

REPORT

CALORIE RESTRICTION, EXERCISE,
HORMONE REPLACEMENT AND PHYTONUTRIENTS FIGHT AGING

AGE CONFERENCE - MADISON, WISCONSIN

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The 2001 annual conference of the American Aging Association, in conjunction with the American College of Clinical Gerontology and American Federation for Aging Research, took place in the lovely university town of Madison, Wisconsin-near the campus known in the scientific community for pioneering calorie restriction studies with primates. The conference confirmed that an explosion of new research is bringing us closer toward the goal of effective anti-aging interventions.

Aging is no longer being described as an inevitable downward spiral about which nothing can be done. On the contrary, no one at the conference seemed hesitant or apologetic about the goal of extending both health span and life span. Genomic studies and stem cell research lead to the hope that dramatic breakthroughs are on the horizon. Until then, however, we can accomplish a lot by utilizing current knowledge.

Exercise prevents pathology, but does not extend maximum life span

The anti-aging benefits of exercise were a major topic at the conference. Gerontologists agree that exercise plays a starring role when it comes to the extension of health span. But, like nutrition, exercise seems to give rise to various quasi-religious dogmas about which type and amount of exercise is best, and what exercise actually accomplishes, especially in terms of longevity. It was refreshing to have Joseph Holloszy, M.D., of Washington University School of Medicine, a pioneer in exploring the impact of exercise on aging, present some solid research data based on his animal studies.

The first of Holloszy's presentations was devoted to the importance of exercise in preventing abdominal obesity and insulin resistance. His overall conclusion is that while exercise can extend average life span, it does not extend maximum life span (the longest life span in a group of animals). Exercise, however, can dramatically affect "secondary aging"-the incidence and severity of diseases associated with aging. It is the aging-related degenerative diseases that often reduce individual life span, or at least "health span." To put it in simple terms, exercise appears to help prevent disease and extend the number of healthy years in old age, an extremely important benefit.

Exercise helps prevent abdominal obesity; at the very least, it reduces the degree of abdominal obesity. Abdominal obesity is the number one cause of secondary aging, according to Holloszy. It is a very reliable marker of insulin resistance in humans and animals. In the rat model, a fattening diet (either a high-fat or a high-sucrose diet) leads to abdominal obesity and insulin resistance. The question of whether abdominal fat actually causes insulin resistance remains unsettled. Since an excess of either dietary fat or dietary sucrose leads to abdominal obesity and insulin resistance, one could argue that it's a matter of excess calories. There is also the view that chronically elevated insulin levels (caused by the wrong diet and lack of exercise) lead to both insulin resistance, due to the downregulation of the insulin receptor, and to abdominal obesity. What is not in doubt is that a large waist circumference

indicates insulin resistance, and a dramatically elevated risk of all the degenerative disorders in which excess insulin is known to play a part.

"Modern human is still genetically designed for the hunter-gatherer lifestyle," Holloszy said. Studies of the few surviving tribes that still practice hunting and gathering have shown that tribe members consume a lot of food (about 3700 calories/day for Amazonian tribesmen; over 4000 calories/day for traditional Eskimos), but they also get a huge amount of exercise. Holloszy showed a colorful slide showing several Amazonian hunters carrying a python they just caught. The men all looked like elite athletes. He then showed a slide of "Mr. America"-a not-so-untypical middle-aged American male, with a huge paunch and spindly extremities. This pathology is the result of underexercising more so than overeating, Holloszy stated. People don't start eating more as they age, rather, they become less and less active.



It turns out that exercise is "extremely effective against insulin resistance and fat cell hypertrophy." According to Holloszy, exercise is even more effective than calorie restriction in keeping the fat cells small. And exercise keeps insulin levels low.

even with a fattening diet. Thus, the type of fat we consume is extremely important.

But Holloszy's main emphasis is on exercise for the prevention of abdominal obesity and insulin resistance. He sees the current epidemic of obesity as alarming, and predicts dire consequences for morbidity and life expectancy, considering that people now become obese at a younger age. "You don't see obese people past the age of 80," he stated. (Note: although approximately 60% of Americans are overweight, according to the most recent studies, only a certain percentage of the overweight are obese or severely obese in the technical sense, with a body mass index of 30 and above.)

