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N-Acetylcysteine Boosts Glutathione Levels, Lengthens Survival Among AIDS Patients

High supplemental doses of the antioxidant N-acetylcysteine (NAC) can boost the body's glutathione levels and increase life expectancy among AIDS patients, according to a new study.

Glutathione is the principal antioxidant found in the body's cells, and it also helps detoxify many hazardous molecules. However, it is not absorbed well from supplements or food, whereas NAC is absorbed very well.

In the first phase of the study, Leonard A. Herzenberg, PhD, a geneticist at Stanford University, explored why low CD4 T-cell counts by themselves do not reliably predict how long an HIV-infected patient will live. CD4 T cells are the immune cells targeted and destroyed by the human immunodeficiency virus, or HIV, which causes AIDS.

"Glutathione deficiency has long been known to be clinically dangerous in man and in experimental animals," Herzenberg wrote in the *Proceedings of the National Academy of Sciences* (March 4, 1997;94:1967-72). "T cell function and viability are markedly impaired in glutathione-depleted T cells."

Herzenberg followed 204 AIDS patients for three years. He found that patients with normal glutathione levels in their CD4 cells generally outlived those with low glutathione levels. Most patients with low CD4 cell counts (under 200 CD4 cells per microliter of blood) and low glutathione levels died within three years.

However, of the 28 people who had very low CD4 cell counts at the start of the study, but maintained normal glutathione levels, 23 survived. That's equivalent to an 80-percent survival rate.

Herzenberg and his colleagues gave the AIDS patients either 3,200-8,000 mg of NAC or a placebo daily for six weeks. After this phase of the study, he offered NAC to all of the patients, and a majority took it for six months.

The NAC boosted blood levels of glutathione, and "subjects who took NAC were roughly twice as likely to survive for 2 years as the subjects who did not take NAC," according to Herzenberg's article.

"The research," he added, "provides the first clear indication that glutathione deficiency plays a pivotal role in determining how quickly the final stages of HIV disease progress."

N-acetylcysteine, the "acetylated" form of the amino acid cysteine, is an approved medical treatment for lung congestion and acetaminophen poisoning.

Both alcohol and the pain-relieving drug acetaminophen deplete glutathione levels, and Herzenberg cautioned that these substances could impair survival in AIDS. □

Just What Is Oxidative Stress?

If you regularly follow research on free radicals and antioxidants, you've probably been noticing a relatively new term: oxidative stress.

Both free radicals and antioxidants (such as vitamins C and E) play essential roles in energy production and overall health. Under ideal circumstances, there is a relative balance, or equilibrium, between free radicals and antioxidants in the body.

But various factors, such as nutritional deficiencies, chronic inflammation or infections, and stress, tip this balance and either increase free radical production or reduce the body's antioxidant defenses against them. These free radicals, sometimes called oxidants or pro-oxidants, can overwhelm the body's antioxidant defenses. The result, called oxidative stress, can increase the risk of heart disease, cancer, and many other diseases.

"Oxidative stress is often partly or totally a cause of various diseases as cancer, atheroma, (and) cataract," wrote French pharmacology professor A. Favier in *Annales de Biologie Clinique* (1997;55:9-16). "But a great number of other diseases as diabetes, (and) infectious processes such as AIDS, creates a secondary free radical overproduction that worsens the evolution of the diseases."

A number of laboratory tests, available to physicians, can measure oxidative stress. These tests measure various byproducts of free radical damage, including conjugated dienes, hydroperoxydes, aldehydes (e,g,, malonaldehyde) hydrocarbides (e.g., ethane and pentane), oxidized proteins (e.g. carbonyl or thiol groups), and DNA derivatives in the urine.

Just as there are many types of free radicals, such as hydroxyl, peroxyl, superoxide, and singlet oxygen radicals, there are hundreds of dietary antioxidants. These protective nutrients, which include vitamins C and E, alpha-lipoic acid, carotenoids, and flavonoids, can relieve oxidative stress by restoring a balance between free radicals and antioxidants and lessening free radical damage. □

Research summaries continue on next page

People Use Alternative Medicine, But Don't Always Tell Their Docs

Several years ago, a study found that one in every three Americans had used some form of alternative medicine over the previous year. In fact, David M. Eisenberg, MD, of Harvard University, reported that people visited alternative medical practitioners more often than they did conventional physicians. (See Eisenberg DM, N*ew England Journal of Medicine*, 1993;328:246-52.)

