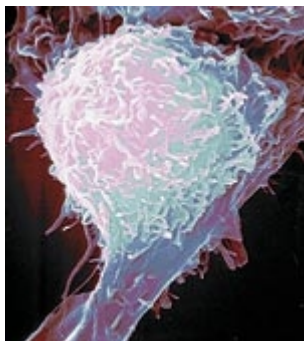


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IN THE NEWS

FDA Delays Promising Prostate Cancer Vaccine



Scanning electron micrograph of prostatic cancer cell, magnified 6,000 times.

In 2004, *Life Extension* reported on a Phase III study showing that men with metastatic prostate cancer who received an immune-boosting vaccine called Provenge™ were eight times more likely to live six months without disease progression than those who did not receive the vaccine.¹ This anti-cancer vaccine, however, was effective only in men with a Gleason score of 7 or less. (Higher Gleason scores are indicative of a more aggressive type of prostate cancer.)

The FDA refused to accept the study results because the agency does not allow retrospective analysis of a subgroup that may have benefited from an experimental drug. To gain FDA approval, Dendreon, the company testing the vaccine, was forced to begin a new study on men with Gleason scores of 7 or less. However, Dendreon continued to follow patients in the original study, and the results continue to be impressive. Of the 75 patients who entered the trial with a Gleason score of 7 or less, those receiving Provenge™ were 3.7 times more likely to be alive after 30 months; this translates into 53% of the Provenge™ group staying alive compared to only 14% of the placebo group. The Provenge™ group also remained pain-free twice as long on average as the placebo group.

A *Wall Street Journal* editorial commented on the FDA's deplorable delay by stating:

"We know that it works, and we know why it works. In any rational regulatory environment, that would be reason to speed Provenge™ to market. But this is the FDA we are talking about."

Fast forward to 2005, and the results of a new clinical study on Provenge™ show that three times as many advanced prostate cancer patients who received Provenge™ were alive compared to patients receiving a placebo. This study evaluated 127 patients with prostate cancer that did not respond to androgen-deprivation therapy (that is, hormone-refractory prostate cancer). Cancer experts consider this patient subset to have a dismal prognosis, with most dying of the disease within a few years. In the Provenge™ study, 34% of the patients receiving Provenge™ were still alive after three years compared to only 11% of men who were randomly assigned a placebo.³

Under FDA regulations, prostate cancer patients with such a dire prognosis had to risk receiving no therapy (the placebo) in the hope that they might be lucky enough to be in the study arm that received the promising drug (Provenge™). Life Extension has advocated that cancer patients with advanced disease should not have to risk receiving a worthless placebo. Historical controls could be used instead of placebos to spare such patients almost certain death.

Prostate cancer kills more than 30,000 American men every year.³ Provenge™ has clearly demonstrated that it improves survival rates, yet the FDA still has not approved it. Considering that the FDA could have approved Provenge™ as early as 2002, the agency's delay in approving this one drug alone may have resulted in the premature death of tens of thousands of men.

—William Faloon

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2. New cancer drugs. *Wall Street Journal*. January 26, 2004.
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Gamma Tocopherol Helps Kill Prostate Cancer Cells



Gamma tocopherol, a member of the vitamin E family, helps kill prostate cancer cells, according to a recent report in the *Proceedings of the National Academy of Sciences*.*

Previous studies indicate that dietary and environmental factors contribute to some cases of prostate cancer, while antioxidants such as vitamin E may mitigate risk. In a study conducted at the Children's Hospital Oakland Research Institute in California, the addition of gamma tocopherol to prostate cancer cell cultures not only inhibited cell proliferation but also caused cell death.

The vitamin E family comprises at least eight structurally related forms, all of which are potent antioxidants. Alpha tocopherol is the most abundant form of vitamin E in the human body and in

nutritional supplements, while gamma tocopherol dominates dietary sources. Importantly, alpha tocopherol supplementation suppresses gamma tocopherol levels in the body.

In the Children's Hospital study, gamma tocopherol demonstrated inhibitory effects on prostate cancer cells. Gamma tocopherol was even more potent in combination with another form of vitamin E called delta tocopherol. Together, the two forms of vitamin E produced cell death in hormone-sensitive—but not hormone-resistant—prostate cancer cells. Moreover, gamma tocopherol had no negative effects on normal prostate cells.