In another lecture, Holloszy examined the impact of exercise on longevity. His studies use the male rat because of this animal's unique property of not compensating for energy expended on exercise with extra food intake (female rats do increase food intake to compensate for exercise and maintain body weight). When provided with a running wheel, male rats run four to five miles a day—a distance that is comparable to that observed in wild male rats. Runners show a striking similarity to sedentary calorie-restricted rats: retarded growth, lower body fat, less energy available for growth and cell proliferation. In fact, runners end up as small as calorie-restricted rats, with even less body fat than sedentary calorie-restricted rats.

The rate of living theory of aging counsels against exercise, since faster metabolism is supposed to shorten life span. Holloszy, however, found that runners tended to live longer than sedentary ad-libitum fed rats. Exercise appeared to produce an extension of the average life span (female rat runners also showed this effect). But sedentary calorie-restricted animals still outlived the runners. Even though the body weight of runners was as low as the body weight of calorie-restricted animals, exercise did not extend maximum life span.

When Holloszy restricted the calorie intake of runners, the runners lived as long as sedentary calorie-restricted rats. (Interestingly, calorie-restricted runners did even more running than non-restricted runners.) Holloszy concluded that exercise has neither a harmful nor a synergistic effect when combined with calorie restriction.

It seems that exercise and calorie restriction act through different mechanisms. Both share features such as low levels of insulin, but it is possible that only dietary restriction produces a sufficient decrease in the free radical production by the mitochondria. Even though ad-lib fed runners and sedentary calorie-restricted rats looked the same and weighed the same, only calorie restriction produced the extension of maximum life span. We know that calorie restriction causes a decrease in the generation of free radicals, but the exact mechanism by which calorie restriction produces life span extension remains unknown.

Usually, men start gaining abdominal fat around the age of 30; in women, this phenomenon is seen mostly after menopause. It turns out that exercise is "extremely effective against insulin resistance and fat cell hypertrophy." According to Holloszy, exercise is even more effective than calorie restriction in keeping the fat cells small. And exercise keeps insulin levels low. Master athletes are known to have low glucose levels and low insulin levels. Low insulin levels indicate sensitive insulin receptors.

Exercise inhibits lipogenic (fat-producing) enzymes. It also induces glucose transport into the muscle that bypasses insulin, thus reducing serum glucose and consequently serum insulin. This glucose transport involves an exercise-induced increase in the so-called GLUT-4 transporters. In mild diabetics, a dramatic improvement in insulin sensitivity can be seen with exercise alone (although the right low-glycemic diet is, of course, recommended).

As for the optimal amount of exercise, there is no "one size fits all" model. It depends on the individual. Mixed exercise including strength training is probably the best kind, Holloszy believes. He also mentioned that DHEA and fish oil have marked protective effects against abdominal obesity and insulin resistance. Fish oil helps lower the degree of abdominal obesity

Since there is no doubt that exercise is beneficial at any age, is there anything we can do to help protect the muscles of the elderly against oxidative stress? It seems that only certain phenolic compounds are effective. Polyphenols, found in grape seed extract, green tea extract, ginseng, oat extract etc., are known to be very potent antioxidants.

Polyphenols also have an anti-inflammatory action. Since there's an increased inflammatory state in aged muscle, the anti-inflammatory action of polyphenols might actually be their chief protective mechanism, one conference participant suggested. Thus, while we should encourage exercise at any age, it might also be wise to think in terms of extra antioxidant and powerful anti-inflammatory protection for the elderly who take up an exercise program. In the past, hardly any attention was paid to inflammation as an important player in the aging process. Now we realize that certain phenolic compounds are extremely effective antioxidants and anti-inflammatories.

