

LE Magazine June 1995

REPORT

Dietary Manipulation Of Aging

Can Calorie Restriction Slow The Aging Process and Extend Maximum Lifespan In Monkeys?

The only method that has consistently been shown to extend maximum life span and slow the aging process in laboratory animals has been calorie restriction without malnutrition. The long history of calorie research begins with the work of nutritionist Clive M. McCay of Cornell University in the 1930s.

McCay was able to extend the maximum lifespan of rats by more than 50% by severe calorie restriction starting very early in life, just after weaning. The side effects of McCay's regimen were also severe, including frequent seizures, postponement of sexual maturation, and premature death. Those who survived the regimen were later switched to a normal diet and went on to live up to two years longer than controls. The longest lived calorie restricted rat survived for more than 1,800 days (the equivalent of about 200 years in humans) in the laboratory of Morris H. Ross at the Institute For Cancer Research in Philadelphia.

Further research has shown that the lifespan extending effect of calorie restriction occurs in mice as well as rats, and that it slows down many of the effects of aging. Roy Walford of UCLA Medical Center was the first to show that mild-to-moderate calorie restriction started in adulthood (in mice) can also slow aging and extend maximum lifespan, although to a lesser degree than in severely restricted animals. Other studies have shown that calorie restriction extends maximum lifespan in water fleas, rotifers, spiders and fish in addition to rodents.

IMPLICATIONS OF CALORIE RESTRICTION RESEARCH

Walford's findings that calorie restriction "works" in adult animals has led him to propose calorie restriction as a means of slowing aging and extending lifespan in humans. Walford's ideas on what he considers to be appropriate calorie and nutrient intake for a life extension diet is found in his book *The 120-Year Diet: How To Double Your Vital Years* (Simon and Schuster, 1986), and in a computer program he designed for this purpose.

The major mystery that remains when considering the life extension effects of calorie restriction is how and why it works! Calorie restriction is a potent research model for the causes of aging. A scientific explanation of the mechanism(s) of action involved in calorie restriction could enable us to design safe, simple therapies to slow aging and extend lifespan without the side effects of severe calorie restriction and the inconvenience of moderate calorie restriction.

EFFECTS ON NEUROENDOCRINE FUNCTION

One of the most promising approaches to searching for the mechanisms of action of calorie restriction is its effects on neuroendocrine function, which plays a critical role in growth, development, sexual maturation, and aging. Since severe calorie restriction postpones sexual maturation and delays physical development, it clearly has a profound effect on endocrine organs such as the pituitary gland, which regulates vital life functions such as reproduction, body temperature, sexual function, blood pressure, and coordination.

In the late 1970s and 80s, Paul Segall and Paola Timiras of the Univ. of California at Berkeley, explored the neuroendocrine effects of restriction of the essential amino acid tryptophan, a type of calorie restriction that also produces anti-aging and lifespan-extending effects. In a remarkable experiment, they were able to get tryptophan deprived female rats, who had been put on a normal diet, to produce healthy offspring at the age of 28 months of age, which would be equivalent to a 70-year-old woman giving birth to a healthy child.

Segall and Timiras discovered profound changes in neurotransmitter levels in the brains of their experimental animals, but were unable to explore the implications of these changes with regard to aging because their funding ran out. No other research team has adequately pursued this line of research.

FREE RADICALS, ANTIOXIDANTS AND CALORIE RESTRICTION

It has been widely speculated that free radicals are involved in aging -- a theory initially proposed by Dr. Denham Harman of the

University of Nebraska Medical Center in Omaha. Experiments with free-radical inhibiting antioxidants by Harman and others have shown that antioxidants such as BHT, BHA, and ethoxyquin increase the average lifespan of mice (especially in short-lived strains (prone to the early onset of lethal diseases), but not maximum lifespan.

Dr. Harman believes that the reason dietary antioxidants haven't been able to extend maximum lifespan in experiments is their failure to get into subcellular mitochondria, the power plants of the cells, where energy is generated and free radical activity is most intense. Harman believes that specially designed antioxidants capable of effectively inhibiting excessive free radicals within mitochondria would produce significant increases in maximum lifespan.

Thus far, the only antioxidant known to have biological effects within mitochondria is Coenzyme-Q10, which has been shown to extend maximum lifespan in one study in mice and mean lifespan in another study in mice. In both these studies, the animals receiving Coenzyme-Q10 remained extraordinarily youthful and vigorous throughout middle and old age. Scientists are now exploring the view that the lifespan extending effects of calorie restriction may occur because the reduction of energy expenditure associated with calorie restriction reduces the generation of free radicals and boosts the activity of internal antioxidant defense systems.

