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N-Acetyl-Cysteine, a Potent Antioxidant, Can Prevent Muscle Wasting and Cancer

N-acetyl-cysteine (NAC), a form of the amino acid cysteine, is emerging as a potent antioxidant—and one that also helps prevent cancer and muscle wasting.

NAC works in two principal ways. It is a precursor to glutathione and a variety of glutathione compounds, which are among the most powerful antioxidant enzymes produced by the body. Numerous studies have found that NAC supplements boost the body's production of glutathione.

Independently of glutathione, NAC prevents mutations to DNA (your genes) from cancer-causing substances and enhances the repair of DNA. It has been used for more than 20 years as a mucolytic (mucous-dissolving) agent in respiratory conditions, as well as an antidote in acetaminophen poisoning.

One recent study looked at whether NAC might prevent cachexia, the loss of body cell mass in patients suffering from cancer, AIDS, severe burns, and trauma. The researchers found that NAC could prevent the loss of cell mass in healthy people as well.

In cachexia, people lose skeletal muscle as the body converts protein into glucose. A team of researchers led by Prof. Wulf Dröge, head of the immunochemistry division at German Cancer Research Center, Heidelberg, Germany, suspected that the conversion of protein to glucose resulted from aberrations in the body's production of energy. Indeed, people suffering from cachexia have low levels of adenosine triphosphate (ATP), the chemical that stores energy in cells.

The researchers investigated amino acid levels among people performing anaerobic exercises, such as weight-lifting and sprinting. They found that anaerobic exercises could lead to decreases in body mass similar to what occurs in cancer patients. But the decreases, the researchers noted, "were almost completely prevented by treatment with NAC," according to their article in the *Journal of Molecular Medicine* (July 1996;74:393-400).

Low blood levels of the amino acids glutamine and arginine and high levels of glutamate were also associated with a loss of body mass. "However, 'anaerobic exercise' or an increased glutamate level does not always cause a loss of body cell mass, as persons with sufficiently high baseline levels of glutamine, arginine, and cysteine remained stable in spite of the 'anaerobic exercise' and

increasing glutamate levels," the researchers wrote.

Other recent reports have addressed the role of NAC in preventing or treating cancer. In a review article published late last year, Silvio De Flora, MD, of the University of Genoa, Italy, noted that NAC may prevent cancer through a number of mechanisms. He wrote in the *Journal of Cellular Biochemistry* (1995;22:33S-41S), that NAC neutralizes free radicals, detoxifies toxic compounds, prevents carcinogens from attaching to DNA, and promotes DNA repair.

In another article in the same journal (1995;24S-32S), Nico van Zandwijk, MD, PhD, of The Netherlands Cancer Institute, described an ongoing study designed to evaluate the role of NAC in preventing lung cancer. Its role here seems logical, van Zandwijk wrote, because of NAC's demonstrated role in preventing and treating other lung disorders, such as bronchitis, seasonal viral infections and chronic obstructive lung disease. □

Vitamin E Succinate Reduces Tumor Growth by Stopping Angiogenesis

There's growing evidence that the succinate form of vitamin E—sold as d-alpha tocopheryl succinate—might have a big advantage over other types of tocopherols in cancer prevention. Both tocopheryl and tocopherol are chemical terms for vitamin E.

Most investigations of vitamin E succinate and cancer have relied on cell-culture studies, which have shown this form of the vitamin to inhibit cancer cell growth. But in a recent experiment with hamsters, Gerald Shklar, DDS, of the Harvard University Dental School, confirmed that supplemental vitamin E succinate inhibited angiogenesis, according to his report in *Oral Oncology, European Journal of Cancer* (1996;32B:114-9).

Angiogenesis is the development of new capillaries needed for tumor growth. The idea of using drugs, such as thalidomide, to stop angiogenesis is being researched aggressively. Shark and bovine cartilage, which have been reported to stop angiogenesis, have emerged as alternative treatments for cancer. However, both forms of cartilage are very expensive.

Shklar found that vitamin E succinate also inhibited tumor growth factor alpha, which promotes cancer

Continues on next page

growth. It might also work by preventing nuclear factor kappa-B, a cancer-promoting protein, from attaching to genes.