Overall, it seems that the longevity-producing metabolic shift can be produced only by restricting caloric intake, and not by exercise. "Calories in, longevity out," as Holloszy remarked. Nevertheless, all the lectures related to exercise pointed out that exercise is extremely beneficial and remarkably effective in helping prevent the diseases of aging. Prevention of disease is by no means trivial, and may mean a considerable gain in both quantity and especially the quality of life.

Calorie restriction and its mimics-our best hope for extended life span?

Calorie restriction continues to puzzle scientists trying to unravel the reason why consuming less food should lead to a dramatic increase in longevity, especially if calorie restriction is started soon after weaning. Even when started in middle age, calorie restriction can still produce 10% to 20% life span extension. It's been found that calorie restriction induces hundreds of biological changes; we are not sure which of these are causal. "Something about energy metabolism is critical for aging and retarded aging," stated Richard Weindruch of the University of Wisconsin, Madison.

Calorie restriction reduces glycolytic metabolism and increases the utilization of fatty acids and protein for energy. Not surprisingly, there is a dramatic drop in serum glucose and insulin levels. The rise in corticosterone in calorie-restricted animals may be chiefly a response to the stress of calorie restriction, helping the animals cope with this stress, and consequently helping them to be more stress-resistant in general. Injecting ad-lib fed animals with glucocorticoids does not produce benefits.

So far, calorie restriction remains the only proven way to extend maximum life span (at least in rodents). It is known to enhance DNA repair and retard the decline of mitochondrial function. What's most important, calorie restriction extends "health span." Calorie-restricted animals stay healthy and active almost to the very end, showing much less cardiovascular disease or degenerative brain disease. Calorie restriction has a proven neuroprotective effect, with less neuropathology and more neurogenesis (production of new nerve cells) being found in calorie-restricted animals. The development of cataracts is also delayed. Calorie-restricted animals tend to die a sudden death, without a long period of terminal illness. If these findings apply to humans, they are of profound significance, since quality of life in the older years is a critical issue, not to mention the soaring costs of health care.



The huge problem with this proven way to extend maximum life span is human unwillingness to restrict food intake. True, there are drugs that effectively diminish appetite, but this gives rise to questions of side effects and long-term safety. The practical answer might lie in "calorie restriction mimics"-foods made with non-metabolizable ingredients. Such foods can create the feeling of satisfaction while providing only a fraction of the calories. 2-deoxyglucose is a standard calorie restriction mimic used in most studies, but it is unsuitable for human consumption due to toxicity. Other calorie restriction mimics are under development; we should hear much more on this subject within a year or two.

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Rick Weindruch suggested that the effectiveness of calorie restriction mimetics can be tested by using the microchip gene arrays to determine the ability of the mimetic to induce gene expression associated with calorie restriction.

Could a low-degree, hunger-free calorie restriction work also, at least in terms of extending health span? Noni Bodkin of the University of Maryland, Baltimore, working with rhesus monkeys, has devised an approach based on keeping body weight steady, based on early adult weight (for a human, this could be the weight at the age of 18 to 20). Frequent weighing is used to determine whether the animal is gaining or losing weight, and the calories in the diet are adjusted accordingly. Monkeys kept on this obesity-

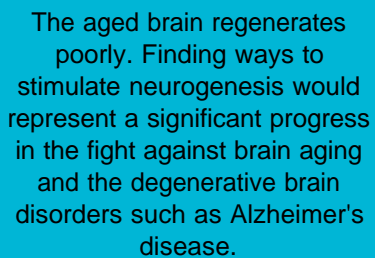
preventing regimen show no age-related rise in blood glucose and insulin resistance. It is too early yet to know the effect on longevity, but it can be expected that the mild calorie restriction needed to maintain optimal youthful body weight will lead to an extension of average life span, due mainly to prevention of diabetes and cardiovascular disease.

Neural regeneration and neuroprotective nutrients

It has been discovered that the brain produces new nerve cells, chiefly in the region of the hippocampus, an important center of learning and memory formation. The new neurons arise from stem cells that first become progenitor cells. Most of the progenitor cells die, however. The aged brain regenerates poorly. Finding ways to stimulate neurogenesis would represent a significant progress in the fight against brain aging and the degenerative brain disorders such as Alzheimer's disease.

