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REPORT

The University of Wisconsin Study

Dietary Restriction and Aging in Rhesus Monkeys

Life Extension magazine presented last month (July 1998 LEF Magazine) the preliminary findings of a ground-breaking study at the National Institute on Aging on how calorie restriction might extend and improve the lives of rhesus monkeys-the closest relative to mankind yet studied. In part two of the series, here are details from a complementary study that also shows promising results.

By Jennifer Christensen and Richard Weindruch

As longevity increases in most parts of the world and baby boomers (among those being, for example, the authors of this article) begin to grow old, the number of older persons in our society is increasing rapidly. This demographic reality has forced health care providers and scientists into a race with time to deal with higher rates of disease and disabilities, rising long-term care needs, and the high medical costs associated with these increases.

Can interventions be discovered by basic and clinical researchers that delay the onset of age-related diseases? Can the results of promising avenues of research be translated efficiently into medical practice so as to increase the number of people who age in a way that is minimally influenced by diseases? And, as is the dominant focus of Life Extension magazine, can strategies be developed to truly retard the aging process and thereby increase the maximum human life span?

Dietary restriction (often called calorie restriction, or calorie restriction with adequate nutrition) is well known among gerontologists and, increasingly, the general populace because it is the only intervention that repeatedly and strikingly increases maximum life span and retards the rate of aging in warm blooded animals (with laboratory rodents being most often studied). Life span extension by dietary restriction depends specifically on a reduction of caloric intake and this must occur without deficiencies of any essential nutrient. Thus, the bottom line of dietary restriction is that it is a state of very healthful "undernutrition without malnutrition."

There are two major issues about dietary restriction and aging that are being investigated. First, we know that caloric intake reduction can slow the aging process in animals such as mice and rats, but how does it actually do so? This is an extremely important question because, when it is answered, researchers will be quite well positioned to develop drugs aimed at triggering the most important actions of dietary restriction and, hopefully, its benefits as well. Note that the goal would be for this to occur in people eating normal caloric intakes.

The second issue concerns whether dietary restriction will be able to retard the rate of aging in animals closely related to humans...for example in nonhuman primates such as rhesus monkeys.

Our group at the University of Wisconsin-Madison is conducting a long-term, longitudinal study called "Dietary Restriction and Aging in Rhesus Monkeys." This project is directed by one of the authors (Weindruch) and is funded by the National Institute on Aging, which is one of the components of the National Institutes of Health. Our study tests the hypothesis that dietary restriction will influence the aging process in a primate species in a manner similar to that observed in rodents. We further hypothesize that dietary restriction's influence will be reflected by an altered rate of change of certain measurable markers of biological aging and, eventually, by increased longevity.

Our monkey dietary restriction study focuses on two major topics in the biology of aging. One is the development of nonhuman primates (in this case, the rhesus monkey) as a model for the study of aging. This species, whose real name is *Macaca mulatta*, is genetically very closely related to humans. A long-lived species, these monkeys have a maximum life span of about 40 years, roughly one-third that of humans. The other major issue we are trying to address is whether or not dietary restriction retards the rate of aging in a primate species.

To achieve this latter goal, the caloric intake of adult female and male rhesus monkeys has been restricted by 30 percent below that previously consumed by each animal. These monkeys are being compared with control animals that are being fed in a conventional

fashion; that is, allowed free access to food for about eight hours per day.

The only other major, highly controlled study of dietary restriction's influence on aging in rhesus monkeys is being carried out by NIA scientists Drs. George Roth, Donald Ingram, Mark Lane and other collaborators in Bethesda, Md. (See Life Extension magazine, July 1998). These two studies should eventually-perhaps in 15 years-provide important data on longevity and disease patterns in a primate species subjected to a dietary restriction regimen.

Our rhesus monkey dietary restriction study began in 1989 when the NIA provided funds to study 30 young adult males, ranging in age from 8 to 14 years. All animals were previously fed the same standard monkey diet in the manner that monkeys are conventionally maintained in most primate facilities. This is done by giving each monkey free access to the food for about eight hours per day, typically from about 8 a.m. to 4 p.m., as well as being given daily treats such as fresh fruits (yes, including bananas), peanuts or raisins.

The restricted monkeys are healthier than the controls, are leaner, have lower levels of circulation glucose and insulin, and have greater insulin sensitivity.

Each animal's normal food intake was determined over a six-month period so that we would have the data needed to establish the level of food restriction on an individual basis. In our view, this is an important consideration because rhesus monkeys, like people, show great individual-to-individual variation in food intake. Also like people, some skinny monkeys are fairly big eaters, whereas some fatter ones are light eaters.

A significant difference between our study and that being conducted by the NIA scientists is that we have based food intakes of the calorically restricted monkeys on the basis of each animal's past intakes, whereas our colleagues at NIA have relied on charts that provide recommended food intakes for animals on the basis of age and body weight.

To initiate the study, 15 of the animals continued to "dine" in the conventional fashion. The caloric intake of the other 15 was gradually restricted, accomplished by reducing the food intake by 10 percent per month for three months. These 30 monkeys are referred to as "Group 1."

The aims of the initial study, from 1989 to 1994, with the Group 1 monkeys were to assess the effects of dietary restriction on potential biomarkers of aging: the function of the immune system, the visual system and the regulation of glucose, and later body composition and metabolic rate.

Group 2 was made up of young females (15 on the control diet and 15 subjected to dietary restriction) at ages very similar to those of the Group 1 males at the onset of dietary restriction in 1989. Dietary restriction was carried out in the same way as Group 1.

