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Vitamin C Signals Stem Cells to Turn into Heart Cells, Initiating a Basic Life Process

Over the past several years, medical research using human embryonic stem cells, obtained from discarded fertilized egg cells after in vitro fertilization procedures, has become a politically and ethically charged issue. But controversy aside, a dramatic new study has found that the normal behavior of these basic cells of life depends in large part on vitamin C.

Human embryonic stem cells are essentially generic cells. They are among the most fundamental unspecialized living cells, which serve as "parent" cells for what will eventually become an entire body. In a developing fetus, small numbers of stem cells divide and give rise to trillions of highly specialized cells, including those that form the heart, lungs, brain, and other organs.

Scientists have labored over exactly how embryonic stem cells start to differentiate and form many different types of cells. It is now clear that vitamin C is essential for that process.

In the study, Richard T. Lee, MD, and his colleagues at the Harvard Medical School, tested 880 chemical compounds for their effect on embryonic stem cells derived from mice. The stem cells were pretreated so that they would emit a green color if they grew into heart muscle cells.

Of all 880 compounds, which are approved for use in people, only one promoted activity in the stem cells, and that was vitamin C.

In the experiment, Lee and his colleagues treated embryonic stem cells with vitamin C for 12 days. During this time, large numbers of the stem cells began transforming into heart muscle cells called myocytes. The cells even began to beat rhythmically, as normal heart cells do.

In addition, vitamin C prompted the expression, or activation, of several cardiac genes, which would have further directed the behavior of the heart cells.

To rule out an antioxidant effect, Lee and his colleagues tested vitamin E and other antioxidants on the stem cells. Again, only vitamin C prompted stem cells to differentiate into heart cells.

The study's findings are significant for a number of reasons. According to Lee, treating embryonic stem cells with vitamin C could facilitate the large-scale production of heart cells, which someday might be administered to treat heart failure.

The findings are significant, also, because vitamin C is well-known as a cell-protecting antioxidant. However, research has shown that vitamin C has many nonantioxidant properties, such as being an enzymatic cofactor in the body's production of collagen, a key protein in tissue.

This particular study showed that vitamin C plays a key role in one of the most basic processes in life, the transformation of stem cells into heart cells and, potentially, into the many other specialized cells forming the body.

Reference: Takahashi T, Schulze C, Lord B, et al. Ascorbic acid enhances differentiation of embryonic stem cells into cardiac myocytes. *Circulation*, March 31, 2003. Electronic publication in advance of print. □

Combination of Vitamins E and C Reduce Progression of Cardiovascular Disease

Taking daily supplements of natural vitamins E and time-release vitamin C for six years can significantly slow the development of cardiovascular disease. That's the finding of a new study by Jukka T. Salonen, MD, PhD, of the University of Kuopio, Finland, and his colleagues.

In 2000, Salonen reported that the vitamin combination reduced the progression of atherosclerosis in men, but not women. The latest study tracks the same subjects for three additional years.

The clinical trial included 440 men and women who ranged from age 45 to 69 years at the start of the study. The subjects were in generally good health other than having elevated blood levels of cholesterol, a risk factor for cardiovascular diseases.

Salonen and his colleagues asked the men and women to take one of four supplements: a combina-

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tion of natural vitamin E (136 IU) and time-release vitamin C (250 mg), vitamin E by itself, vitamin C by itself, or a placebo.

The subjects' progression of cardiovascular disease was measured with sophisticated ultrasound analysis of the interior thickness of the carotid artery, technically known as carotid artery intima-media thickness. The carotid artery is a major blood vessel in the neck, and this type of thickening is considered a marker of overall risk for cardiovascular disease.

The benefits of the antioxidant vitamins were far more pronounced in men than in women. In men taking both vitamins E and C, carotid-artery thickness was reduced by 37 percent, compared with those taking placebos. In women taking vitamins E and C, carotid-artery thickness was reduced by only 14 percent, which was not considered statistically significant.