Mark Mattson of the National Institute on Aging in Baltimore, Maryland, found that calorie restriction is one effective means of increasing neurogenesis in rats and mice. Calorie restriction also increased the survival of the new nerve cells. The neuroprotective benefit of calorie restriction is "dramatic and consistent." Mattson postulated that the mechanism involves greater production of BDNF (brain-derived neurotrophic factor). BDNF is higher in the hippocampus and cerebral cortex of calorie-restricted animals. We also know that neurodegenerative disorders are characterized by a deficiency of BDNF. BDNF is released in response to mild stress on the cells. The calorie-restricted rodents also showed more resistance to stress when exposed to various toxins and traumas meant to mimic stroke, Parkinson's disease and other pathologies. It could be argued that thanks to the mild stress of calorie restriction, the nervous system of calorie-restricted animals becomes more resistant to more severe stress.

Fortunately, calorie restriction is not the only way to increase neurogenesis. Gerd Kempermann, M.D., of the Max Delbrueck Center for Molecular Medicine in Berlin, presented a fascinating lecture on the impact of enriched environment. This environment is created for rodents by putting them in larger cages with other animals, thus insuring social interaction, and by supplying "mental stimulation" in the form of tunnels to explore and novel objects.



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When weaning rats are put into an enriched environment, they show almost double the rate of neurogenesis when later sacrificed at a young age and compared with rats in non-enriched cages. In old age, the environmentally enriched animals show triple the neurogenesis as compared with controls. If the enrichment extends from weaning until old age, the old rats show four times the neurogenesis as the non-enriched rats. The hippocampal area is thicker in enriched animals, showing a greater number of neurons and dendritic connection.

Interestingly, even when the enrichment is withdrawn, increased neurogenesis continues. Kempermann theorizes that enrichment in early life promotes stem cell survival and neurogenesis. The enrichment needs to be introduced after weaning; pre-weaning enrichment does not affect adult hippocampal neurogenesis. Simply more physical exercise, obtained by attaching a running wheel to the cage, also increases neurogenesis.

Glucocorticoids (including cortisol, our chief stress hormone) suppress neurogenesis, as does glutamate. Estrogens increase neurogenesis. Phenolic compounds such as those found in blueberries and black currants increase neurogenesis. Many drugs also enhance neurogenesis. These include all known antidepressants and lithium. The old tricyclic antidepressants are apparently as effective at enhancing neurogenesis as the SSRIs.

We now understand that lack of neurogenesis is a crucial factor in depression, and that any agents that increase neurogenesis tend to be effective in combating depression. Hence it is not surprising that exercise works well against depression. The key to the prevention and treatment of depression is neurogenesis.

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One participant asked whether environmental enrichment (and hence dramatically enhanced neurogenesis) influences life span. Kempermann replied that enrichment probably does prolong life span. Mark Mattson joined in with an unqualified yes. Human epidemiological studies also indicate that social and mental stimulation is associated with better health and longer survival. According to some experts, social stimulation and overall mental stimulation may in fact be more important for longevity than exercise and diet (excluding the calorie-restricted diet).

Understanding factors that enhance neurogenesis will provide another extremely important tool in the struggle to prevent the ravages of aging. Alzheimer's disease continues to be a growing nightmare. For a long time, the treatment was focused mainly on trying to raise the levels of acetylcholine. But the main pathology in Alzheimer's disease is not so much shortage of neurotransmitters as the massive neuronal loss in the cortex and the hippocampus. The brain literally atrophies. Increasing the levels of neurotransmitters is not the answer in the advanced stages, since "there is no one home to answer"-the neurons are no longer there.

The good news is that ibuprofen has been shown to reduce the deposition of amyloid plaque. Celebrex also had some positive effect, but the results did not reach statistical significance. Expensive new anti-Alzheimer's drugs are in the process of development, but effective protection can be bought for pennies a day (by the way, aspirin is also protective, but to a lesser degree).

