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## IN THE NEWS

### Omega-3 Fatty Acids Stabilize Atherosclerotic Plaques



Heart disease can be seen as the symptom of lipid-containing plaques in the walls of the coronary arteries, carotid arteries, aorta, and peripheral arteries. In at least one-half of all first heart attacks, however, the plaques are hemodynamically insignificant—that is, they do not block arteries or cause chest pain. These plaques become clinically significant when they release fragments that lodge in smaller blood vessels, causing occlusion and depriving the neighboring tissues of blood and oxygen. By either direct pathological examination or with the assistance of magnetic resonance imaging, arterial plaques can now be assessed and classified as either stable or unstable.

With this in mind, researchers at the University of Southampton (UK) designed a prospective, randomized, double-blind clinical trial to determine the effect of dietary omega-3 fatty acids in 162 patients scheduled to undergo carotid endarterectomy for advanced atherosclerosis.\* The patients were given capsules containing omega-3 fatty acids in amounts known to be cardioprotective, capsules containing omega-6 fatty acids, or capsules containing a mixture of oils comparable to a typical Western diet. At the time of surgery, arterial sections were obtained and classified by a cardiopathologist as stable or unstable based on plaque morphology and degree of macrophage infiltration.

Compared with participants who received omega-6 fatty acids or a blend of Westernized diet oils, those receiving omega-3 fatty acids had a greater than 50% increase in stable versus unstable plaques. The investigators hypothesized that arterial plaques are dynamic structures and responsive to dietary modification.

Increasing dietary omega-3 fatty acids by consuming fish or supplements is cardioprotective, reduces atherosclerosis, prevents sudden deaths caused by unstable plaques, and decreases the likelihood of future heart attacks. Scientists believe this protection is conferred by the anti-inflammatory properties of omega-3 fatty acids.

—Dean S. Cunningham, MD, PhD

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#### Reference

\* Thies F, Garry JM, Yaqoob P, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. *Lancet* 2003 Feb 8;361(9356):477-85.

### Anti-Prostate Cancer Vaccine Shows Promise

At the June 2004 annual meeting of the American Society of Clinical Oncology, Johann Vieweg, MD, associate professor of urology and immunology at Duke University Medical Center, presented exciting findings on an immunotherapeutic vaccine he is testing against prostate cancer.

Unlike traditional vaccines that when administered protect the recipient from acquiring a disease, immunotherapeutic vaccines facilitate the destruction of an existing disease. Dr. Vieweg's vaccine provokes an immune attack against cells that overexpress telomerase, a polypeptide that is silent in normal human cells but abundantly expressed in more than 85% of all tumor cells, including those of the prostate, breast, lung, colon, and kidney. Telomerase is known to protect tumor cells from undergoing preprogrammed cell death, yet because of these differences in expression, telomerase can serve as an immunological target, thereby making tumor cells vulnerable while preserving the integrity of normal cells.



Of the 20 men with prostate cancer who are enrolled in Dr. Vieweg's study, 19 were able to successfully generate their own specific immune T cells with cytotoxic activity against telomerase-associated tumor cells and without appreciable side effects. As a result, the typical 2.9-month doubling time for prostate-specific antigen (PSA) in the blood increased to 100 months. PSA doubling time is a convenient measure of a prostate cancer patient's response to treatment—the longer the doubling time, the better the response.

Furthermore, 9 of 10 subjects who initially had detectable levels of circulating prostate cancer were found to have a significant reduction or complete absence of these cells following vaccination. In the study's next phase, the subjects will receive booster vaccinations to prolong their immunity and

presumptive protection from prostate cancer.

Unfortunately, while the few men participating in the study have benefited, many other eligible men will not. The telomerase vaccine is in Phase I/II clinical trials as a product in development for Geron Corporation, and it may well be years before this promising vaccine is made available to the public.

—Dean S. Cunningham, MD, PhD

## Short-Term Statin Use Depletes CoQ10 Levels

In a new study on statin use published in the *Archives of Neurology*, researchers at Columbia University in New York report that even a short course of statin therapy dramatically reduces levels of coenzyme Q10 (CoQ10).<sup>\*</sup> This finding, the researchers noted, could explain the troubling side effects of statin therapy, which include exercise intolerance, muscle pain, and other indicators of muscle dysfunction.