"The present 6-year data provide a confirmation for our 3-year findings, demonstrating that the combination of supplemented reasonable doses of vitamin E and slow-release vitamin C, taken with meal, may slow down the progression of carotid atherosclerosis in healthy hypercholesterolemic persons," wrote Salonen and his colleagues.

Reference: Salonen RM, Nyyssonnen K, Kaikkonen J, et al. Six-year effect of combined vitamin C and E supplementation on atherosclerotic progression. The antioxidant supplementation in atherosclerosis prevention (ASAP) study. *Circulation*, 2003;107:947-953. □

B Vitamins Reduce Risk of Breast Cancer Among Women Who Drink Alcohol

Diets rich in folic acid may reduce a woman's risk of breast cancer, particularly if she is in the habit of consuming a daily alcoholic drink.

Shumin M. Zhang, MD, ScD, of the Harvard School of Public Health, tracked the health of almost 33,000 women participating in the ongoing Nurses' Health Study. Between 1980 and 1999, 712 of the women were diagnosed with breast cancer.

Zhang compared the diets and blood levels of folic acid and vitamins B6 and B12 in these women and 712 women without the disease.

Overall, women with the highest blood levels of folic acid were 27 percent less likely to be diagnosed with breast cancer.

However, high blood levels of folic acid were especially protective in women who consumed one or more alcoholic drinks daily. Women who drank 15 grams or more of alcohol daily were 89 percent less likely to develop breast cancer, if they also consumed a lot of folic acid.

Moderate drinkers had a 28 percent lower risk of developing breast cancer, if they had high blood levels of folic acid.

High levels of vitamins B6 and B12 also provided some benefits. Women with the highest blood levels of vitamin B6 were 30 percent less likely to develop breast cancer. Premenopausal, but not postmenopausal, women with high levels of vitamin B12 had a 64 percent lower risk of developing breast cancer.

The B vitamins likely protect against breast cancer for two reasons. One, they are involved in the body's production of DNA, so low vitamin levels may lead to excessive genetic damage. Two, alcohol interferes with the absorption of folic acid and increases its excretion.

Reference: Zhang SM, Willett WC, Selhub J, et al. Plasma folate, vitamin B6, vitamin B12, homocysteine, and risk of breast cancer. *Journal of the National Cancer Institute*, 2003;95:373-380. □

Taking Beta-Carotene Supplements May Lower Cataract Risk Among Smokers

Smokers have an above-average risk of developing cataracts, likely because tobacco smoke generates cell-damaging free radicals in the body. A diet high in carotenoids may offset some of the damage and, according to a recent study, beta-carotene supplements might as well.

William G. Christen, ScD, of Brigham and Women's Hospital, Boston, and his colleagues analyzed data from the Physicians' Health Study, which asked 22,000 male physicians to take either a 50 mg beta-carotene supplement or a placebo every other day for 12 years.

Overall, beta-carotene supplements did not reduce the risk of cataracts. However, smokers who took beta-carotene supplements had a 26 percent lower risk of developing cataracts.

Smokers who took placebos were 65 percent more likely to develop cataracts.

Reference: Christen WG, Manson JE, Glynn RJ, et al. A randomized trial of beta-carotene and age-related cataract in US physicians. *Archives of Ophthalmology*, 2003;120:372-378. □

Ginkgo Supplements Reverse Eye Damage in "Normal-Tension" Glaucoma

Extracts of the herb *Ginkgo biloba* can reverse some of the eye damage in patients with normal-tension glaucoma, according to a short-term study by Italian physicians.

Typically, patients with glaucoma experience increased intraocular eye pressure and damage to the

optic nerve, which can result in blindness. In normal-tension glaucoma, which accounts for about 30 percent of all glaucoma cases in the United States, patients have damage to the optic nerve but maintain normal intraocular eye pressure.