Polyphenol power: less inflammation, more dopamine release

Polyphenols have also attracted the attention of researchers. Polyphenols such as those found in green tea extract have an anti-inflammatory action, and are also potent iron chelators. Iron plays a pivotal role in Alzheimer's and Parkinson's disease. Epigallocatechin gallate (EGCG), the main active ingredient in green tea extract and one of the most powerful iron chelators we have, was used by Moussa Youdim, a pharmacologist in a center on Parkinson's in Haifa, Israel, in his studies of Parkinson's disease in an animal model of the disease.

Besides chelating iron, EGCG and green tea extract in general also induce antioxidant enzymes (SOD and catalase) and have an anti-inflammatory action by inhibiting the activation of NFkB, a transcription protein that translocates to the nucleus and initiates a destructive inflammatory cascade. Youdim tested the protective properties of various doses of EGCG in prevention of neuronal death when the animals' brains are injected with 6-hydroxydopamine or MPTP. It turned out that pre-treatment with EGCG protected the cells, as long as the dose was not excessive (extremely high doses of catechins are toxic and lead to cell death through apoptosis). EGCG could prevent mitochondrial collapse and thus save neurons and prevent dopamine depletion.

EGCG may also turn out to be a good preventer of Alzheimer's disease. It has been shown to increase soluble amyloid (the "good amyloid"). Interestingly, EGCG-fed animals were also leaner. Youdim thinks this may confirm the recent findings that green tea has an anti-obesity effect.

Youdim thinks that the most effective treatment of brain diseases necessitates the use of many agents. One of these is likely to be rasagiline, a MAO-B inhibitor related to deprenyl. Cholinesterase inhibitors also show promise, but only when combined with other drugs.

Youdim stressed that the best approach to reducing the ravages of brain diseases is preventive. "By the time you see the symptoms, it's too late," he said. "It's like falling down the Grand Canyon-how are you going to stop the fall?" It makes vastly more sense to use neuroprotective measures, including anti-inflammatories, exercise, mental and social stimulation, and phenolics such as green tea extract (the caffeinated kind is more effective than decaf; it has been established that caffeine helps lower the risk of Parkinson's disease. Chocolate is also neuroprotective, Youdim said).

A participant observed that Chinese Americans have much lower incidence of Alzheimer's disease and other neurodegenerative diseases; this may be related to the custom of drinking tea.

Ginkgo biloba (in a standardized extract) has also been shown to be amazingly effective in protecting against neuronal death, even when administered after the neurotoxin was injected. In the case of amyloid beta, ginkgo protected against its toxicity if administered up to eight hours after the amyloid injection. For other toxins, ginkgo was able to achieve hippocampal cell rescue for up to two hours post-treatment.

The whole ginkgo extract has been shown to be more effective than any of the individual flavonoids. The ginkgo terpenes by

themselves are not effective.

Other phytonutrients known to be neuroprotective include resveratrol and quercetin, the powerful phytoestrogens found in red wine. Resveratrol (a phytoestrogen similar in chemical structure to DES) has been shown to rescue nerve cells after exposure to toxins. The neuroprotective mechanism may depend chiefly on anti-inflammatory properties of phytonutrients. Epidemiological studies show that those people who drink moderate amounts of red wine later have a lower incidence of Alzheimer's disease and macular degeneration.

One cannot discuss the neuroprotective properties of polyphenols without mentioning the amazingly powerful anthocyanins found in blueberries and bilberries. Even when added to an already adequate diet, blueberry extract has been shown to increase dopamine release and improve various cognitive markers in aged rats. For instance, middle-aged rats fed blueberries show more exploratory behavior. Learning and motor skills are enhanced. The most powerful active ingredients appear to be anthocyanins, found mainly in the skin of blueberries. While proanthocyanidins are also very effective antioxidants, anthocyanins are more powerful anti-inflammatories, according to the studies at Tuft University. Hydroxycinnamic acid, found inside the blueberry (anthocyanins are mainly in the skin), is also an excellent antioxidant and anti-inflammatory, as measured by its ability to reduce the pathology induced by amyloid beta and tumor necrosis factor alpha (TNF alpha).