A widely prescribed class of drugs that reduce harmful cholesterol levels, the statins include Pravachol® (pravastatin), Zocor® (simvastatin), and Lipitor® (atorva-statin), which was used in the Columbia study. CoQ10 is a natural antioxidant and cofactor that is crucial to cellular energy metabolism. The body's natural production of CoQ10 declines with age and drops precipitously with statin use.



In the Columbia study, a majority of patients' CoQ10 levels dropped by as much as 49% after just two weeks of therapy. The study authors recommended CoQ10 supplementation as a preventive measure for patients taking Lipitor® or other statins.

High low-density lipoprotein (LDL) is implicated in atherosclerosis, which may lead to heart disease and stroke. Reducing cholesterol is a recommended health goal for most adults. While attention to diet helps, not all cholesterol comes from fatty foods; cholesterol is also manufactured within the body. Statins are effective because they interfere with one stage of a biochemical pathway that leads to the production of cholesterol. Because CoQ10 is created downstream by the same pathway, statins block its synthesis as well, making CoQ10 supplementation crucial for those taking statins.

—Dale Kiefer

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### Reference

\* Rundek T, Naini A, Sacco R, Coates K, DiMauro S. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. *Arch Neurol*. 2004 Jun; 61(6):889-92.

## Sex Hormones Implicated in Prostate Enlargement

The enlargement of the prostate gland that occurs with aging, known as benign prostatic hyperplasia (BPH), makes its appearance in most men while they are in their thirties. By the age of 80, approximately 85% of men have BPH. Up to one-third of men between 40 and 79 years of age have severe symptoms of BPH, including difficulty initiating urination, a weak urine stream, or awakening from sleep to urinate more than two or three times each night.

With more and more men are opting for testosterone supplementation to enhance their overall health, it is important to ascertain whether such therapy will correspondingly increase the risk of BPH. To date, the epidemiological evidence has not implicated serum testosterone levels in adversely affecting prostate health, nor have men who have received hormone replacement therapy been shown to have a higher rate of either prostate cancer or BPH.

Researchers at Gazi University in Ankara, Turkey, sought to determine the association, if any, between the serum concentration of sex hormones and severe symptoms of BPH.\* The study enrolled 61 men who were scheduled for radical surgery as a treatment for BPH, along with 45 asymptomatic matched control subjects. Although the degree of hyperplasia increased with age, the only significant relationship between hyperplasia and hormone levels involved estradiol. Estradiol levels were significantly higher in men with greater than 50 grams of hyperplastic tissue. The fluctuation of circulating hormones that occurred as a function of age was similar between the BPH group and control group. Specifically, free testosterone levels declined with age, while estradiol, prolactin, and gonadotropin levels increased.

The authors concluded that it is unlikely that serum concentrations of sex hormones are related to BPH, but rather it is the increasing ratio of estradiol to free testosterone that is important in the development of BPH.

—Dean S. Cunningham, MD, PhD

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\* Tan MO, Karabiyik I, Uygur MC, Diker Y, Erol D. Serum concentrations of sex hormones in men with severe lower urinary tract symptoms and benign prostatic hyperplasia. *Int Urol Nephrol*. 2003;35(3):357-63.

## IN THE NEWS

### Antioxidants May Protect Against Hearing Loss



Recent research published in the medical journal *Laryngoscope* lends further credence to the belief that supplemental antioxidants may protect the inner ear from traumatic and age-related hearing loss.<sup>1</sup>

In a study conducted at Southern Illinois University, scientists studied the effects of supplemental vitamin E on hearing loss induced by a potent anticancer drug, cisplatin. Rats receiving vitamin E before an injection of cisplatin sustained far less damage to the sensory hairs of the inner ear than rats that did not receive vitamin E. Scientists believe that cisplatin damages hearing in much the same way that normal aging erodes hearing; both conditions are believed to be the result of free-radical damage.<sup>2,3</sup> Scientists hypothesize that vitamin E and other antioxidants are able to

neutralize damaging free radicals before they affect sensitive sensory hairs in the inner ear.