The numbers may be going up, according to a study of patients at four medical practices in Portland, Ore.

Nancy C. Elder, MD, of Oregon Health Sciences University, analyzed questionnaires completed by 113 patients, some of whom also discussed their feelings about conventional and alternative medicine in detail.

Fifty percent of the patients acknowledged that they had used or were currently using some form of alternative medicine, according to Elder's report in *Archives of Family Medicine* (Mar / Apr 1997;6:181-4). "Our study, and others, found that patients with the medical problems that not only make up a large percentage of the family physician's caseload, but that are also more difficult for traditional Western medicine to 'cure' are commonly the ones for which patients seek alternative care. These include back problems, anxiety, depression, and chronic pain," Elder wrote.

Chiropractic, the most common alternative therapy, was used by 42 percent of the patients. It was followed by massage (32 percent), herbal medicines (30 percent), megavitamins (24 percent), and meditation (21 percent). Acupuncture, homeopathy, and naturopathy were each used by 10 percent of the patients. Some patients used more than one or two alternative therapies.

Some of the patients criticized "medicine's limitations and narrow-mindedness," according to Elder. One , when asked why she did not discuss alternative medicine with her physician, explained, "Why would I bother sharing any kind of information that I might know about how this [alternative therapy] seemed to help me—they don't want to hear it and I don't want to get yelled at by them."

"Our participants," noted Elder, "desired practitioners who would 'listen' and 'accept.' This is not a new concept in the understanding of the physician-patient relationship, yet alternative health care providers are often seen as more caring and willing to listen." □

Vitamin K Strengthens Bones

Vitamin K, a nutrient needed for blood clotting, also appears important for maintaining strong bones. The vitamin activates at least three proteins, including osteocalcin, which are needed for bone formation.

James Sadowski, PhD, and his collaborators at Tufts University, Boston, gave nine healthy young men and women 420 mcg of vitamin K daily. The amount is about four times greater than the RDA.

After 15 days, the subjects' osteocalcin levels increased significantly, and tests suggested that bone density also increased, according to Sadowski's article in the *American Journal of Clinical Nutrition* (March 1997;65:779-84). □

Selenium Intake Drops in Europe

Selenium intake varies greatly depending on where a person lives and where his food is grown. The mineral is needed by the body to make glutathione peroxidase, a powerful antioxidant enzyme, which plays an important role in preventing cancer, heart disease, and infertility.

But at least in Europe, selenium intake is falling—and likely increasing the risk of a variety of diseases.

The average consumption of selenium in Britain is now 34 mcg daily, about half of what it was 22 years ago. This decrease is reflected in lower blood levels of selenium as well, according to an editorial by Margaret P. Rayman, PhD, of the University of Surrey, in the *British Medical Journal* (Feb 8, 1997;314:387-8).

The decline in selenium consumption is largely because of fewer imports of selenium-rich wheat from North America. Because of tariffs on imports and changes in breadmaking, European breadmakers have shifted to low-selenium wheat.

"Is it not time to consider addressing the problem of low selenium intakes?," Rayman wrote. "In Britain virtually all farm animals get mineral supplements which have included selenium since 1978, when its efficacy in preventing animal disease was accepted. Should we humans be lagging so far behind? Perhaps it is time to consider measures such as those adopted in Finland, another country with low soil selenium, which has been adding sodium selenate to its fertilisers since 1984...In the meantime, judicious use of supplements (staying well below the toxic level of 800 mcg / day) or a daily helping of Brazil nuts, the richest natural source of selenium, would seem our best option." □

CoQ10 Supplements Alter Platelets, Reduce Cardiovascular Risk

Coenzyme Q10 (CoQ10), a vitamin-like substance, can strengthen weak hearts in patients suffering from cardiomyopathy and chronic heart failure. It's also of benefit in ischemic heart disease.

Many of CoQ10's benefits have been attributed to its role in producing energy or as an antioxidant. But a recent study suggests that CoQ10 might work in part by turning off blood platelet cells. The reasoning is sound: free radicals promote platelet activation and aggregation (clotting), and other antioxidants (e.g., vitamin E, beta-carotene, and selenium) have been found to reduce platelet aggregation.

Victor L. Serebruany, MD, PhD, of the Union Memorial

Hospital, Baltimore, gave 15 men and women 200 mg of CoQ10 daily for 20 days, then analyzed how their platelet size and activity changed.