Meanwhile, other recent studies show that vitamin E succinate can stop the growth of prostate cancer cells and retrovirus-induced cancers, according to research described in *Nutrition and Cancer* (1995;24:161-9 and 171-85). The acetate form of vitamin E also has an inhibitory effect, but it is much weaker than the succinate. □

Sticks and Stones May Break My Bones...and Generate Free Radicals

Whether it happens by accident or intentionally (as during surgery), a broken or damaged bone hurts. That same broken bone generates large numbers of free radicals that can injury nearby cells, according to Martyn C. R. Symons, PhD, of the London Hospital Medical College.

As a result, a broken bone might increase your need for antioxidants.

Symons investigated free radical formation by breaking fresh animal bones in a controlled laboratory setting. He used electron-spin resonance spectroscopy to measure unpaired electrons. Symons found that peroxy radicals were the most common type produced, apparently from the collagen rather than from the mineral matrix in bone, according to his article in *Free Radical Biology & Medicine* (1996;20:831-5).

"I suggest that if these radicals are of any importance in fracture, they must be of far greater importance in operations involving the cutting of bones using any type of saw," Symons wrote. "This is because, in effect, there are thousands of 'breaks' for each movement of the saw..." □

Malnutrition in the Hospital Wards

The measurement of body mass may be more effective than a routine assessment by a dietician when it comes to identifying general malnutrition among hospitalized patients.

The implications are profound. "Malnutrition reduces skeletal and cardiac muscle function so making chest infections and cardiac failure more common. The risk of chest infections is further increased by an impairment of immune function," wrote J. M. D. Nightingale, MD, in the *Journal of the Royal Society of Medicine*, 1996;89:144-8).

Nightingale, a gastroenterologist, studied 84 patients at the Leicester Royal Infirmary, England. Three methods were used to determine general, but severe, malnutrition: the loss of more than 10 percent of weight loss over the previous three months, and measurements of body mass index and mid-arm muscle circumference.

Recent loss of body weight pointed to the most cases of malnutrition (27 percent). When all three methods were combined, 35 percent (29 out of the 84) of the

patients were identified as malnourished. Only 28 percent of the malnourished patients had been examined by a dietician.

This research project "concerns the detection of patients who are already malnourished," wrote Nightingale. "In (the) hospital there is a second group of patients who are not malnourished but are at a high risk of becoming so. To optimize hospital nutritional care, both patient groups need to be identified..." □

Soy Genistein Early in Life Protects Against Cancer Later

The earlier in life a woman begins consuming genistein, a flavonoid found in soy foods, the lower her long-term risk of breast cancer might be.

Genistein competes with hormonal estrogen for cellular receptor sites and inhibits the estrogenic effects of natural and synthetic forms of the female hormone. These effects reduce the carcinogenic effect of estrogen, and many scientists believe that lifelong consumption of soy genistein lowers the risk of breast cancer in women. For example, Asian women eating high-soy diets have a lower risk of breast cancer than do American women eating relatively little soy.

Now, researchers at the University of Alabama, Birmingham, have shown in animal experiments that the consumption of genistein before puberty greatly reduces the risk of breast cancer later in life.

A team of researchers headed by Coral A. Lamartiniere, PhD, fed genistein or a placebo to prepubescent laboratory rats. Later, all of the rats were exposed to a chemical carcinogen.

The animals given genistein developed almost 50 percent fewer tumors compared with those given the placebo, according to Lamartiniere's article in *Carcinogenesis* (July 1996;17:1451-7). They also had slightly longer menstrual cycles. That's consistent with the longer cycles experienced by Asian women (who are at a low risk of breast cancer) compared with Americans. □

Elderly Who Are Unhealthy Typically Lack Antioxidants

Elderly people with diseases and disabilities have lower blood levels of antioxidant nutrients and higher cholesterol levels than either healthy old or young people. That in itself doesn't prove that antioxidants prevent age-related diseases, but it is consistent with a large body of evidence suggesting that they do.

Andrea Mezzetti, MD, of the Institute of Medical Physiopathology, Chieti, Italy, studied three groups of people: (1) 100 men and women over age 80 without any history of serious disease; (2) 62 men and women over 80 suffering from stroke, dementia, Alzheimer's, Parkinson's, or arthritis; and (3) 91 people between

the ages of 20-70 without disease or disabilities.

Mezzetti found that blood levels of vitamins E and C, thiols (e.g., glutathione), and oxidized cholesterol were associated with aging. Elderly people with diseases had lower levels of vitamins E and C, beta-carotene, and thiols than did either healthy elderly or healthy younger people. But even in the healthy elderly, levels of vitamins E and C were significantly lower than in healthy younger people, according to an article in the *Journal of the American Geriatric Society* (July 1996;44:823-7).