Gamma tocopherol exerted effects on prostate cancer cells by blocking sphingolipid metabolism, rather than through its antioxidant action. Sphingolipids are major structural components of cell membranes that mediate cell cycle control and cell death. By blocking the pathway for sphingolipid metabolism, gamma tocopherol deprives cancer cells of this required compound, ultimately leading to cell death.

The study results indicate that certain forms of vitamin E may be useful in preventing and treating some cancers.

—Linda M. Smith, RN

Reference

* Jiang Q, Wong J, Fyrst H, Saba JD, Ames BN. Gamma-tocopherol or combinations of vitamin E forms induce cell death in human prostate cancer cells by interrupting sphingolipid synthesis. *Proc Natl Acad Sci USA*. 2004 Dec 21;101(51):17825-30.

Judge Rejects EU's Proposed Supplement Ban

A European judge declared a proposed ban on thousands of herbal, vitamin, and food supplements "invalid" in a recent ruling. Advocate General Leendert Geelhoed of the European Court of Justice in Luxembourg said the proposed health food directive infringed upon European Union (EU) principles of "legal protection, legal certainty, and sound administration." The court will deliver a final verdict in June 2005.

EU governments approved the Food Supplements Directive in 2002, but gave manufacturers until July 12, 2005, to submit scientific evidence supporting the safety of their ingredients. Once approved, these ingredients and products would be added to a "positive list" of substances permitted for use in health foods. Such legislation would threaten at least 5,000 products containing more than 200 nutrients, including vitamins, minerals, and plant extracts.

The decision in Luxembourg follows protests from hundreds of doctors and scientists, as well as a legal challenge from the British health food industry. The British Health Foods Manufacturers Association, the National Association of Health Stores, and the Alliance for Natural Health argued that the proposed law was unnecessary and that the cost of compliance would be prohibitive for many small firms with a long history of making safe products. Approximately one third of British women and one fourth of men in the UK use supplements estimated to be worth at least \$627 million yearly in US dollars.

The opinion from the Advocate General is not legally binding on the rest of the European Court judges, but is followed by the full court in the majority of final rulings.

—Elizabeth Wagner, ND



Soy Lowers Blood Sugar, Insulin in Postmenopausal Women

Soy isoflavones, a type of phytoestrogen, lower fasting blood glucose and insulin levels in postmenopausal women, according to a study conducted at the National Taiwan University Hospital.¹

Soy isoflavones are a popular alternative to synthetic hormone replacement therapy, with some epidemiological studies suggesting that they help alleviate menopausal symptoms and decrease the risk of cancer and heart disease.²

In their study, Taiwanese researchers found that modest amounts of soy isoflavones are as potent as conjugated estrogen in lowering blood glucose and insulin levels.¹ The six-month trial examined two groups of postmenopausal women. One group received 100 mg of isoflavones daily, while the other group received a standard dose of 0.625 mg of conjugated estrogens. Both groups also took 300 mg of calcium a day. The researchers measured fasting glucose and insulin levels at baseline and at three and six months.

Compared to baseline values, fasting glucose and insulin levels declined significantly in both groups. Glucose levels fell to 85% and 83% of baseline levels in the isoflavone and estrogen groups, respectively. Similarly, insulin levels dropped to 67% and 56% of baseline values in the isoflavone and estrogen groups, respectively.

Soy isoflavones appear to protect against aberrant glucose metabolism in postmenopausal women. By lowering blood glucose and insulin levels, soy isoflavones may help protect against metabolic syndrome and diabetes.

—Linda M. Smith, RN

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IN THE NEWS

Quercetin Protects Nerve Cells from Oxidation



Quercetin, a bioflavonoid found in many fruits and vegetables, may protect nerve cells from the oxidative damage associated with conditions like Alzheimer's disease, report investigators at Cornell University.*

The human central nervous system is highly sensitive to oxidative stress, making it vulnerable to neurodegenerative diseases such as age-related cognitive decline and Alzheimer's. Scientists have studied many antioxidants, including vitamin C, as potential therapeutic agents against neurodegeneration. The Cornell group has now demonstrated that quercetin is better than vitamin C at protecting nerve cells from damage due to oxidative stress.