Supporting this view are reports that the activities of the body's primary antioxidant enzymes catalase (CAT), glutathione peroxidase (GPX), and superoxide dismutase (SOD), which decline with advancing age, are increased by calorie restriction in rat and mouse livers; as well as evidence that the metabolic "footprints" of oxidative changes in lipids, proteins and DNA, which increase with advancing age, are reduced by calorie restriction in mouse livers. In contrast, no such changes were found in the rat livers in another study.

In a more recent study by scientists at the University of Wisconsin in Madison, it was found that calorie restriction increased the activity of CAT and GPX, but not SOD in rat skeletal muscle. Another finding in this study was that, in normally fed rats, there was a 48% decrease in muscle mass (in their upper hind limb), which did not occur in the calorie restricted rats!

EXTENDING THE MODEL TO MONKEYS

Recently, two research teams set up projects to determine if the antiaging effects of calorie restriction in rodents can be extended to monkeys, which are much closer to humans on the evolutionary scale. If the model proves to be applicable to monkeys, the researchers will be searching for the causes of the antiaging effects of calorie restriction. They will be focusing special attention on the role of free radical mechanisms in aging, but will also be gathering evidence of other possible mechanisms of action.

The problems of assessing aging in monkeys are formidable. The major problem is the length of their lifespan, which is measured in decades rather than years. This makes it impractical to use maximum lifespan as a means of evaluating potential antiaging effects. (This problem is, of course, even worse in humans.)

Another problem is the paucity of credible noninvasive "biomarkers of aging" to provide good information about the biological age of monkeys. Such biomarkers are necessary to attempt to assess the possible antiaging effects of specific regimens or therapies. Some proposed biomarkers of aging, such as changes in brain chemistry and structure, can only be measured after animals have been sacrificed. This is far easier to do in rodents, which are relatively inexpensive and short-lived compared to monkeys.

THE UNIVERSITY OF WISCONSIN STUDY

One of the calorie restriction studies in monkeys is being conducted at the University of Wisconsin in Madison under the direction of Richard Weindruch, who has conducted many calorie restriction experiments (with Roy Walford) at UCLA Medical Center in Los Angeles.

The Wisconsin study involves 30 male rhesus monkeys, who were 8-14 years old (9.3-year average) at the beginning of study in April 1989, and who had lived their entire lives at the Wisconsin Regional Primate Center. Following a 3-6 month period when baseline data were obtained, 15 monkeys were assigned to a control group and given free access to a semipurified diet for 6-8 hours per day. The other 15 monkeys have been fed the same diet at 70% of their baseline intake levels.

Testing on both the calorie restricted and control groups has been conducted at 6-month intervals. Among the measures assessed in the monkeys have been body dimensions and composition, physical activity, oxygen consumption, insulin levels and glucoregulation, ocular functions, nail growth, cardiovascular functions, and hematological functions.

IMPROVED CARBOHYDRATE METABOLISM IN MONKEYS

Thus far, the Wisconsin scientists have found that calorie restriction has been producing the same antiaging effects in monkeys as in rodents. They've found, for example, (after 30 months of study) that plasma fasting concentrations of glucose and insulin

were significantly lower and that glycosylated hemoglobin levels were slightly lower in calorie restricted monkeys than in control animals. (There is evidence that women with elevated glycosylated hemoglobin levels have a higher than-normal incidence of atherosclerotic vascular disease.)

On the other hand, red blood cell density, which normally increases with advancing age, and antioxidant enzyme levels, which normally decrease with advancing age, were not altered appreciably in the calorie restricted monkeys in contrast to significant alterations in these functions in calorie restricted mice and rats. It may be, however, that such changes will occur later in the study when the animals have been on the calorie restricted diet for a longer period of time.

THE NIA STUDY

The second calorie restriction study in monkeys is being conducted by scientists at the National Institute On Aging (NIA). It was started in 1987 with 30 male rhesus monkeys, 1-5 years old, and 30 male squirrel monkeys, 1-10 years old, under the direction of Don Ingram of NIA's Gerontology Research Center in Baltimore. The animals housed in the NIH Animal Center in Poolesville, Maryland, were divided into experimental and control groups.

The NIA scientists formulated a semisynthetic diet based upon established nutritional requirements for monkeys, supplemented with vitamin and mineral supplements. All the animals were given free access to food for a month, whereupon the experimental animals began receiving 10% less food for three consecutive months. There has been periodic testing of a variety of physiologic and biochemical functions in an attempt to assess the effects of calorie restriction on aging in the experimental animals.

