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Cancer Susceptibility Related to Cell Damage, Poor Diet, and Inadequate Repair of Genes

The development of cancer entails more than a simple exposure to a carcinogenic substance. It's caused by a complex interplay between exposure to hazardous substances, free radical damage to deoxyribonucleic acid (DNA, which forms your genes and chromosomes), protective dietary antioxidants, and DNA's inherent ability to repair itself.

Stimson P. Schantz, MD, of the Memorial Sloan-Kettering Cancer Center, New York, recently explored this interplay in a human case-control study. Schantz compared the diets of 167 patients diagnosed with head and neck cancers to those of 177 healthy subjects. He also analyzed the subjects' sensitivity to mutagens by measuring how prone their DNA was to breakage. Schantz and other researchers have proposed that people highly sensitive to mutagen-induced DNA breaks have the greatest risk of developing cancer.

"The purpose of the present study was to establish...the significance of mutagen sensitivity as an independent risk factor for disease....We hypothesized...[that] free radical oxygen damage represents a basis for cancer initiation," Schantz wrote in *Laryngoscope* (June 1997;107:765-81). "The overall probability of developing disease would reflect a balance between environmental exposure, nutritional habits that may protect against that exposure, and an inherited susceptibility to DNA damage."

His paper is a trove of information related specifically to head and neck cancers—and, by implication, to many other types of cancer as well.

For example, current tobacco users were more than six times more likely to develop head and neck cancers than were nonsmokers. Passive smoking increased the risk of cancer by three times. In addition, high consumption of liverwurst, eggs, ice cream, beef, liver, pork, and fried chicken were associated with an increased cancer risk.

Schantz also analyzed white blood cells from his subjects to determine their sensitivity to mutagens—that is, how easily their cells' DNA would break. Many mutagens generate free radicals, which damage DNA through deletions or rearrangements. People who were especially susceptible to mutagens were almost five times more likely to develop head and neck cancers.

Why were some people more sensitive to mutagens? Some of them might have inherited genes that do not efficiently repair themselves. Other people seemed to consume low levels of antioxidant nutrients that protect DNA from mutagens.

A combination of mutagen sensitivity and low vitamin C intake boosted the risk of cancer by almost 16 percent. Low vitamin E increased risk by 14 percent, low cryptoxanthin by 12 percent, and low lycopene by 8 percent. People who were mutagen sensitive and consumed large amounts of alcohol—more than 100 drinks per month—were 45 times more likely to develop head and neck cancer.

In contrast, people who consumed large amounts of antioxidants were less likely to develop head and neck cancer. High intake of fruits and vegetables, particularly apples, tomatoes, and green salads, was protective. Schantz confirmed the role of antioxidants by incubating white blood cells from the study's participants with a mutagenic compound. Cells that were also exposed to vitamins E, C, and A developed fewer DNA breaks.

"The findings of this case-control study, as well as previous in vitro and epidemiologic studies, point to the relevance of free radical oxygen (FRO) damage and its repair as important determinants of head and neck carcinogenesis," Schantz wrote. "FRO is generated by a variety of mechanisms, including both normal endogenous metabolism and various carcinogenic exposures....the ability to effectively repair FRO-induced genetic damage would thus be critical to the prevention of cell death and/or mutational events." □

Creatine Supplements Increase Exercise Performance

Creatine has long been a staple of body builders who swear that the compound increases their energy levels and enables longer workouts. A new study unequivocally supports its performance-enhancing effects.

Energy in the body is contained and released by adenosine triphosphate (ATP). After ATP releases its energy, it is converted to adenosine diphosphate (ADP). Creatine plays an essential role in recycling ADP back to ATP.

In a double-blind study, 14 active men underwent two sessions of bench press and squat exercises without supplementation. Each session was separated by six days. For six days prior to a third session, half of the men received 25 grams of creatine monohydrate daily and the others received a placebo.

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"Creatine supplementation resulted in a significant improvement in peak power output during all...jump squats and a significant improvement in reptitions during all...bench presses," wrote William J. Kraemer, PhD, of Pennsylvania State University, University Park, Penn., in the *Journal of the American Dietetic Association* (July 1997;97:765-70). Body mass also increased, but Kraemer speculated that this was the result of water retention, rather than of new muscle. No changes in strength or body mass were seen in the men receiving a placebo.