Another cohort, Group 3, also was initiated, and included 16 male rhesus monkeys, eight on a calorie-restricted diet and eight controls, all of similar ages as Group 1 at the onset of restriction. Group 3 is distinct in that these monkeys are undergoing surgical biopsies so that we can study liver, muscle, spleen and other tissues in alternate years. This has provided us with the opportunity to conduct biochemical studies of tissues well studied in diet-restricted rodents, but not yet studied in a primate species.

To date, it is clear that a 30-percent reduction in calorie intake can be safely imposed on rhesus monkeys. In fact, in agreement with the findings from the NIA study, several findings indicate that the restricted monkeys are healthier than the conventionally fed controls, are much leaner, have lower levels of circulating glucose and insulin, and have greater insulin sensitivity. This means that the insulin in the blood actually works better to remove glucose in the restricted monkeys.

Also, leptin, a hormone involved in appetite control made by fat cells, is much reduced in the diet-restricted monkeys. This makes sense, because they have much less body fat. We also find that blood lipids are beneficially altered by dietary restriction.

There is a very strong rationale for investigating mitochondria in the context of dietary restriction. Mitochondria are the minute structures within cells that serve as the power plants. As a consequence of their normal metabolic activity, mitochondria produce free radicals, highly reactive molecules often derived from oxygen. Free radicals carry an unpaired electron on their surface that makes them prone to causing damage to other molecules they may encounter. Denham Harman first proposed in 1956 that free radicals may be involved in aging, although it was unclear at that time where they may be coming from. It was not until more than 20 years later that scientists discovered that mitochondria are important sources of free radical production.

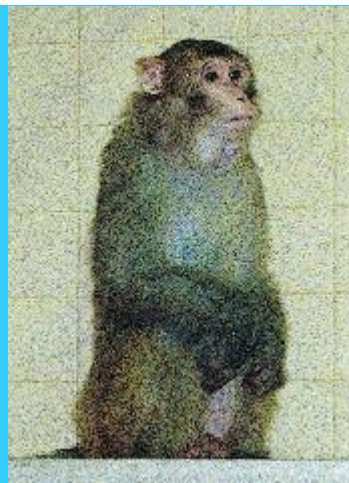


NORMAL DIET

- **Food intake daily:** 662 calories
- **Body weight:** 31.5 pounds
- **Body fat:** 26%

MEASURES OF HEALTH

- **Abdominal measure:** 24.4 inches
- **Body Mass:** 47.6 (kg/m²)
- **Basal glucose:** 74 (milligrams per deciliter of blood)
- **Basal insulin:** 44 (micromoles/milliliter)
- **Insulin Sensitivity:** 1.8 (x 10⁻⁴)
- **Leptin:** 5.8 (ng/milliliter)



REDUCED DIET

- **Food intake daily:** 488 calories
- **Body weight:** 20.5 pounds
- **Body fat:** 8.6%

MEASURES OF HEALTH

- **Abdominal measure:** 16.5 inches
- **Body Mass:** 34.2 (kg/m²)
- **Basal glucose:** 53 (milligrams per deciliter of blood)
- **Basal insulin:** 10 (micromoles/milliliter)
- **Insulin Sensitivity:** 9.1 (x 10⁻⁴)
- **Leptin:** 1.0 (ng/milliliter)

The current mitochondrial free radical explanation of aging partly derives from an understanding of how mitochondria produce a molecule known as ATP (adenosine triphosphate), the molecule that provides energy for many essential cellular activities such as the making of proteins, pumping of ions across cell membranes and muscle contraction, to name a few. The synthesis of ATP takes place by a complex sequence of reactions known as the electron transport system and oxidative phosphorylation, which occurs in the inner membrane of mitochondria. Using oxygen, these reactions extract energy from nutrients and use it to manufacture ATP. However, free radicals are also produced as a consequence of this process. Thus, the aging process may be a result of our cells carrying out very basic function: producing the energy required for life.

Mitochondria are also special structures because they contain their own unique genetic material, known as the mitochondrial DNA. Although mitochondrial DNA makes up only a very tiny fraction of the total DNA in a cell (more than 99.9 percent of the DNA is in the cell's nucleus), it codes for some essential molecules involved in the mitochondrial processes that make ATP. An emerging theme is that mitochondrial DNA mutations, accumulating over a life span, contribute to aging, cancer and other degenerative diseases. As investigators have discussed, it is well known that the assembly of functional mitochondria requires the joint expression of both mitochondrial and nuclear genes.

Further, the mutation rate for mitochondrial DNA is much higher than for nuclear genes, leading to the view that aging and certain major degenerative diseases (for example, Parkinson's and Alzheimer's diseases, ischemic heart disease and diabetes) may be partly due to the accumulation of mitochondrial DNA mutations leading to deficits in ATP production.

A discovery of great potential importance is the correlation of the accumulation of mitochondrial DNA deletions with aging; that is, mitochondrial genomes with big pieces missing. We are investigating the role that mitochondrial DNA deletions may play in the loss of skeletal muscle mass with aging, known as "sarcopenia." This age-associated loss of skeletal muscle contributes to a loss of strength and an overall increase in physical frailty. Sarcopenia is an important biological component in the age-associated increase in the

occurrence of injurious falls, immobility, and the need for hospitalization or nursing home placement.

Much of this work has not yet involved the monkeys from the three cohorts because these animals are not yet old enough to display sarcopenia. Instead, we have studied normally fed, old rhesus monkeys, which are losing muscle mass, as well as old rats and mice subjected to dietary restriction, so we can better know what to study when our dietary restriction monkeys reach appropriate ages.

Continuation of article at -- Thigh muscle samples from...

[Back to the Magazine Forum](#)

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