Running on One-Third Empty

Primates on a low-cal diet are in a metabolic slow lane, perhaps to longer life

By CHRISTINE MLOT

Franz, a 17-year-old rhesus monkey, is busy moving hand to mouth, stuffing his cheek pouches full of the pellets of food that have just been poured into his feeder. In minutes, it's empty. Only then does he begin to chew, pausing occasionally to take a drink of water, play with the metal gizmos clipped to his cage, or bare his teeth in a mild threat to the strangers who today showed up with the chow.

Across the room, Damion is having a more leisurely meal, picking through the pellets with pencil-thin fingers, occasionally dropping one out of reach. "He really wastes a lot," says his caretaker.

It's the morning feeding at the Wisconsin Regional Primate Research Center in Madison. Franz and Damion are among the 75 rhesus monkeys taking part in an extensive, long-term study designed to get to the crux of an astonishing physiological phenomenon: Substantial undernutrition without malnutrition keeps a body living longer and in better condition.

For the past 8 years, Franz has been getting 30 percent less than the amount he'd take for himself; Damion has been getting about the amount he'd normally eat. Franz is also getting supplemental vitamins and minerals to prevent deficiencies. The diets differ only in total carbohydrates, proteins, and fats.

Since rhesus monkeys in captivity live for 30 to 40 years, it will be a couple of decades before any life extension can be documented. Nevertheless, the animals are now entering middle age, when age- and diet-related diseases start to crop up in humans and other primates. The two rhesus groups represented by Franz and Damion are beginning to diverge in health and physiology—in both predicted and unexpected ways.

"It's an important time," says Joseph W. Kemnitz, one of the animal physiologists who started the Wisconsin study in 1989 with funding from the National Institute on Aging. Altogether, the NIA is spending an estimated $6.5 million annually to study the effects of calorie-restriction on about 250 primates, including groups at the National Institutes of Health animal center in Poolesville, Md. (SN: 8/27/88, p. 142), and the University of Maryland at Baltimore.

Two video stills of 9-year-old rhesus monkeys. The smaller one (right) has been eating a nutritionally complete, but calorie-restricted, diet from a young age.

It's well known that reducing calories extends by 30 percent or more the life span of organisms ranging from spiders and water fleas to mice and rats (SN: 10/5/91, p. 215). Yet these animals live at most for years, not decades. The primatologists hope their study, besides testing for longevity in a longer-lived species, will suggest points of dietary or drug intervention for age-related diseases like cancer and diabetes. They are also seeking insight into the still inscrutable mechanism of aging.

Results from the primate studies so far fall in with theories that point to metabolism, or energy use—glucose use in particular—as central to the aging process. As in earlier work, total energy consumption is the key. Reducing fat alone does not extend life. The increased longevity goes beyond the effects of avoiding diseases associated with obesity.

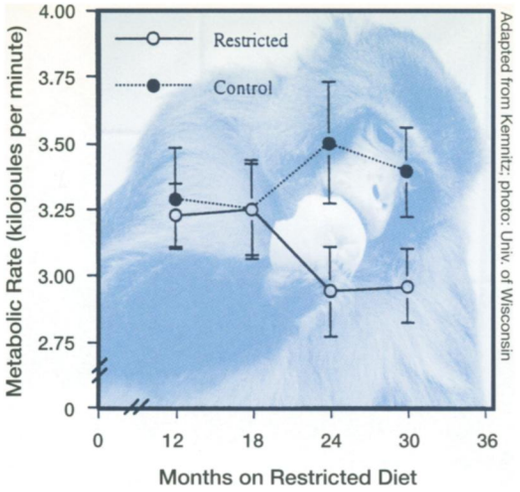
Each day, the researchers put one of the animals through a biannual battery of bone scans, blood tests, and measurements. Monkey by monkey, they are putting together a picture of aging slowed down. Perhaps learning how to read the functional age of an individual, the researchers say, will help in the care of the aging human population.

By standard clinical measures, the calorie-restricted animals are the picture of health. They have low blood pressure and low cholesterol, and their triglyceride concentrations—another risk factor for heart disease—are less than half those in nonrestricted animals. The concentrations of high-density lipoprotein (HDL), the heart-healthy form of cholesterol, are especially good.

Some of the calorie-restricted monkeys could be called scrawny, although most look sleek and taut, not gaunt. They weigh, on average, one-third less than normal monkeys, carrying 10 percent body fat rather than 25 percent. Their bones are less dense, probably from bearing a lighter load, says Kemnitz. When the diet is started at an early age, the bones remain shorter and smaller in diameter.

Calorie-restricted monkeys are noticeably miniaturized. "Everything is smaller," says Kemnitz.

Their body temperature is down as well, by about half a degree. Just as calorie-restricted animals like Franz have become ultra-efficient at getting food inside themselves, their metabolic rates



The metabolism of the calorie-restricted monkeys dropped after a year and a half on the diet and then remained low.

seem to have geared down, generating less heat to balance the reduced fuel intake.

"Metabolism is reset from a growth and reproductive strategy to a survival strategy," says NIA molecular physiologist George S. Roth. Roth spoke during a symposium on the biology of aging at last month's meeting of the American Association for the Advancement of Science (AAAS) in Seattle.