After CoQ10 supplementation, the subjects had a lower percentage of large platelet cells and a higher percentage of small platelet cells. This change was significant because large platelets are more likely than small platelets to form clots. "Our study revealed a significant reduction of the activated platelets after CoQ10 supplementation," Serebruany wrote in the *Journal of Cardiovascular Pharmacology* (Jan 1997;29:16-22).

In addition, all of the subjects had a decrease in cell receptors for vitronectin, a glycoprotein that promotes platelet aggregation. In nine of the 15 subjects, the decrease in cell receptors was significant. □

Vitamins C and E Protect Cells Against DNA Damage

Vitamins C and E prevent damage to deoxyribonucleic acid (DNA), but they work in different ways. Strands of DNA, a complex protein, form the chemical basis of genes, which control everything from hair color to the risk of disease.

In a recent experiment, V. J. McKelvey-Martin, PhD, exposed lymph cells to various doses of x-rays or hydrogen peroxide. X-rays can directly damage DNA, and hydrogen peroxide can generate free radicals that damage it. The DNA damage is described as a mutation, and mutated DNA is a cause of aging and cancer.

Higher doses of x-rays and hydrogen peroxide increased the amount of DNA damage. Both vitamins C or E, added to the cell cultures, decreased the rate of DNA damage. However, the combination of vitamins C and E did not have a "consistently additional protective effect over single supplements..." McKelvey-Martin wrote in *Nutrition and Cancer* (1997;27:122-30).

Instead, vitamin C was most protective against x-ray damage, and vitamin E offered greater protection against hydrogen peroxide-induced damage.

The difference in effect may be related to where each vitamin most actively quenches free radicals in cells. Vitamin E is a fat-soluble antioxidant, and vitamin C is water soluble.

"As hydrogen peroxide is added to the cell culture during treatment, it must pass across the cell membrane to come into contact with the DNA. Because of alpha-tocopherol's [vitamin E's] location in the [fatty] cell membrane, it may play a more dominant role than ascorbic acid in the protection against hydogen peroxide," wrote McKelvey-Martin. "Conversely, ionizing radiation can pass directly into the aqueous phase of the cell, where it can induce radical formation close to the DNA. In this situation, ascorbic acid may play a more dominant role than alpha tocopherol in radical scavenging." □

Beta-Carotene Might Need Vitamin C to Complete Its Job

People have wondered why, in two studies, beta-carotene increased the risk of lung cancer among heavy smokers and drinkers. The reason, according to a British chemist, may be that the smokers did not consume enough vitamin C.

T. George Truscott, PhD, of Keele University, England, found that antioxidants work in steppingstone fashion to neutralize free radicals. According to Truscott's experiments, vitamin E may be the first antioxidant to quench free radicals from smoke. As a result of this chemical reaction, vitamin E becomes a free radical, but beta-carotene recycles the radical back to vitamin E. Beta-carotene then becomes a free radical, which can be restored with vitamin C.

Smokers generally have lower blood levels of vitamin C, partly because the free radicals generated by cigarette smoke deplete antioxidants and also because smokers eat relatively few vitamin C-rich fruits and vegetables. With the vitamin C steppingstone missing, the beta-carotene radicals remain unquenched and capable of damaging cells.

According to Truscott's article in the *Journal of the American Chemical Society* (Jan 22, 1997;119:621-2), "the low levels of antioxidants, such as ascorbic acid, in smokers compared to nonsmokers, may be related to the apparent failure of beta-carotene to offer any benefit to this group [of smokers]..."

Another reason might be that synthetic beta-carotene was used in the clinical trials of smokers. Synthetic beta-carotene contains only the all-trans isomer (configuration), whereas natural-source beta-carotene supplements also contain the antioxidant 9-cis isomer, according a letter by Jack J. Challem in the *Journal of the National Cancer Institute* (Feb 19, 1997;89:325).

Soy Genistein and Daidzein as Estrogen Replacement Therapy?

Estrogen replacement therapy reduces the risk of heart disease in women, but many women don't want to take hormones because of the increased risk of cancer.

Genistein and daidzein, the most potent antioxidant isoflavonoids in soy, may turn out to be a safe alternative, according to J. Koudy Williams, DVM, of the Bowman Gray School of Medicine, Winston-Salem, NC.

Both nutrients have very weak estrogenic activity, and they block the cell-proliferating properties of hormonal estrogen.