In their study, the Cornell researchers used a cell line with nerve-like characteristics. The cells were pre-incubated for two hours with either quercetin or vitamin C, and the treated cells were then exposed to hydrogen peroxide, a significant inducer of oxidative damage. Quercetin was more protective than vitamin C, and less cell death occurred in the quercetin-treated cells than in those treated with vitamin C. Quercetin also protected nerve cell membranes more than did vitamin C. This is significant because the researchers believe that loss of cell membrane integrity contributes to neurotoxicity. Larger doses of quercetin or vitamin C conferred greater protection from oxidative stress.

These findings suggest that quercetin offers significant antioxidant protection to nerve cells. Quercetin may therefore help to prevent or manage Alzheimer's disease and other neurodegenerative conditions associated with oxidative stress.

—Linda M. Smith, RN

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DHEA Improves Cardiovascular Health

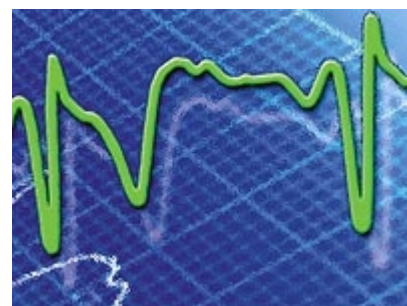
DHEA (dehydroepiandrosterone) improves blood flow and other measures of vascular health, report researchers at Australia's Monash University.*

Epidemiological studies have linked age-related decline in DHEA levels with decreased longevity and an increased risk of heart disease. The Australian team's findings, published in the *Journal of Clinical Endocrinology and Metabolism*, help elucidate the mechanisms by which DHEA benefits the cardiovascular system.

Using in-vitro studies, the investigators demonstrated that DHEA, like estrogen and testosterone, stimulates endothelial cells to divide. The endothelial cells lining blood vessels are critically important in cardiovascular health, as injury to such cells leads to the formation and progression of atherosclerotic plaque. DHEA expands the endothelial cell pool, possibly providing a ready source of cells able to "patch" areas of blood vessel injury. Additionally, DHEA provoked endothelial cells to produce greater amounts of nitric oxide, a vasodilator and powerful protector of the heart and blood vessels. DHEA exerted its effects on endothelial cells independently of both estrogen and androgen receptors.

The researchers also administered 100 mg per day of DHEA to 36 healthy postmenopausal women for three months. Using measures of blood vessel function, they showed that DHEA increased blood vessel dilation and reduced blood pressure. Moreover, DHEA supplementation led to increased blood flow and reduced cholesterol levels.

DHEA appears to be both safe and effective in improving cardiovascular health. Its mechanisms of action include optimizing blood flow, blood pressure, and cholesterol, in addition to supporting the health of endothelial cells. As DHEA supplements may be



contraindicated in those with a history of hormone-related cancer, always consult with your physician before considering supplementation.

—Linda M. Smith, RN

Reference

* Williams MR, Dawood T, Ling S, et al. Dehydroepiandrosterone increases endothelial cell proliferation in vitro and improves endothelial function in vivo by mechanisms independent of androgen and estrogen receptors. *J Clin Endocrinol Metab.* 2004 Sep;89(9):4708-15.

Berry Extracts Help Prevent Ulcers

Berry extracts help kill the bacteria that cause most ulcers and improve the efficacy of prescription ulcer therapy, according to a report from Creighton University in Omaha, NE.*

Helicobacter pylori (*H. pylori*), a bacteria that infects the stomach and small intestine, is associated with up to 90% of cases of peptic ulcer disease, as well as with gastric carcinoma and one type of lymphoma. *H. pylori* may also be linked to gastroesophageal reflux disease, or heartburn. Conventional treatment of *H. pylori* employs antibiotics combined with an inhibitor of acid secretion and/or a bismuth compound. Treatment failure is common, due either to difficulty in adhering to the complex medication regime or to the bacteria's resistance to antibiotics.