In the study, Luciano Quaranta, MD of the University of Catania, Italy, and his colleagues treated 27 patients with visual-field damage caused by normal-tension glaucoma. He asked them to take 40 mg of ginkgo extract or placebos three times daily for four weeks. Then, after an eight-week washout period (without any supplements), the ginkgo supplements and placebos were reversed in the patients. Thus, each patient took ginkgo and placebos for four weeks during the study.

Quaranta used two techniques to assess visual field damage. He found that visual-field damage decreased, on average by about 20 to 24 percent, depending on the technique he used.

The findings are significant because established eye damage from glaucoma is generally believed to be irreversible.

Although Quaranta recommended a long-term study, he acknowledged that ginkgo extract "could play a major role in the treatment of glaucoma."

Reference: Quaranta L, Bettelli S, Uva M, et al. Effect of Ginkgo biloba extract on preexisting visual field damage in normal tension glaucoma. *Ophthalmology*, 2003;110:359-364. □

Type of Fish Consumed May Reduce or Increase Risk of Heart Disease

Men and women who eat tuna or any type of baked or broiled fish at least three times a week have a significant lower risk of dying from some types of heart disease. However, high consumption of fried fish may increase the risk of heart disease.

Dariusz Mozaffarian, MD, of the University of Washington, Seattle, and his colleagues, analyzed the eating habits and health of 3,910 men and women. The subjects were at least 65 years old, and they were free of cardiovascular disease in 1989 and 1990.

After a little more than nine years of follow-up, 247 of the subjects had died from ischemic heart disease, including 148 deaths from arrhythmias, and 363 nonfatal heart attacks.

People who consumed tuna or baked or broiled fish at least three times weekly had a 49 percent lower risk of death from ischemic heart disease and a 58 percent lower risk of death from arrhythmias. Fish consumption did not seem to reduce the risk of nonfatal heart attacks.

In contrast, people who regularly consumed fried fish or fried-fish sandwiches has a slightly

increased risk of death from ischemic heart disease.

Tuna and many common types of baked and broiled fish are rich in omega-3 fatty acids, which are known to reduce the risk of heart diseases. Fried fish is made from species with low omega-3 levels, and frying increases the amounts of trans fats and oxidized omega-6 fats, which may increase the risk of heart disease.

Reference: Mozaffarian D, Lemaitre RN, Kuller LH, et al. Cardiac benefits of fish consumption may depend on the type of fish meal consumed. *Circulation*, 2003;107:1372-1377. □

Vitamin/Mineral Supplement Lowers Risk of Infections in Diabetes

People with diabetes are more likely to develop infections compared with nondiabetics. But taking a daily multivitamin/multimineral supplement can significantly reduce the risk of infections and lost work days.

Thomas A. Barringer, MD, of the Carolinas Medical Center, Charlotte, N.C., and his colleagues asked 130 adults to take a daily multivitamin/multimineral supplement or placebo for one year. Two-thirds of the subjects, who ranged from 45 to 64 years of age, were overweight and about one-third had type 2 diabetes.

Although the supplement did not influence the overall risk of colds, flus, or gastrointestinal infections, it did significantly reduce the risk among people with diabetes.

Only 17 percent of diabetics taking the supplement had infections, compared with 93 percent of the diabetes taking placebos. In addition, none of the supplemented diabetics missed a day of work, whereas 89 percent of those taking placebos missed at least one day of work.

The researchers noted that people with diabetes commonly have some nutritional deficiencies, which may impair their ability to fight infections.

Many of the vitamins in the supplement were one to three times higher than recommended daily amounts.

"Multivitamin and mineral supplements are convenient and relatively inexpensive," Barringer and his colleagues wrote. "If our results are confirmed in a larger trial, the widespread implementation of this preventive measure could have a substantial economic impact and could ease the burden of suffering in our society."