Older people had higher levels of oxidized cholesterol, one sign of oxidative stress, and elderly people with diseases had the highest levels of oxidized cholesterol. Among all of the subjects, higher levels of oxidized cholesterol correlated with lower levels of vitamin C.

"The body's susceptibility to oxidative stress is conditioned by the overall balance between [free] radical generation and antioxidant potential at tissue level," Mezzetti wrote. "However, aging per se, and age-related degenerative diseases, may induce changes that favor a systemic antioxidant/pro-oxidant imbalance, which will eventually result in oxidative stress." □

Vitamin Deficiencies Common in Elderly, Setting the Stage for Disease

Vitamin deficiencies, which cause or contribute to a variety of diseases, are fairly common, according to a study published by French researchers.

J. C. Guillard, MD, of Dijon, France, estimated vitamin intake based on diets and then measured blood levels of vitamins in 337 apparently healthy middle-age subjects.

Based on dietary data, low levels of vitamin B1 were found in 5 percent of men and 7 percent of women, low B6 in 11 percent of men and 28 percent of women, low vitamin C in 6 percent of men and 3 percent of women, low vitamin D in 87 percent of men and 91 percent of women, and low vitamin E in 8 percent of men and 13 percent of women. Low vitamin intakes were considered those that amounted to less than 50 percent of the French Recommended Dietary Allowances (RDAs).

When Guillard measured blood levels, 15 percent of men and 20 percent of women had low vitamin D and 13 percent of men and 15 percent of women had low vitamin E, according to an article in the *Annals of Nutrition & Metabolism* (1996;40:24-51).

Even among most of the other vitamins measured, such as vitamin B12, folic acid, vitamin A, and vitamin B12, levels were borderline and indicated "a moderate risk of vitamin deficiency."

"Our results (as [in] other studies performed in France and in other industrialized countries) raise the issue of the health significance of marginally deficient vitamin status," Guillard wrote. □

How Free Radicals Derail Brain Cells

Most brain researchers recognize that beta-amyloid protein fibers play a principal role in Alzheimer's disease. These fibers, like a microscopic tangle of wires, choke neurons and lead to their death.

The details of why beta-amyloid protein is so dangerous to brain cells have not been entirely clear. But now, an international group of researchers led by Shi Du Yan, MD, of the Columbia University College of Physicians and Surgeons, has identified and described some of the key steps in what happens.

According to Yan's article in *Nature* (Aug 1996;382:685-91), it's generally known that beta-amyloid protein generates free radicals and is a major antioxidant stress to neurons. This oxidative stress causes much of the damage to brain cells, but not always directly.

According to Yan's findings, beta-amyloid protein also attaches to the cell receptors for advanced glycation end products (AGEs). True to their acronym, AGEs are chemical compounds that contribute to the aging of cells.

These cell receptors then stimulate the activity of microglia, brain cells that scavenge for free radicals and other cellular waste products. Unfortunately, microglia also release some free radicals and other toxins, further damaging neurons. The process is exacerbated because microglia eventually move toward and become part of beta-amyloid deposits on neurons.

Not surprisingly, antioxidants can slow down this damaging process, just as they can quench free radicals in other parts of the body. Yan found that N-acetylcysteine (see page 1) and probucol could reduce oxidative stress in brain cells. Probuco is a cholesterol-lowering drug recently identified as an antioxidant. □

Vitamin D Slows Progression of Osteoarthritis of the Knee

The development of osteoarthritis, which affects about 10 percent of people over age 65, can probably be slowed with vitamin D, according to a report in *Annals of Internal Medicine* (Sept 1, 1996;125:353-9).

The vitamin is obtained by consuming foods enriched with vitamin D, supplements, or simply by spending some time in the sun. Sunlight catalyzes the conversion of cholesterol in the skin to vitamin D.

Timothy E. McAlindon, MD, of the Boston University Arthritis Center, studied 516 patients enrolled in the Framingham Heart Study.

People eating little vitamin D were two to four times more likely to have more serious osteoarthritic knee problems than those who consumed 100 percent of the vitamin's RDA daily. The RDA for vitamin D is 400 IU.