Concluded Kraemer: "Athletes participating in a resistance training program may benefit from creatine supplementation because the supplementation allows them to complete their workouts at a higher intensity." □

Low Beta-Carotene Associated with Rheumatoid Arthritis

Low blood levels of antoxidant nutrients are associated with the subsequent development of rheumatoid arthritis and lupus erythematosus. The link between low beta-carotene and rheumatoid arthritis is particularly strong.

"For more than two decades, free radical oxidation products have been identified in synovial fluid, especially in fluid drawn from inflamed joints," wrote George W. Comstock, MD, of the Johns Hopkins University School of Hygiene and Public Health, Baltimore, and his colleagues, in the *Annals of the Rheumatic Diseases* (1997;56:223-25).

Comstock and his colleagues analyzed levels of beta-carotene, vitamin E, and vitamin A from blood samples obtained in 1974. They then studied how levels of these nutrients correlated to people who remained healthy and who developed disease.

Levels of the three nutrients were lower in all of the patients who later developed arthritis or lupus compared with those who did not develop the disease. However, the only statistically significant relationship was between low beta-carotene and the development of rheumatoid arthritis. People who developed arthritis had blood levels of beta-carotene that averaged 29 percent less than in healthy subjects. □

Flavonoids Strengthen Capillaries, Reduce Inflammation and Edema

The flavonoids, water-soluble pigments found in plants, have since 1936 been recognized for their role in maintaining the integrity of capillaries, the body's smallest blood vessels. Two recent studies confirmed that flavonoids reduce capillary permeability (leakiness), inflammation, and edema (fluid retention).

In one series of experiments, Peter Rohdewald, DSc, PhD, of Westfälische Wilhelms University, Germany, and Hungarian colleagues tested Pycnogenol, an extract of the bark of the French maritime pine tree containing about 40 different antioxidants. They found that Pycnogenol significantly reduced edema in the ears of mice and the paws of rats. When they applied a Pycnogenol-containing gel to the backs of rats, it prevented the breakage of blood vessels after ultraviolet light exposure, according to a report in *Pharmazie* (1997;52:380-2).

In a separate group of experiments, Brazilian and Swiss researchers used a combination of two citrus flavonoids (90 percent diosmin and 10 percent hesperidin) to reduce capillary permeability induced by histamine, bradykinin, and leukotriene B4. All three compounds, which are involved in allergic or inflammatory reactions, increased capillary leakage in hamsters. According to an article by Eliete Bouskela, MD, PhD, and Kossi A. Donyo, MD, in *Angiology* (May 1997;48:391-9) the flavonoid combination significantly decreased blood vessel permeability and adhesion of white blood cells, which promotes the inflammatory process. □

Garlic Slows Bladder Cancer Growth

Supplements of "aged garlic extracts" can reduce the size of bladder cancers, according to recent experiments.

Donald L. Lamm, MD, of West Virginia University, Morgantown, transplanted bladder cancers into laboratory mice and then treated them with injections of the Bacillus Calmette-Guérin (BCG) vaccine, garlic extract, or saline solution (placebo). BCG is the most effective conventional treatment for superficial bladder cancer, but its toxicity limits its use in some patients.

In one experiment, all of the animals receiving high doses of garlic has significant decreases in their tumor size. However, the garlic-*injected* animals died from the treatment.

So in a subsequent experiment, Lamm added different concentrations of *supplemental* garlic to the animals' drinking water for one month before and two months after injecting them with cancer cells.

According to Lamm's report in the journal *Cancer* (May 15, 1997;79:1987-94), tumor growth slowed by 37 percent among mice receiving 50 mg of garlic per 100 milliliters of water and 59 percent in those getting 500 mg garlic per 100 milliliters of water.

"The effects occurred without treatment-related mortality or evidence of side effects...Because no toxicity was observed and the greatest effect was observed with the highest dose of [garlic], it is possible that higher doses may be even more beneficial," Lamm wrote.

In a separate study, Anne-Marie Le Bon, PhD, of the Unité de Toxicologie Nutritionnelle, INRA, France, analyzed the effect of specific garlic compounds on breaks on deoxyribonucleic acid (DNA). Such DNA breaks can lead to genetic damage and cancer cells.