The study's findings echo similar research published in recent years. In 2002, Yale University researchers determined that hearing loss correlates with both age and noise exposure. They found that subjects with higher vitamin E levels tend to suffer less loss of hearing than patients with low vitamin E levels.<sup>4</sup> Likewise, in a study conducted in Israel in 2003, human subjects with sudden hearing loss of unknown origin were more likely to recover their hearing after treatment with supplemental vitamin E than patients who did not receive the antioxidant.<sup>5</sup>

Other recent studies have noted a hearing-protective effect for other supplemental antioxidants, including resveratrol,<sup>6</sup> vitamin C, melatonin,<sup>2</sup> and acetyl-L-carnitine and alpha-lipoic acid.<sup>3</sup>

—Dale Kiefer

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#### References

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2. Seidman MD, Khan MJ, Bai U, Shirwany N, Quirk WS. Biologic activity of mitochondrial metabolites on aging and age-related hearing loss. *Am J Otol*. 2000 Mar;21(2):161-7.
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### Fossils Record Dramatic Gain in Human Longevity

A considerable increase in early human life span may have been a key factor in shaping modern civilization, according to a new fossil study published July 5, 2004, in the *Proceedings of the National Academy of Sciences*.

Scientists at the University of Michigan and University of California, Riverside, analyzed the ratio of older to younger adults in 750 hominid tooth samples from successive time periods, assessing the significance of differences in rates of molar wear. Their findings showed that the number of people surviving to an older age more than quadrupled during the early Upper Paleolithic Period around 30,000 BC, when *Homo sapiens* was becoming established in Europe.

In the study, the researchers defined “old” to be at least double the age of reproductive maturation. “While the age of reproductive maturation may have varied in early human groups, if it were 15, then age 30 would be the age at which one could theoretically first become a grandmother,” Caspari noted.



The jump in longevity may have been a key factor in the shaping of modern civilization. Larger numbers of older people provided distinct evolutionary advantages such as tighter social relationships and kinship bonds, as well as allowing greater efficiency in the accumulation and transmission of more specialized knowledge from older, experienced individuals to younger generations. This so-called “grandmother hypothesis” posits that grandmothers are useful because of the knowledge they pass on to reproductive-age daughters and their daughters’ offspring.

Longer life span would also have increased the number of years available for reproduction, working to promote population expansion, and creating social pressures that led to the growth of trade networks, increased mobility, and more complex systems of cooperation and competition.

“There has been a lot of speculation about what gave modern humans their evolutionary advantage. This research provides a simple explanation for which there is now concrete evidence: Modern humans were older and wiser,” the study’s co-authors wrote.

—Dean S. Cunningham, MD, PhD

## Scientists Identify Gene Thought to Control Aging

Researchers at the Mayo Clinic in Rochester, MN, were searching for genetic causes of cancer when they stumbled on something unexpected—a gene that controls important aspects of aging.\*

According to findings published in the journal *Nature Genetics*, the scientists discovered that mutant mice lacking a certain gene, dubbed BubR1, die of old age five times faster than normal mice. This glaring discrepancy in life span suggests that the protein coded by BubR1 is involved in maintaining normal life span. Mice without this protein show numerous early signs of accelerated aging, including thinning skin, a weakening immune system, infertility, cataracts, and spinal abnormalities.

Turning their attention to normal mice—which have the gene and thus the BubR1 protein—researchers discovered that BubR1 protein levels normally decrease with age. This prompted speculation that a decline in BubR1 protein may be responsible for at least some of the physiological decline associated with aging.

Because BubR1 protein levels dwindle in the testis and ovaries of normal mice with advancing age, scientists hypothesize that the protein decrease may be responsible for infertility and certain age-associated birth defects, such as Down’s syndrome, in humans. BubR1-lacking mutant mice are infertile due to an inability to pass the correct number of chromosomes to reproductive germ cells. Down’s syndrome and other common birth defects associated with advanced age in humans result when a fertilized egg contains an incorrect number of chromosomes.

This intriguing discovery provides new insight into the complexities of aging and may help scientists to better understand and eventually treat some of the disorders associated with human aging.

—Dale Kiefer

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\* Baker DJ, Jeganathan KB, Cameron JD, et al. BubR1 insufficiency causes early onset of aging- associated phenotypes and infertility in mice. *Nat Genet.* 2004 Jul;36(7):744-9. Epub 2004 Jun 20.

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