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## REPORT

Continued from Eat Less - But Do Eat Lots of Blueberries

Other lectures and poster presentations also suggested that lipoic acid reduces oxidative stress in the mitochondria of the heart muscle, and raises the levels of ascorbate and glutathione in the heart and liver mitochondria. The restoration of ascorbate levels was particularly striking: supplemental lipoic acid was able to restore cardiac ascorbate levels in old rats to those found in young rats.

Since lipoic acid functions as a mitochondrial coenzyme essential for the oxidation of the alpha-keto acids in the energy-producing Krebs cycle, its importance for efficient energy production by the mitochondria seems obvious. It is probably by increasing mitochondrial energy output that lipoic acid is able to lower blood glucose levels and the formation of harmful glycation products. Lipoic acid is thus emerging as an extremely important anti-aging agent.

(Parenthetically, there was also a lecture on the decrease of glycation products with the use of a "glyconutritional." The speaker would reveal only that the product contains a substantial amount of mannose and fucose.)

Deprenyl (selegiline) and its new close analog rasagiline are of great interest because they not only slow down aging, but may produce life span extension. Both deprenyl and rasagiline selectively increase the activity of antioxidant enzymes superoxide dismutase (SOD) and catalase, especially in dopamine-producing regions of the brain. The lecture given by Dr. Kitani revealed that rasagiline (and thus probably also deprenyl) also increases SOD and catalase activity in the heart and the kidneys. Interestingly, the lower dose was more effective than the higher dose. Rasagiline does not seem to offer any advantages over deprenyl, a drug used by some anti-aging researchers. Dosage is obviously crucial.

Still other ways to protect the aging brain were mentioned, such as anti-inflammatories (let us hope that the new COX-2 inhibitors such as Celebrex and Vioxx will prove much safer than nonselective NSAIDs such as ibuprofen and aspirin). Since inflammation-related damage to the brain starts to show up already in midlife, one should not wait until old age to begin a preventive anti-inflammatory treatment.

Estrogen replacement in postmenopausal women has also been shown to help prevent Alzheimer's disease. In fact, like many other phenolic compounds, estrogens are potent antioxidants. A sufficient dose of estrogen can totally prevent lipid peroxidation in brain cell membranes. However, like most antioxidants, estrogens need to be recycled back to their antioxidant state, or else they can act as pro-oxidants. Here glutathione appears to play a critical role. Hence a woman taking estrogen replacement should be aware of the need to keep her glutathione levels as high as possible. This can be accomplished by taking lipoic acid, N-acetyl-cysteine (NAC), and anthocyanins such as those contained in blueberries and bilberries.

Besides their antioxidant effects, estrogens also increase the release of acetylcholine, activate various methylating enzymes, act to prevent the formation of the amyloid plaque, decrease the production of pro-inflammatory cytokines, and much more. The benefits of estrogen replacement for brain health are beyond question: the higher the dose and the longer the duration of supplementation, the greater the protection against dementia. The point is to supplement estrogen in a safe way. Taking glutathione-raising supplements is a very important step toward making estrogen replacement safer.

It is possible that men can obtain similar neuroprotective benefits from testosterone replacement, since the male brain converts a significant portion of testosterone into estradiol. In fact, older men have higher estradiol levels than women of the same age who are not taking hormones. This has been cited as one factor that may explain the dramatic female prevalence of Alzheimer's disease. Since 40% of women over 80 (and over 50% of women over 90) suffer from this terrible disorder, at an enormous cost to society, spreading information about the many ways to prevent it or at least delay Alzheimer's disease is of enormous importance.

Antioxidants such as vitamins C and E have been documented to protect the brain. However, it turns out that the bioflavonoid called

quercetin, present in onions, apples, and especially in ginkgo biloba, is particularly effective, as are anthocyanins (bilberry extract and blueberries are a rich source of anthocyanins). Anthocyanins have been found to be more protective against free radical damage induced by the beta-amyloid protein than vitamins C and E. As Dr. Bruce Ames of Berkeley pointed out, gamma tocopherol is needed for scavenging nitrogen free radicals, such as the dangerous peroxinitrite radical.

Speaking of nitrogen, a new class of synthetic antioxidants called nitrones is also showing great promise. Nitrones react with free radicals to form nitroxides, which are further converted to harmless compounds. Besides acting as antioxidants, nitrones also have a significant anti-inflammatory effect. In animal studies, they have been shown to help prevent cognitive dysfunction and extend longevity.

Using a variety of antioxidants seems more effective in protecting the brain than relying on any single antioxidant.

Finally, heat shock proteins also appear to prevent damage to the neurons. After a discussion of various ways to protect the brain against aging, including calorie restriction and neuroprotective agents, one conference participant asked, "Wouldn't it be cheaper to just give the animals a sauna every day or every other day?" Indeed it would. It was quickly pointed out, however, that calorie restriction, a particularly effective way of slowing down brain aging, also provides a multitude of benefits that are difficult to replicate in any other way. Nevertheless, regular sauna remains a very promising and much underutilized anti-aging treatment.

### **Osteoporosis does not discriminate between the sexes**

Barbara Drinkwater, a public health expert at the Pacific Medical Center, debunked some popular myths about osteoporosis. The number one myth is that only postmenopausal women lose bone density, and thus only women need to worry about osteoporosis. In fact, older men are the fastest growing population at risk for osteoporosis. Thirty percent of all hip fractures occur in men. Though typically men are affected at a later age than women, due to a more gradual decline in their sex hormones, male spinal bone loss starts already in middle age, and is significant enough to eventually result in the phenomenon of a stooped "little old man." Thus it is not just the proverbial "little old lady" who suffers from osteoporosis.