Le Bon measured DNA breaks caused by aflatoxin B1 (AFB1), N-nitrosodimethylamine (NDMA), or methylnitrosourea (MNU) in the liver cells of laboratory rats. All three compounds caused DNA breaks. When the

mice were pretreated with three garlic compounds—diallyl sulfide, diallyl disulfide, and allyl mercaptan—AFB1- and NDMA-induced DNA breaks were significantly reduced. According to Le Bon's article in *Cancer Letters* (Mar 19, 1997;114:131-4), diallyl disulfide had the greatest effect, reducing DNA damage from AFB1 by 82 percent. □

Form of Vitamin A Might Help Reverse Emphysema

A recent animal study offers promise that vitamin A derivatives might reverse emphysema. The condition, which affects about 2 million Americans (mostly smokers), enlarges and atrophies the lungs' alveoli, structures that exchange oxygen and carbon dioxide.

Last year, Gloria De Carlo Massaro, MD, and Donald Massaro, MD, of the Georgetown University School of Medicine, Washington, D.C., reported that supplements of all-trans-retinoic acid, a form of vitamin A, increased alveoli formation by 50 percent in rat lungs.

In their latest experiments, reported in *Nature Medicine* (June 1997;3:675-7), the Massaros chemically induced emphysema—and abnormal alveoli enlargement—in a group of laboratory rats. Among the rats subsequently given all-trans-retinoic acid, alveoli returned to normal.

The human body converts beta-carotene in part to all-trans retinoic acid. □

Contrary to Opinion, Iron and Vitamin C Don't Increase Radicals

Some researchers have believed that the combination of high vitamin C and iron generates free radicals and causes oxidative damage to cells. A new study, on premature infants, showed the opposite: that high levels of vitamin C protect against iron-induced lipid peroxidation—that is, free radical damage to fats in the body.

Balz Frei, PhD, newly appointed scientific director of the Linus Pauling Institute, Oregon State University, Corvallis, noted that previous *in vitro* experiments have shown that vitamin C, in the presence of iron in the blood, can generate large numbers of free radicals.

In his latest study, using blood drawn from premature infants, Frei reported that the oxidation of blood fats increased only when vitamin C levels dropped to low levels. As long as vitamin levels remained normal or slightly above normal, lipid peroxidation was inhibited.

When Frei and his colleagues added iron to blood taken from five healthy adults, he found that the vitamin C and iron did interact. However, the interaction did not lead to increased lipid peroxidation—again, as long as vitamin C was at normal or above normal levels.

Vitamin C "clearly acted as an antioxidant, not a pro-oxidant, toward lipids in iron-overloaded plasma," Frei wrote in the *Journal of Biological Chemistry*, June 20, (1997;272:1556-60). □

Beta-Carotene, Vitamin E Work in Tandem to Control Cholesterol

A study with rabbits has shown that beta-carotene can lower levels of the so-called "bad" low-density lipoprotein (LDL) form of cholesterol, and that vitamin E supplements prevent free radical damage to LDL.

Judy A. Driskell, PhD, of the University of Nebraska, Lincoln, fed rabbits a heart-disease-promoting diet, consisting of 0.5 percent cholesterol, 3 percent peanut oil, and 3 percent coconut oil for eight weeks. She and her colleagues gave some of the rabbits a weekly intravenous injection of beta-carotene, dietary supplements of vitamin E, or a combination of both nutrients.

"Beta-carotene is transported predominantly with LDLs and dietary supplementation with beta-carotene leads to considerably increased beta-carotene levels in the LDLs," Driskell wrote in the *International Journal of Vitamin and Mineral Research* (1997;67:155-63).

Beta-carotene decreased total cholesterol and LDL levels and reduced the size of cholesterol deposits on the thoracic aorta, and decreased intima thickness. (The intima is the innermost layer of blood vessel walls, and its thickness is regarded as a risk factor for heart disease.) Beta-carotene did not reduce the free radical oxidation of LDL, considered an early stage in the development of coronary heart disease.

That, however, is where vitamin E pitched in. While it did not affect blood cholesterol levels, it did slow down the oxidation of LDL. Vitamin E also reduced the size of cholesterol deposits on the thoracic aorta and decreased intima thickness.

"Significant correlations were also found between plasma LDL alpha-tocopherol (vitamin E) and beta-carotene concentrations," Driskell wrote. "These may imply that alpha tocopherol protected beta-carotene from decomposition." □

Alpha-Lipoic Acid Corrects Sciatic Nerve Problem

Neuropathy, or nerve damage and pain, is a common complication in diabetes and some other conditions. Alpha-lipoic acid may bolster the sciatic nerve against damage more effectively than high-tech recombinant human nerve growth factor (rhNGF).