The Nebraska researchers demonstrated that berry extracts not only inhibit the growth of *H. pylori*, but also render it more susceptible to clarithromycin, one of the antibiotics used to eradicate the bacteria. *H. pylori* bacteria were incubated with extracts of raspberry, strawberry, cranberry, elderberry, blueberry, or bilberry, or with a combination of all six berries, for 18 hours. The mixture was then incubated with clarithromycin for an additional hour prior to growth assessment on Petri plates. All of the berry extracts inhibited *H. pylori* growth and increased its sensitivity to clarithromycin better than controls. The combined extracts exhibited greater potency than did the individual berry extracts.

Because of the serious nature of its associated medical conditions, anyone who tests positive for *H. pylori* should seek treatment. The Nebraska study suggests that the use of non-antibiotic supplements such as berry extracts improves the efficacy of antibiotic treatments.

—Linda M. Smith, RN

Reference

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Dr. Stephen Spindler Honored for Longevity Research



Established in 2003 by the Methuselah Foundation, the Methuselah Mouse Prize (“M Prize”) is a cash award that recognizes excellence in the field of longevity research. It honors scientific teams that most dramatically prevent aging and lengthen life in the laboratory mouse known as *Mus musculus*. The Longevity Prize honors scientists who most extend life span in a single mouse, and the Rejuvenation Prize recognizes those who most sharply delay aging in a middle-aged mouse.

Stephen Spindler, PhD, a member of the Life Extension Foundation Scientific Advisory Board, received the first-ever Methuselah Mouse Rejuvenation Prize at the Gerontological Society of America conference in Washington, DC, on November 21, 2004. Chair of the department of biochemistry at the University of California Riverside, Dr. Spindler found that caloric restriction increased life span and substantially decreased age-related mortality in middle-aged mice. Deaths from tumors also declined in the same mice. Caloric restriction led to changes in gene expression that may account for its longevity-promoting effects. These findings suggest that pharmaceutical and other compounds may be able to mimic changes in gene expression induced by caloric

restriction, and thus prolong life in a similar fashion. Dr. Spindler's findings were published in the *Proceedings of the National Academy of Sciences* in April 2004.*

“Caloric restriction works even in old animals to immediately extend life span and reduce the rate of tumor growth,” said Dr. Spindler. “We believe that therapies that reproduce the effects of caloric restriction on gene-expression biomarkers in humans may similarly reduce the incidence of age-related disease and extend life span.”

The nonprofit Methuselah Foundation is committed to defeating age-related disease and extending the healthy human life span. “We are very proud to honor Dr. Spindler and his main financial supporter, the Life Extension Foundation, for their historic and groundbreaking research,” said Methuselah Foundation Chairman and Chief Science Officer Dr. Aubrey de Grey. “The M Prize is meant to inspire and encourage this kind of serious scientific progress and innovation in extending the healthy human life span.”

Dr. de Grey, who was instrumental in establishing the prize, added, “If we are to bring about real regenerative therapies that will benefit not just future generations, but those of us who are alive today, we must encourage scientists to work on the problem of aging. The M Prize is a catalyst for research into this field. The defeat of aging is foreseeable, if we take steps to make it happen.”

Methuselah Foundation President David Gobel said the prize “is meant to inspire and encourage serious scientific progress and innovation in extending the healthy human life span. We believe the Methuselah Mouse Prize can effectively raise public optimism and enthusiasm about potential human application of successful life-extending interventions used on laboratory mice that have already reached an advanced age.”

The M Prize is funded entirely by private donations from individuals and organizations supporting longevity research and innovation, including the X PRIZE Foundation, the Foresight Institute, and the Life Extension Foundation. A recent donation from biotechnology pioneer Dr. William Haseltine brought the M Prize to the \$1 million mark. For more information, please visit www.mprize.org.

—Elizabeth Wagner, ND

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* Dhahbi JM, Kim HJ, Mote PL, Beaver RJ, Spindler SR. Temporal linkage between the phenotypic and genomic responses to caloric restriction. *Proc Natl Acad Sci USA*. 2004 Apr 13;101(15):5524-9.

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