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REPORT

Eat Less -
But Do Eat
Lots of
Blueberries
by Ivy Greenwell

The 1999 joint conference of the American Aging Association (AGE) and the American College of Clinical Gerontology was widely regarded as particularly exciting. There was a feeling of optimism about the tremendous progress in our understanding of the aging process, and the emerging knowledge of how to slow it down.

We already have the knowledge of how to prevent or at least delay many age-related degenerative diseases that were once regarded as "normal aging." Soon we may have the means to effectively extend our life expectancy, and ultimately even the maximal life span of our species.

Caloric restriction promotes longevity

According to the current consensus, calorie restriction is the only reliable way to extend maximum life span (as opposed to average life span). Most of our free radical production comes from the energy-producing activities in the cell organelles known as mitochondria. As we age, the mitochondria become more and more damaged, producing less ATP (our energy molecule) and more superoxide radicals, which in turn further damage these tiny "energy furnaces." The rate of mitochondrial damage could be a key factor in determining the rate of aging. Calorie restriction translates into lower levels of free radical production in the mitochondria. But other physiological phenomena associated with calorie restriction are also likely to play a role in promoting longevity. Dr. Mark Lane of the National Institute on Aging in Baltimore presented a summary of the effects of calorie restriction.

Calorie restriction is known to reduce serum glucose and insulin levels. Both of these typically rise with age and age-related increased obesity. High glucose levels lead to the formation of harmful glycation products as glucose cross-links with body proteins such as collagen. Elevated insulin in turn has a number of harmful effects, including more production of inflammatory prostaglandins, which suppress the immune response, among many other negative consequences.

Dr. Lane stressed that there is a huge difference in baseline insulin levels between old calorie-restricted animals as compared to controls. The lowering of serum glucose and insulin is one of the earliest and most dramatic results of calorie restriction, and is perhaps the primary way in which calorie restriction works to extend life span.

It is intriguing that the famous *daf-2* gene in the nematode *C. elegans* is related to insulin pathways. When *daf-2* is altered to reduce its activity, the worms age more slowly.

Calorie restriction also produces an elevation in the levels of stress hormones known as glucocorticoids. It is a moderate stressor, mobilizing the body's defenses in a benign way. Thus, except for the stress of cold temperature, calorie-restricted animals have better stress tolerance, which contributes to longevity. Not surprisingly, they also have an attenuated inflammatory response to inflammatory agents, and are resistant to a variety of toxins. Researchers speculate that being exposed to mild stress (calorie restriction) upregulates defenses to major stress.

In addition, calorie-restricted animals show evidence both of lower production of free radicals in the mitochondria, and of better antioxidant defenses, as shown by increased catalase activity. Finally, there are changes in growth hormone secretion and insulin-like growth factor-1 (IGF-1) levels. While the growth hormone pulses are better preserved in calorie-restricted animals (which do not show the typical age-related rise in somatostatin), their serum IGF-1 levels are lower, which may give them increased resistance to



tumors. When injections of IGF-1 are given to calorie-restricted animals, they lose their tumor resistance. It seems that growth factors and oxidative stress use the same pathway to activate cell proliferation.

Dr. William Sonntag of Wake Forest University stressed that serum IGF-1 levels are hardly the whole story. We have to look at tissue levels of free IGF-1 before we can truly conclude anything about the role of IGF-1 in calorie restriction. Such measurements are currently difficult to conduct. Dr. Sonntag also pointed out that aging calorie-restricted rodents maintain a high vascular supply to the brain and learning ability. In addition, they show better immune function, greater cellular protein synthesis, and better preservation of bone mass and skin thickness than controls.

Considering the controversy about growth hormone replacement, it needs to be stressed that only pharmacological levels of growth hormone are implicated in a shorter life span (as implied by shorter life spans of transgenic mice that produce abnormally high amounts of growth hormone). Growth hormone replacement at normal levels does not seem to affect life span.

An additional difference between calorie-restricted animals and controls is a decrease in long-chain polyunsaturated fatty acids and increased oleic acid (a monounsaturated fatty acid abundant in olive oil) in the tissues of calorie-restricted individuals. The result of this altered fatty-acid profile may be lower levels of proinflammatory prostaglandins, which are derived from arachidonic acid.

Finally, calorie-restricted monkeys do not show the steep decline in DHEA characteristic of aging primates. This raises the possibility that a less severe calorie restriction combined with DHEA supplementation might produce results comparable to those of more severe calorie restriction. Rick Weindruch, however, stated that supplementing rodents with DHEA in addition to standard calorie restriction did not produce benefits beyond those of calorie restriction.

Do we already have any human data relevant to the benefits of calorie restriction observed in rodents and rhesus monkeys? Perhaps the closest we have is a National Institute on Aging study of 900 non-diabetic human volunteers, which found that men with the lowest insulin levels seem to live the longest.