"There is hope that a dietary alternative that...does not increase the risk of breast and uterine cancer, and does not require 'pill-taking' may be appealing to women," Williams wrote in *Fertility and Sterility* (Jan 1997;67:148-54).

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Quick Reviews of Recent Nutrition Research

• Natural versus synthetic vitamin E

Japanese researchers gave seven healthy women, ages 21-37, supplements of natural and synthetic vitamin E. The bioavailability of natural vitamin E was substantially greater than that of synthetic vitamin E, and a dose of 300 mg of synthetic vitamin E had about the same bioavailability of 100 mg of natural vitamin E. (On labels, "d-alpha tocopherol" indicates natural vitamin E, whereas "dl-alpha tocopherol" indicates synthetic vitamin E. —Editor)

Kiyose C, et al., *American Journal of Clinical Nutrition*, 1997;65:785-9.

• Vitamin E and lung health

As people age, they're more prone to lung infections and inflammatory diseases. These conditions increase the risk of free radical damage, or oxidative stress. In a study of 178 elderly men and women, ages 70-96, researchers found that vitamin E, but not vitamin C, was associated with normal lung function.

Dow L, et al., *American Journal of Respiratory and Critical Care Medicine*, 1996;154:1501-4.

• Spices as antioxidants

Herbal remedies have been used for centuries, and recent research suggests that the antioxidant activity of herbs is one of the principal reasons why they work. In an analysis of common herbs, researchers found cinnamon to be an extremely potent antioxidant. Pimento and bay were also powerful antioxidants.

Anderson JG, et al., *Journal of the Royal Society of Medicine*, 1996;89:540.

• Vitamin E succinate and breast cancer

Vitamin E succinate is an effective anti-tumor compound in cell-culture studies, and its anti-proliferative effect may be related to how it interacts with cell membranes. Related succinate compounds seem to have similar effects.

Djuric Z, et al., *Cancer Letters*, 1997;111:133-9.

• Nutritional treatments for migraine

Two nutritional supplements, magnesium taurate and the omega-3 fish oils, may have roles in the prevention of migraine headaches.

McCarty MF, *Medical Hypotheses*, 1996;47:461-6.

• Vitamins C and K attack prostate cancer cells

Both vitamins C and K protect against prostate cancer. In a cell-culture study, a combination of vitamins C and K, in a 100:1 ratio, enhanced their individual anti-tumor activity by as much as 20 times. Other studies have shown similar effects against breast, oral, and endometrial cancers.

Venugopal M, et al., *Cell Biology International*, 1996;20: 787-97.

• Zinc protects blood fats from oxidation

In a study of 118 elderly Italian men and women, researchers assessed the effects of vitamin A and zinc on the oxidation of blood fats. Zinc supplements—25 mg daily for three months—decreased oxidation of blood fats, but vitamin A did not. "Adequate zinc intake or supplementation could play an important role in the prevention and/or modulation of diseases in elderly people," the researchers wrote.

Fortes C, et al., *European Journal of Clinical Nutrition*, 1997;51:97-101.

• Triglyceride supplement raises cholesterol levels

Medium-chain triglycerides, used by some athletes to boost energy, may also increase cholesterol levels. In a study of nine patients, the triglycerides increased cholesterol levels by 29 mg/deciliter.

Cater NB, et al., *American Journal of Clinical Nutrition*, 1997;65:41-5.

• Cholesterol levels lowered with oleic acid

Oleic acid, a monounsaturated fatty acid found in olive and sunflower oils, prevents the oxidation of the high-density lipoprotein (HDL) form of cholesterol.

Sola R, et al., *Free Radical Biology and Medicine*, 1997;22:1037-45.

Soy Genistein and Daidzein

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Williams fed 22 rhesus monkeys heart-disease-promoting high-fat diets. Half of the animals were given soy protein with intact genistein and daidzein, and the other half were given soy protein without these isoflavonoids.

When the animals' hearts were stimulated with acetylcholine, the female monkeys consuming genistein and daidzein responded by dilating normally. The isoflavones had no apparent effect on the hearts of male monkeys.

"These findings contribute to the growing body of evidence suggesting that a dietary supplement potentially may provide a viable alternative to traditional hormone replacement therapy," Williams concluded.

Other studies strongly suggest that genistein and daidzein can reduce the risk of breast cancer, partly because they block more powerful estrogens and also because they function as antioxidants. □

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