The research update on blueberries included information on increased neurogenesis, increased membrane fluidity, increased levels of signaling molecules, increased protease activity, and direct antioxidant and anti-inflammatory effect in muscles. While serum levels of anthocyanins are highest within an hour or so of consumption, the "downstream effects" may manifest themselves much later. James Joseph, the head of neuroscience at the Human Nutrition Research Center at Tufts University in Boston, stated that while dopamine release can be brought back to youthful levels with blueberry extract, only partial cognitive improvement is achieved.

There is no clear answer as to whether wild or cultivated blueberries confer the most benefits. Cultivated blueberries produced greater improvements in some areas of cognitive function, wild blueberries in other areas. It has also been found that anthocyanins are absorbed better when they are heated. Thus, you may want to consider having a slice of freshly baked blueberry pie-preferably made with a calorie restriction mimetic, of course.

Currently, Joseph is also studying black currants. He recommends eating "fruits and vegetables of color"-the more intense the color, the better. Deep-colored berries, plums and grapes are the richest in phytonutrients such as polyphenolics (including anthocyanins, also available in bilberry extract). If compounds such as those found in blueberries turn out to be effective in the prevention of brain dysfunction, then we are lucky indeed.

At last, we have the first human study using blueberries-in this case, 50 pounds of flash-frozen blueberries per subject. Joseph briefly described the Dansbury MS Blueberry Study, also presented by Rolf Martin during the post session. MS patients were chosen partly due to folk medicine's use of blueberries to ameliorate MS. Eighteen MS patients were recruited; 13 provided useful data. After a practice period, choice reaction time improved by almost 8% when one to two cups of blueberries were consumed every day for six weeks. Most subjects also reported an improvement in mood, energy and overall health. A more extensive study seems warranted.

It's exciting to see that the focus in chemoprevention of brain diseases is widening to include the prevention of inflammation. At a previous conference, one participant stated, "If we can prevent inflammation, we can prevent Alzheimer's disease." Thus, the anti-inflammatory properties of flavonoids are of enormous practical significance. Lipoic acid is another potent anti-inflammatory, shown to be highly neuroprotective in animal studies (a study on the aging-retarding effects of lipoic acid on brain function in rats was presented at the 1999 AGE conference in Seattle). Fish oil and ibuprofen are two other anti-inflammatory agents proven to reduce the risk of Alzheimer's disease.

It is also important to remind the reader that estrogens or estrogens plus natural progesterone have been shown to help prevent neural loss. In men's brains, a portion of testosterone is converted to estradiol. Correct (physiological) hormone replacement is likely to become part of the neuroprotective regimen.



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Finally, stem cell research represents yet another promising venue in the search for an effective treatment of degenerative brain diseases. We now know, for instance, that mobilized bone marrow stem cells can enter the circulation and can, through their plasticity, support other organ systems by replacing damaged cells in the liver, muscle or brain. If we learn to manipulate the activity of stem cells, we might even achieve life span extension.

If no preventive measures are taken, there may be as many as 12 million Alzheimer's patients by the year 2040, Dr. Joseph and other speakers warned. If a person lives to the age of 90, his or her chances of developing Alzheimer's disease rise to 50%. The current annual cost of Alzheimer's care is estimated at between \$80 and \$100 billion in the U.S. alone, and may eventually equal the budget of the Defense Department.

We would be wise to remember Dr. Youdim's warning about the "Grand Canyon effect." The main focus should be on prevention. We can't afford to wait until symptoms become obvious and disabling.

Hormone research update

Growth hormone continues to be both the most promising and the most controversial anti-aging hormone therapy. Dr. Mitchell Harman reviewed the results of his study, which achieved spectacular results such as 21% loss of body fat in men when growth hormone was combined with testosterone. Because of the serious side effects, however, Harman is opposed to growth hormone replacement as it is currently administered, and is waiting for more developments in the field of growth hormone releasers before continuing his research. One of these releasers, ghrelin, has already been found to be quite effective; unfortunately, ghrelin has been shelved because Merck executives decided that HMOs would be unwilling to pay for ghrelin, and thus there would not be enough profit.