David R. Tomlinson, PhD, of the Royal London School of Medicine and Dentistry, treated diabetic rats with either alpha-lipoic acid or rhNGF to promote nerve growth and nerve function.

"One of the few agents available in sophisticated medical practice is alpha-lipoic acid (thioctic acid), which is licensed in Germany and has demonstrated efficacy in both experimental and clinical use against diabetes-associated neurological deficits," Tomlinson wrote in

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Quick Reviews of Recent Research

• Safety of chromium picolinate confirmed

Cell-culture studies published a couple of years ago reported that chromium picolinate, a popular mineral supplement, could cause chromosome breaks. However, many of the normal cell-protective mechanisms do not exist in cell cultures. In a study with laboratory rats, researchers found that very large doses of chromium, equivalent to 1,050 mg daily for an adult person, had no discernible toxic effect.

Anderson RA, et al., *Journal of the American College of Nutrition*, 1997;16:273-9.

• Vitamin E preserves brain cells

A recent study reported that vitamin E supplements slowed the progression of Alzheimer's disease. Using laboratory rats, researchers found that free radicals swelled brains cells and deformed nerve cells. In addition, brain cells stopped releasing acetylcholine, a key neurotransmitter. However, supplemental vitamin E protected brain and nerve cells against free radical damage.

Urano S, et al., *European Journal of Biochemistry*, 1997;245:64-70.

• Carotenoids linked to low breast cancer risk

Although dietary intake of antioxidants is associated with a lower risk of cancer, relatively little research has explored the relationship between carotenoids and breast cancer. Researchers used a food questionnaire to compare intake of beta-carotene, vitamin A, and vegetables among 3,543 women with breast cancer and 9,406 healthy controls. Consumption of either carrots or spinach, both high in beta-carotene and other carotenoids, more than twice a week was associated with a 44 percent reduced risk of breast cancer.

Longnecker MP, et al., *American Journal of Epidemiology*, 1997;11:S28 (Abstr #112).

• Carotenoids associated with better glucose control

Using data collected in 1988 and 1991 for the National Health and Nutrition Examination Survey III, researchers looked for relationships between blood levels of several carotenoids and normal glucose tolerance, impaired glucose tolerance, and diabetes. Low levels of two carotenoids, beta-carotene and lycopene, were related to glucose intolerance and high fasting insulin levels—both signs of adult-onset diabetes.

Ford ES, et al., *American Journal of Epidemiology*, 1997;11:S86 (Abstr #343).

• N-acetylcysteine slows neural degeneration

A mutant strain of mice, called "wobblers," is used to model motor-neuron degeneration. Treated with N-acetylcysteine (NAC), wobbler mice benefited from a reduction in motor neuron loss and elevated levels of the antioxidant glutathione peroxidase in their spinal cords. The mice also gained muscle mass and muscle fiber in the triceps and flexor carpi ulnaris, increasing function of the animals' forelimbs.

Henderson JT, et al., *Journal of Neuroscience*, 1996;16: 7574-82.

• Milk fats may reduce cancer risk

Fats are essential nutrients, though many people consume excessive or unbalanced levels of fats. This review article noted that several components of milk fat lower the risk of various types of cancer in cell-culture studies. Among them are conjugated linoleic acid, which inhibits growth of breast, colon, and other cancers; sphingomyelin, which slows the proliferation of cancer cells; and butyric acid, which can induce cell differentiation (normalization) or trigger cancer cell death.

Parodi PW, *Journal of Nutrition*, 1997;127:1055-60.

• Plant hormone stretches life expectancy

As another example of the many health-promoting substances found in fruits and vegetables, researchers studied kinetin, a growth hormone for plants. Adding kinetin to the diets of fruit flies resulted in higher levels of catalase (an antioxidant enzyme) and greater longevity, but lowered reproductive abilities. Earlier studies found that kinetin increased life expectency in cultured human cells. However, there appears to be an optimal range because high doses shortened life expectancy.

Sharma SP, et al., *Biochemistry and Molecular Biology International*, 1997;5:869-75.

Alpha-Lipoic Acid...

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Neuroscience Letters (1977;222:191-4).

Both alpha-lipoic acid and rhNGF increased some neurotrophic substances in the laboratory animals. However, only alpha-lipoic acid normalized levels of a key neurotrophic compound, called neuropeptide Y-like immunoreactivity, in the sciatic nerve.

Wrote Tomlinson: "The observations here offer an interesting insight into the potential efficacy of alpha-lipoic acid as an agent directed at diabetic neuropathy." □

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