Reference: Barringer TA, Kirk JK, Santaniello AC, et al. Effect of a multivitamin and multimineral supplement on infection and quality of life. *Annals of Internal Medicine*, 2003;138:365-371. □

Quick Reviews of Recent Research

• More research supports natural vitamin E

Studies with adults have found that natural vitamin E is assimilated twice as efficiently as the synthetic form of the vitamin, resulting in double the levels in blood and tissues. In this study, researchers fed 77 infants formula containing 20 IU of natural vitamin E, 10 IU of natural vitamin E, or 13.5 IU of synthetic vitamin E. Blood levels from 10 IU of natural vitamin E were equivalent to 13.5 mg of synthetic vitamin E, confirming the superior absorption of natural vitamin E.

Stone WL, et al. *American Journal of Clinical Nutrition*, 2003;77:899-906.

• Aloe vera has potent antioxidant properties

Aloe vera gel has long been used as a folk remedy to ease the pain of burns and to speed the healing of wounds. In a cell-culture experiment, researchers tested the antioxidant properties of some of the chemical compounds found in *Aloe vera*. These compounds were found to have anti-inflammatory properties, which might partly explain the plant's health benefits.

Yagi A, et al. *Planta Medica*, 2002;68:957-960.

• Pycnogenol® improve cholesterol ratios

Researchers asked 25 healthy men and women to consume 150 mg of Pycnogenol, an antioxidant extract of French maritime pine trees, for six weeks. Blood samples were taken at the start of the study and then again after three and six weeks. Tests indicated that antioxidant levels increased in the subjects' blood. In addition, two-thirds of the subjects had significant reductions in "bad" low-density lipoprotein levels and increases in "good" high-density lipoprotein cholesterol levels.

Devaraj S, et al. *Lipids*, 2002;37:931-934.

• Curcumin may kill cancer cells

Curcumin, found in the curry spice turmeric, is a potent antioxidant. In a laboratory experiment, researchers exposed human multiple myeloma cells (a type of cancer) to curcumin to determine whether it might have anti-cancer activity. Curcumin suppressed the growth and triggered the death of the cancer cells. The herbal ingredient also decreased the activity of several gene-related factors that could stimulate cancer cells.

Bharti AC, et al. *Blood*, 2003;101:1053-1062.

• White tea has anti-cancer properties

White tea, the least processed form of tea, contains higher levels of some antioxidants than does green tea. Researchers investigated the effect of white tea on mice bred to develop cancers of the gastrointestinal tract. The mice were fed green tea, white

tea, sulindac (an anti-inflammatory drug known to reduce cancers in these mice), a combination of white tea and sulindac, or plain water for 12 weeks. Both sulindac and green tea reduced the number of tumors by about half. White tea was somewhat more protective, and a combination of white tea and sulindac was the most protective, reducing the number of tumors by about 75 percent.

Orner GA, et al. *Carcinogenesis*, 2003;24:263-267.

• Antioxidants reduce risk of preeclampsia

Preeclampsia is a leading cause of maternal and infant death during pregnancy. Several studies have found that the condition involves elevated levels of free radicals and an increased ratio of plasminogen activator inhibitor (PAI-1) to PAI-2. In an earlier study, researchers found that supplemental vitamins E and C significantly reduced the risk of preeclampsia in pregnant women. In this follow-up study, the researchers investigated the effect of vitamins E and C on PAI-1 and PAI-2 in 192 pregnant women, many of whom were at risk of developing preeclampsia. The vitamin supplements raised PAI-2 levels, improving its ratio to PAI-1, and also lowered free radical levels, signs of reduced preeclampsia risk.

Chappell LC, et al. *American Journal of Obstetrics and Gynecology*, 2002;187:777-784.

• Antioxidants of benefit in Crohn's disease

Patients with Crohn's disease, a form of inflammatory bowel disease, often have higher blood levels of free radicals and lower levels of antioxidants. Fifty-seven patients with mild or inactive Crohn's disease were asked to take a combination of vitamin E (800 IU) and vitamin C (1,000 mg) or placebos daily for four weeks. By the end of the study, several indicators of free radical activity indicated had decreased, but disease activity remained stable, possibly because of the study's short duration.

Aghdassi E, et al. *American Journal of Gastroenterology*, 2003;98:348-353.

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