The development of effective growth hormone releasers, which could maintain growth hormone at youthful physiological levels, appears to be of great importance. We now know that growth hormone receptors exist in the brain, and that growth hormone stimulates neurogenesis (the production of new nerve cells). It is possible that growth hormone helps prevent Parkinson's disease. In addition, growth hormone has a tremendous impact on sleep, the maintenance of lean body mass and prevention of obesity, and on sexual function.

Recent studies on testosterone confirmed its impact on muscle growth. Part of testosterone's mechanism of action could be anti-glucocorticoid. Glucocorticoids upregulate myostatin, a protein that acts as a muscle-growth inhibitor. Testosterone reverses this effect.

Another benefit of testosterone is its ability to lower serum beta amyloid, and thus probably help prevent Alzheimer's disease.

There are still very few studies of the benefits of testosterone replacement for postmenopausal women. The existing studies agree that testosterone produces an increased sense of well-being in women, including greater sexual satisfaction. As for raloxifene, it does have positive effects on bone mass, but its inability to raise HDLs and its lack of effects on cognitive function are a disappointment.

Mary Lou Voytko of Wake Forest University School of Medicine, North Carolina, presented findings on the neurotrophic and neuroprotective effects of estradiol in ovariectomized rhesus monkeys. Estrogen withdrawal has been found to have a negative impact on learning, memory, attention (the ability to screen out distracting stimuli) and motor skills. It is also associated with more neuron loss in the hippocampus. Overall, estrogen deficiency appears to accelerate brain aging. Estrogen replacement, on the other hand, has many neuroprotective benefits, including "a significant enhancement of the dopaminergic system," according to Voytko. Interestingly, this study found greater benefit of estrogen replacement on the memory of older rather than ovariectomized monkeys. It is possible that higher levels of adrenal hormones in younger animals play a role.

Another speaker, Samuel Gandy of New York University, presented findings that showed estradiol diminishes the generation of amyloid beta by 50%. Testosterone is probably just as beneficial. A study done in Perth, Australia, found a twofold rise in plasma amyloid in men undergoing androgen depletion therapy due to prostate cancer.

While the field of hormone replacement remains riddled with controversy, current knowledge points to a prevalence of benefits, especially in terms of quality of life and the extension of health span.

In the famous words of Jonathan Swift, "Every man desires to live long, but no man would be old." The quest is not only for more quantity of life, but for more quality as well; for extended health span as well as extended life span. Journalists who seek to be provocative sometimes ask researchers in the field of aging, Do we really need more old people in wheelchairs? Fortunately, extending life span seems to go hand in hand with extending health span. As the lectures at this conference documented again and again, when animals or people live longer, they also stay healthy and active almost up to the very end.



Fortunately, the means to a longer, healthier life are within our reach, even before more aggressive interventions such as gene therapy or stem-cell implants become available. Anyone can take ibuprofen, green tea extract and bilberry extract to lower the risk of brain diseases. Anyone can adopt a program of regular exercise, and choose a diet rich in phytonutrients, fiber, fish oil or other omega-3 fatty acids, but relatively low in calories. A conference like this helps clarify such points, teaching us that high-intensity strength training works best for building muscle, for instance, or that a continuous hormone replacement regimen appears safer than sequential (cyclic) replacement for menopausal women.

A very important addition to our anti-aging knowledge this year came from the lectures on neurogenesis. Physical, mental and social stimulation are all important for the enhancement of neurogenesis. Early childhood stimulation (enriched environment) may be of special importance, with consequences that last a lifetime. Certain hormones and drugs also induce more neurogenesis, as does calorie restriction. This area of research is extremely important,

since neurogenesis is critical to the prevention and treatment of degenerative brain diseases and depression.

Depression is a huge public health problem, and is in many ways connected with obesity, heart disease, diabetes and cancer. As Dr. Moussa Youdim pointed out, depression precedes neurological symptoms in brain diseases. Thus, the discovery that the healing of depression involves increased neurogenesis is of monumental importance.

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