NO CHANGES SEEN THUS FAR

The NIA scientists have looked closely at several immune system functions, which decline with advancing age in aging monkeys, and at plasma glucose and insulin levels, which are elevated in aging monkeys. Thus far, the NIA scientists have failed to find any significant changes in these parameters in the experimental animals, in contrast to the anti-aging effects in carbohydrate metabolism found by the Wisconsin scientists in their calorie restricted animals, and the general anti-aging effects found by many scientists in mice and rats.

The NIA scientists speculated about the fact that they have yet to see any anti-aging effects in their animals after four years of study as follows:

"Four years of dietary restriction relative to the life span of the monkey is...only a relatively short time period, and it may require lifelong restriction or restriction over a greater period of life to see effects in the primate. "

The Wisconsin scientists further believe that the NIA scientists have not yet seen any anti-aging effects in their animals because of a lower degree of calorie restriction in the NIA study. As they put it:

"in our study, food intake was measured during an extended baseline period, and food allotments for monkeys subsequently on dietary restriction were calculated from their individual baseline levels. In the other study, food allotments for restricted monkeys were based on tables of expected intakes, which appear to overestimate the levels of intake by adult animals. This difference in design resulted in a smaller actual reduction in intake for their monkeys on dietary restriction than for ours. "

THE BIOSPHERE-2 STUDY IN HUMANS

On Sep. 26, 1991, four men and four women, 25-67 years of age, entered (via airlock) Biosphere-2, an enclosed 3.15 acre space containing an ecosystem near Tucson, Arizona. The large glass-and-steel structure houses seven biomes: rain forest, savanna, ocean, marsh, desert, agricultural land, and a habitat for humans and animals. Biosphere-2 is "open" in that sunlight and electric power can enter and heat can be removed. The free transfer of electronic information is also permitted. However, all organic material, water, and virtually all air is recycled and all food is raised within the enclosure.

After the "Biospherians" had been in their special ecosystem for a while, they realized that they would be unable to raise as much food as had been anticipated, but that their diet was rich in nutrients. Since one of the Biospherians (the only doctor in the group) was Roy Walford of UCLA Medical Center, a pioneer in calorie restriction research who contends that a low calorie, low fat, high-complex-carbohydrate, low-animal food diet should slow aging and extend lifespan in humans, it was decided that the Biospherians provided a unique group to test Walford's theory over a six-month period.

WHAT THE BIOSPHERIANS CONSUMED

During the course of this study, the Biospherians consumed an average of 1,780 calories a day and performed about 3-4 hours of heavy labor every day. Their diet was largely vegetarian with an intake of six varieties of fruit (banana, fig, guava, lemon, papaya, and kumquat); five types of grain (oats, rice, sorghum, wheat, and corn) split peas, peanuts, three varieties of beans, 19 vegetables and greens, white and sweet potato; and small quantities of goat milk and yogurt, goat meat, pork, chicken, fish, and eggs.

To supplement this diet, they also took daily vitamin/mineral supplements, which included 100% of "safe and adequate" amounts of vitamin A, vitamin B-12, vitamin C (500 mg), vitamin E (400 IU), vitamin D, and folic acid. A wide variety of tests were performed on the Biospherians, including standard blood and urine analyses and other more specialized tests.

AGING-RELATED FUNCTIONS IMPROVE

Dr. Walford, who was both subject and researcher, found physiologic changes similar to those seen in calorie restricted rodents, in the food restricted Biospherians. Among the findings in the study subjects--in addition to weight loss--was a 35% drop in serum cholesterol levels, a marked decrease in serum glucose levels, and improvements in lymphocyte and neutrophil function, two measures of the health of the immune system. The conclusion of the study was that "...radical and possibly beneficial changes in physiologic risk factors can be produced in normal affluent individuals in Western countries quickly and reproducibly by dietary manipulation. "

GOING ON THE WALFORD DIET

Members who'd like to go on the Walford Diet, or some variation of it, would find it useful to obtain a unique, interactive computer program designed by Dr. Walford to help people find their optimal diet for health and longevity. A new, updated version of this program will be available shortly. We'll be bringing you more information about this program in a future issue of Life Extension Magazine.

Since the Walford diet is not a temporary measure intended for short term weight loss, but is a lifelong program to regulate how much of different types of food you consume, the Life Extension Foundation recommends high nutrient, meal replacement products for those of you who may need help in achieving the type of calorie restriction proposed by Walford.

The most nutritious meal replacement product we recommend is Life Mix--a unique blend of very small amounts of highly nutritious foods developed by nutritionist Lillian Grant, whose clients include movie and TV stars. Life Mix can be mixed with almost any liquid--such as water, milk, or fruit juice--to produce a delicious, nutritious multi-food drink. Life Mix contains many of the same grains, vegetables, and fruits featured in the Biospherian's diet.

[Back to the Magazine Forum](#)

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