The saddest fact is that 80% of osteoporosis victims are undiagnosed and go untreated. Furthermore, surveys have shown that 90% of women think that taking calcium is enough to prevent osteoporosis. Another large percentage of women believe that exercise alone can save their bones, and that the best bone-building exercise is walking. To test this hypothesis, a 12-month study examined the effect of a one-hour lunchtime walking program on bone density. Unfortunately, the results were negative. However, it was also found that active women have 6% more bone density.

Weight lifting is known to produce an increase in bone mass. Nevertheless, it is premenopausal women who respond faster to stress on the bone, again pointing to the importance of hormones in bone building. There is simply no escaping the conclusion that the most reliable way to prevent osteoporosis is hormone replacement. But this is not the end of the story. The most exciting finding suggests that hormone replacement therapy combined with the right exercise gives the best results: it makes it possible for older women to have bones comparable in mass and strength to those of women in their 20s. This is an example of how an age-related degenerative disorder, once regarded as part of "normal aging," can be entirely prevented and even reversed.

Another way in which exercise has an additive effect is by preventing fractures through developing and preserving a better sense of balance, and thus making falling down less likely. Estrogen replacement likewise improves the sense of balance.

Biphosphonates are an important development for those women who have reasons to avoid estrogen replacement. It is possible, however, that only hormones can maintain the viability of bone cells (osteocytes) responsible for the microarchitecture and resilience of the bone tissue. There is also evidence suggesting that a combination of hormone replacement therapy and biphosphonates has a greater effect on bone density than either one alone.

Unfortunately many women still seem unaware that the dramatic loss of bone mass after menopause is due to the loss of hormones, rather than to sudden dietary calcium deficiency. Only 30% of postmenopausal women choose to stay on hormone replacement therapy for more than one year. Typically these are educated women ("exclusively," one conference participant commented), rather than women with the highest risk factors for heart disease and/or osteoporosis.

Perhaps the introduction of designer estrogens, such as raloxifene, will change all that. Though it is not as effective as standard hormone replacement therapy, raloxifene has proven to dramatically diminish the risk of breast cancer as well as to sustain bone mass. On the other hand, raloxifene has side effects such as hot flashes and blood clots. There is also a theoretical possibility that by interfering with the action of estradiol in the brain, raloxifene might lead to depression and maybe even hasten neurodegeneration. Note that a significant percentage of tamoxifen users complain of depression. And, like tamoxifen, raloxifene may also raise the risk of cataracts and other eye damage. It must be emphasized, however, that this is only a theoretical speculation. We simply do not have the data on long-term effects of raloxifene. In terms of benefits for bone and the cardiovascular system, it is clearly second-rate compared with standard hormone replacement therapy. Women would appreciate other options with proven safety.

A disappointing feature of this lecture was the lack of any mention of the effects of vitamins D, E and K, magnesium, boron, zinc, anti-inflammatory fatty acids, and soy estrogens on bone health. Ipriflavone, a chemically transformed soy phytoestrogen also known by the brand name of Ostivone, has now been documented to prevent bone loss. It is also possible that natural soy phytoestrogens, if taken in a sufficient dose, might have benefits for preserving bone mass.

### **Centenarians: all in the genes?**

An ongoing study of centenarians was the topic of this year's Hayflick lecture. Dr. Eugenia Wang of McGill University in Montreal presented her data on Taiwanese centenarians. Using advanced genetic techniques, she focused especially on the genes involved in apoptosis-the self-destruction of cells that the body wishes to eliminate. These apoptotic genes may be a significant determinant of longevity, since the survival of dysfunctional cells is detrimental to the organism.

Another genetic determinant of longevity is the APOE-2 allele (an allele is a normal variant of a gene). The APOE gene seems to govern the susceptibility to cardiovascular disease and Alzheimer's disease. It is actually a gene coding for the cholesterol transport apolipoprotein E. APOE-2 is twice as frequent in centenarians. Jeanne Calment, who lived to be 122, was found to have APOE-3, which is also regarded as a beneficial allele. These alleles developed late in the human evolution. A fascinating speculation is that perhaps here we are seeing "the grandmother effect": the grandchildren of long-lived grandmothers may have had a survival advantage due to a healthy older woman being available to take care of them (especially if the mother should die in childbirth).

The link between APOE-4 allele and susceptibility to Alzheimer's disease is so strong that it might be worthwhile to seek developing gene therapy for those carrying it. One conference participant, however, claimed that if you eliminate or significantly inhibit inflammation, Alzheimer's disease would not develop. Inflammation can be eliminated or sufficiently inhibited by using NSAIDs such as ibuprofen (the new selective NSAIDs such as Celebrex promise to work as well with greater safety), quality fish oil, polyphenols and/or estrogen replacement. Antioxidants are also promising, especially vitamin E, though it should be pointed out that antioxidants often have an anti-inflammatory effect, and this is certainly true of high doses of vitamin E.

The debate over the relative importance of genes vs. environment is by no means over. Currently, scientists lean to the view that about 40 - 50% of one's life expectancy is determined by one's genes. According to Dr. Wang, it seems that there are 20 "master genes" that promote longevity. Her goal is to identify those genes.

Sharing her less formal observations of centenarians, Dr. Wang commented on their striking mental sharpness even at a very old age. As an example, she showed an intricate pair of baby booties made from scratch by a Taiwanese woman aged 100. The same woman also smoked until the age of 76, and chewed carcinogenic bitter nuts. Apparently centenarians tend to be remarkably resistant to cancer.

In her future research, Dr. Wang plans to also examine various behavioral traits associated with centenarians, such as optimism and social connectedness.

Continuation of Report

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