto, PhD, in *Biochemical and Biophysical Research Communications* (Nov 22, 1995;216:1006-12). □

# Quick Reviews of Recent Research

## • Quercetin inhibits leukemia cells

In a cell-culture study, researchers found that quercetin, a flavonoid found in many plants, inhibited DNA synthesis in leukemia cells. The effect was noted 24 hours after the addition of quercetin, and it was dose related—the higher the dose of quercetin, the more leukemia-cell DNA synthesis was slowed. After two to three days, high doses of quercetin completely inhibited DNA synthesis. After quercetin was removed, DNA synthesis resumed in the cells.

Uddin S and Choudhry MA, *Biochemistry & Molecular Biology International*, July 1995;36:545-50.

## • Fats, antioxidants, and Parkinson's

Researchers compared the eating habits of 110 patients with Parkinson's disease and 287 normal patients. They discovered that the Parkinson patients consumed substantially more dietary fat than did the normal patients, but both groups ate about the same amount of antioxidant vitamins in food. High fat intake increases the body's requirement for antioxidant nutrients, which apparently was not compensated for among the Parkinson patients. The consequence was greater lipid peroxidation (free radical damage to fats), which can aggravate the disease.

Logroscino G, et al., *Annals of Neurology*, 1996;39:89-94.

## • Fish oil and superoxide radicals

Diets rich in fish oils have been associated with a reduced risk of coronary heart disease. The fish oils reduce the tendency toward platelet aggregation and arrhythmia. They also inhibit the inflammatory process, which generates large number of free radicals. In an experiment, researchers fed two groups of monkeys a diet promoting heart disease. One group of monkeys also received fish oils. The monkeys eating fish oils had lower levels of damaging superoxide radicals in their heart muscle.

Supari F, et al., *Circulation*, 1995;91:1123-28.

## • Fiber and coronary heart disease

In a study of 43,000 male physicians, researchers found that diets high in fiber were protective against coronary heart disease and heart attack. The benefits of fiber were independent of fat intake, suggesting that fiber was protective regardless of fat consumption. The major dietary sources of fiber were vegetables, fruit, and cereal, but "cereal fiber was most strongly associated with a reduced risk of myocardial infarction."

Rimm EB, et al., *Journal of the American Medical Association*, Feb 14, 1996;275:447-51.

## • Curcumin and colon cancer

Curcumin, found in the spice tumeric, may reduce the risk of colon cancer. Researchers administered a chemical known to cause colon cancer in rats. About half the rats also received curcumin. After one year, 81 percent of the rats eating their regular diet developed cancer, and 38 percent of those were invasive cancers. In contrast, only 47 percent

of the mice getting curcumin had tumors. Furthermore, tumors in the curcumin-fed rats were generally smaller and less likely to be invasive.

Rao CV, et al., *Cancer Research*, 1995;55:259-66.

## • Gamma- and alpha-tocopherol levels

Researchers found that patients with coronary heart disease had lower levels of gamma-tocopherol than alpha-tocopherol, compared with healthy subjects. In a separate study, a researcher found that levels of alpha- and gamma-tocopherol varied during the course of pregnancy. During gestation, alpha-tocopherol levels rose steadily, peaking just before delivery, and then decreased after delivery. Gamma-tocopherol levels reached their peak at mid-gestation, then decreased until one month after delivery.

Ohrvall M, et al., *Journal of Internal Medicine*, 1996;239:111-17. Al Senaidy AM, *Molecular and Cellular Biochemistry*, 1996;154:71-5.

## • Chlorophyll and cancer prevention

Chlorophyll, the green pigment found in plants, may have a role in preventing cancer. In a study on rainbow trout fed a carcinogen, researchers found that chlorophyllin, a food-grade derivative of chlorophyll, could inhibit the formation of adducts and liver cancer. Adducts are chemicals that attach carcinogens to DNA, setting the stage for cancerous changes. The benefit of chlorophyllin was dose related and, at its maximum, inhibited up to 77 percent of cancerous changes.

Breinholt V, et al., *Cancer Research*, 1995;55:57-62.

## • Olive oil and breast cancer risk

A study of 2,368 women found that diets high in olive oil, vegetables, and fruits reduced the risk of breast cancer, whereas high intake of margarine increased the risk. Eating olive oil at least once a day decreased the risk of breast cancer by 25 percent, whereas eating margarine as little as four times a month increased the risk by about 10 percent. High intake of vegetables and fruits reduced cancer risk by 12 and 8 percent, respectively.

Trichopoulou A, et al., *Journal of the National Cancer Institute*, 1995;87:110-116.

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