In the May American Journal of Physiology: Endocrinology and Metabolism, Kemnitz's group describes the metabolic rate of adult monkeys over the first 30 months of calorie restriction. Metabolism seems to be reset after about 18 months on the diet, during which period the animals experience the biggest drop in weight.

"There's a response to try to conserve energy," says Kemnitz. "When they stabilize at a lower weight, there's a continued reduction in energy expenditure, which would have to be the case because they're eating less."

The researchers now plan to compare how different organs respond to the calorie restriction to see whether some reduce their metabolism more than others.

The lower the metabolism, the less oxygen is consumed and the fewer free radicals from oxygen are available to damage cells. Many researchers suspect that damage by free radicals plays a role in the aging process. To pinpoint this mechanism in the monkeys, the researchers plan to examine the membranes of mitochondria, where cellular energy and free radicals are produced.

The basic fuel molecule that gets burned in metabolism is the sugar glucose. If the body doesn't respond correctly to glucose circulating in the bloodstream, the result can be type II diabetes, a diet-related disease in adults that has reached near-epidemic proportions in the United States. The calorie-restricted monkeys seem to be avoiding diabetes, one of the clearest health benefits of the primate study so far, says Kemnitz.

At the start of the Wisconsin study, insulin concentrations after fasting indicated that four of the monkeys had a genetic risk of diabetes. Two of them were put on the restricted diet. Four years later, four monkeys in the control group, but none in the restricted group, had signs of an impaired response to blood sugar. The impaired group included the two at-risk animals. Last year, one of them developed full diabetes; that monkey is now on insulin.

In animals, including people, the body's response to insulin falls off with age. Cells take up less glucose, leaving too much in the bloodstream. The calorie-restricted animals have so far maintained tight regulation of glucose and insulin. Their glucose concentrations are about three-quarters of those in the control animals, and their insulin concentrations are about one-third.

With less glucose circulating in the system, there seems to be less of another problem. In glycation, glucose molecules stick to proteins and other essential molecules, gumming up a cell's smooth functioning and possibly contributing to aging. Cataracts are one result of the process. Restricted monkeys show less glycation of hemoglobin and collagen. This glycation may turn out to be a useful measure of health or functional age.

Another intriguing, but more uncertain, marker may be the concentration of DHEAS, the sulfated form of the steroid dehydroepiandrosterone, which typically declines with age. Calorie-restricted monkeys experience a drop in DHEAS, but in one group of male monkeys started on calorie restriction as juveniles, DHEAS remained slightly higher than in control monkeys, according to NIA researcher Mark A. Lane. Other studies have not found a difference in DHEAS concentrations in calorie-restricted and nonrestricted animals.

Although diet books and magazines have begun to recommend calorie restriction as a key to a longer and healthier human life, Roth and other primate researchers do not. "It would be premature to make any dietary recommendations," Roth said at the AAAS meeting.

Even given the dramatic health benefits, it's hard to imagine many people adopting a daily diet that would be the caloric and nutritional equivalent of a couple of cans of Slimfast, when more palatable health-promoting advice, such as eating five fruits or vegetables a day, has had relatively few takers in the United States. There are other important impacts of the calorie-restricted regimen that haven't been thoroughly studied—behavior, cognition, and reproductive health.

Calorie restriction started at an early age seems to delay the onset of sexual maturity by about a year, although once the monkeys mature, their hormone cycles seem to be normal. None of the calorie-restricted monkeys has been bred. In other calorie-restricted species, female reproduction seems to shut down.

Behavioral and cognitive studies have only recently been started. In a report slated for publication in Physiology and Behavior, James L. Weed and the NIA group confirm with ultrasonic monitors and video what caretakers and casual observers have noticed: The restricted monkeys are more active, especially around feedings. Unlike stature and metabolism, appetite doesn't seem to diminish with calorie restriction.

There are clues from other work that the impact of diet, especially the fats consumed, can affect the brain and, consequently, behavior. Some provocative epidemiological studies have found associations between criminality or psychiatric problems and low cholesterol, for example (SN: 3/11/95, p. 157).

At Wake Forest University's Bowman Gray School of Medicine in Winston-Salem, N.C., researchers have looked at the behavior of primates in a study of heart disease and diet. Behavioral scientist Jay R. Kaplan and his colleagues have reported in several recent papers that cynomolgus monkeys with low concentrations of cholesterol in their blood are more aggressive and antisocial than monkeys with high cholesterol.

The researchers suspect the mood-mediator serotonin may be involved, since the low-cholesterol monkeys also have significantly lower concentrations of a serotonin by-product in their spinal fluid. No one is sure of a mechanism or how much of the finding is relevant to calorie-restricted monkeys or to people. "Nutritional effects on behavior is a rich area," says Kaplan, "and we know almost nothing about it."

The next few years should further illuminate the behavior and physiology of the calorie-restricted monkeys. If they keep to the patterns of other studies, many will eventually die of the proverbial old age, with no signs of a specific disease.

For Kemnitz and other researchers, the goal is not necessarily to extend the end point of human life but to improve the quality of it by finding ways to avoid or delay the debilitating diseases of old age. Good health in old age will only become more important—and to more people. Life expectancy in the United States has already risen in this century—to 79 for women and 73 for men—and it continues to rise. According to this trend, one-fourth of the U.S. population will be older than 60 by the year 2020.

At the rate they're going, Franz and his calorie-restricted cohort could still be around then, too. □