Editor's note: Excess vitamin D can cause irreversible side effects. If you plan to take more than 400 IU daily, please consult with your physician. □

Quick Reviews of Recent Research

• Antioxidant vitamins and tumor growth

Researchers have previously suggested that, at very low doses, vitamin C might actually function as a pro-oxidant, generating free radicals. That's consistent with one of the findings of this study: low doses of vitamin C promoted the growth of tumor cells, but high doses inhibited growth. There's more, though. Of several antioxidants tested, beta-carotene was the most effective in reducing tumor growth. Furthermore, a combination of four nutrients—vitamins A, C and E, and beta-carotene—was far more effective than only two or three of them in slowing tumor growth.

Prasad KN and Kumar R, *Nutrition and Cancer*, 1996;26:11-19.

• Vitamin E and anticoagulant drugs

Over the years, some doctors have been concerned that vitamin E, a mild anticoagulant, might potentiate the effects of prescription blood-thinning drugs and lead to longer bleeding times. In a placebo-controlled study of 25 patients, doctors found that 800-1,200 IU of vitamin E daily did *not* increase the blood-thinning effect of warfarin, a common anticoagulant drug. Ironically, and inexplicably, inert dummy pills did increase the blood-thinning effect of warfarin in two patients.

Kim JM and White RH, *American Journal of Cardiology*, 1996;77:545-6.

• Vitamin E cures yellow nails

Yellow nail syndrome (YNS) is a rare condition that includes discoloration of fingernails, chronic bronchitis and lung infections, and lymphedema (swelling because of a lymphatic obstruction). Doctors reported the successful treatment of a 27-year-old woman with prescription drugs to improve lung function, plus 800 IU daily of vitamin E. They also noted that zinc supplements might also be helpful in treating YNS, possibly because both nutrients quench free radicals.

Luyten C, et al., *Dermatology*, 1996; 192:406-8.

• Fish oil capsules ease Crohn's disease

An estimated 500,000 to 1 million Americans suffer from Crohn's disease, a particularly severe type of inflammatory bowel disorder. Because fish oil is recognized as an anti-inflammatory, doctors gave nine 500 mg capsules daily to 39 patients for one year. Their responses were compared with 39 patients given a placebo for the same time. Sixty-nine percent of those taking the dummy capsules had relapses of Crohn's disease. In contrast, only 28 percent of patients taking fish oil suffered relapses.

Belluzzi A, et al., *New England Journal of Medicine*, 1996;334:1557-60.

• Carbohydrates, pregnancy, and low-weight infants

Although a pregnant woman should eat for two, it's

important to watch what is eaten. In this revealing study, researchers found that women who ate a lot of carbohydrates—starchy and sugary foods—early in their pregnancy were more likely to give birth to low-birth-weight infants. The study, which looked at 538 women, also found that women who ate relatively little protein late in their pregnancy also tended to deliver low-birth-weight infants. The reason for the association between high-carbohydrates, low-protein, and low-birth-weight infants wasn't clear. *Editor's note:* This is admittedly speculative, but high-carbohydrate diets often reflect a junk-food diet that provides fewer vitamins and minerals than a more balanced diet.

Godfrey K, et al., *British Medical Journal*, 1996;312:410-4.

• Nitrous oxide anesthesia and low vitamin B12

It is well established that the chronic recreational use of nitrous oxide gas can destroy vitamin B12 and cause symptoms of nerve damage. Apparently, nitrous oxide used as anesthesia during surgery can have the same deleterious effect. Doctors reported the case of a 70-year-old woman who had anesthesia for 105 minutes during surgery. Ten days later, she developed a general sense of weakness and leg pains, and four weeks later could not walk and suffered sharp pain when touched lightly on the legs. Her blood B12 levels were a fraction of normal, and she improved after receiving B12 injections. The unanswered question: how many subtle cases of anesthesia-induced B12 deficiency go unrecognized?

Nestor PJ and Stark RJ, *Medical Journal of Australia*, 1996;165:174.

• Antioxidants counter dioxin-induced cancer

The pollutant dioxin is a powerful tumor promoter and nerve toxin. In a cell-culture study, researchers found that several antioxidants blocked the tumor-promoting effects of dioxin. The antioxidants used included vitamins C and E and mannitol, a type of sugar that also scavenges hydroxyl free radicals.

Wölfle D and Marquardt H, *Carcinogenesis*, 1996;17:1273-8. □

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