It is not only diabetics who show premature aging. The results of calorie restriction studies strongly imply that in order to preserve good health and slow down aging, one needs to maintain serum glucose and insulin levels within the low-normal range. Some of the scientists present at the conference were already practicing calorie restriction. The usual objection is that most people would be either unwilling or unable to lower their calorie intake. It is possible, however, that we could get around this problem with the use of "fake carbohydrates," such as are commonly found in products designed for diabetics, and/or the use of supplements that inhibit the absorption of glucose.

Do long-lived beings come in small packages?

A team from Southern Illinois University, headed by J. Mattison, presented intriguing findings on the longevity of Ames dwarf mice. These mice are infertile mutants that are only about one-third the size of their normal siblings and they live much longer.

The dwarf mice have lower blood glucose and lower body temperature than normal mice, but they eat the same amount of food (or more) per gram of body weight. In addition, they are not lean and can even become obese. Thus it must be concluded that their longevity is not related to voluntary calorie restriction. The authors are in the process of studying whether imposed calorie restriction can extend the already exceptional life span of dwarf mice even further.

The dwarf mice do not bear fewer tumors than normal mice, but their tumors have a later onset and appear to grow more slowly. It is also interesting that old dwarf mice do not show much "cognitive decline," as measured by performance on various learning tasks.

Do these findings apply to humans? It is usually pointed out that human dwarfs suffer from various deformities and pathologies. In a private communication, however, one of the authors of the study, Dr. A. Bartke of Southern Illinois University, revealed that during a recent endocrinology conference, a human geneticist from Emory University presented data on patients with mutations at the same locus as the Ames dwarf mice. It appears that this subcategory of human dwarfs (first described in the early 1900's as the "little people of Krk") do live a very long time.

As Dr. Bartke states, "there seems to be something about being small that predicts longer life. It may be small size per se, perhaps some size-related 'efficiency,' less load on the heart or something of this sort. Or the size is a marker for something else that is very important, for example the amount of food and energy metabolism-oxidative radicals? Insulin?-it takes to reach certain adult size and to maintain a body of this size. Smaller people also may have reduced risk for cancer, which could be what makes them live longer, or it could be a sign that they age more slowly."

Preventing premature aging

A very interesting and somewhat offbeat lecture pertained to the life span of dogs. Michael Hayek of the Iams Company pointed out that indeed small dogs live longer. Smaller dogs such as Fox Terriers can live up to 19 years, whereas Great Danes tend to die when they are five or six years old. Irish Wolfhounds are likewise short-lived. The cells from larger dogs have been found to undergo fewer cell divisions than cells from small dogs. The cells from small dogs can replicate for a longer time, showing more resistance

to cellular senescence.

It has also been found that Fox Terriers (chosen as the model of a smaller dog) have superior lymphocyte proliferation, giving them an immune advantage.

When the physiological changes associated with canine aging are examined, three primary factors emerge: elevated glucose and insulin levels, increasing immune dysfunction, and an increase in the pathological intestinal flora. Luckily for dog owners who wish their pets to live as long as possible, these three factors can be easily counteracted.

In older dogs, just as in older humans, we see slow glucose clearance and much greater rise in insulin after a meal. It has been found that the chief problem is the inclusion of rice in dog food. Rice causes higher blood sugar and elevated insulin, with consequent increase in body fat (interestingly, this does not happen in young animals). Fortunately, dogs seem to respond well to the exclusion of rice and inclusion of fiber. Fiber is beneficial for the intestinal flora. In addition, dog food can be made to include nutrients especially designed to promote healthy intestinal bacteria. Dog food should also include antioxidants such as vitamin E and beta-carotene in order to promote immune health.

Thus, it is relatively easy to improve the health of dogs by simply improving the nutritional quality of dog food. The same easy measures—the exclusion of high-glycemic carbohydrates and addition of antioxidants and fiber—appear to have enormous anti-aging implications for humans as well. It is ironic that pet food is engineered according to research findings, while millions of children are being raised on junk food, and the elderly tend to eat a notoriously poor diet.

Ways to slow down brain aging

Lipoic acid was also discussed as an important means to slow down brain aging. Brain diseases are the eighth leading cause of death. Part of the pathology that is seen in cerebral aging is an increase in the levels of iron, together with a parallel decrease in tissue ascorbate. This leads to increased levels of free radicals in the brain tissue, and neural dysfunction and death. The study by Jung Suh and colleagues at the Linus Pauling Institute found a significant reversal of this pattern in rats receiving 4mg/day of lipoic acid. Lipoic acid produced a 60% reduction in the total tissue iron in the forebrain, and a "substantial" increase in forebrain ascorbate (vitamin C) levels. Other brain regions did not appear responsive to lipoic acid. This suggests that the forebrain, a region involved in cognition, has a special facility for the uptake and metabolism of lipoic acid. Lipoic acid's neuroprotective properties most likely comprise its ability to chelate free iron, in addition to its antioxidant effects, and the ability to regenerate ascorbate.

Continuation of Report

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