Lean Living

Scientists seek to understand why underfed animals live significantly longer

By LAURA BEIL

Affectionately named N/R_{40}-243, she achieved special distinction among the woodchip-lined cages of ordinary $C3B10RF_1$ mice. While other mice were eating as much as they pleased and living to the ripe old age (for mice, at least) of 30 months, N/R_{40}-243 was among those given 60 percent less Purina Lab Chow. The reduction extended her life to 54.6 months, making her possibly the oldest mouse ever known.

N/R_{40}–243 at 53 months.

While the life-extending benefit of underfeeding has been shown only in small animals such as protozoans, guppies, spiders, water fleas and rats, the data linking diet restriction with aging are just conclusive enough to make a person reconsider having those two dips of double-chunk fudge ice cream. In every species studied so far, being thin has meant living longer.

But after demonstrating that many strains of animals live longer when they weigh less than nature dictates, researchers have yet to answer the big question: Does it work in primates?

The National Institute on Aging is now trying to find out. A group of scientists is one year into an experiment to see if thin monkeys will live longer than ones of normal weight. Dozens of cages in Poolesville, Md., house rhesus monkeys and squirrel monkeys of different ages that are part of the first test of diet restriction in primates.

Twice each day, scientists take the 90 monkeys from a common area where they frolic most of the time, and put them into individual cages to eat their brunches or early dinners. All the animals spend the next few hours nibbling Monkey Chow, but some are eating about 30 percent less than their neighbors.

"We're not starving them," assures principal investigator George Roth. "We've just put them on a diet."

Roth's experiment is the first of its kind, perhaps because other scientists may have been nagged by the fact that a monkey can live for 40 years, and publish-or-perish circles of scientific inquiry do not promote 50-year experiments. But if all goes well, Roth and his colleagues will not need to have their children collecting the data from the experiment, as the investigators are not measuring survival rates, but tracking a dozen or so changes that can occur when a monkey's body ages. Some thyroid hormone and testosterone levels go down, the immune system becomes weaker, bones become more brittle, fingernails grow more slowly, body temperature drops a little. "Within three to five years [from now] it's quite possible we'll see a change," says Roth.

The link between diet and longevity is nothing new. In 1935, Clyde McCay of Cornell University in Ithaca, N.Y., published a paper telling of white rats that normally live about two years living nearly four when they ate less. In the more than 50 years since, scientists have tested some creative possibilities for increasing animals' life expectancies — among them organ removal, severe exercise and manipulation of hormone levels. So far, no method of tinkering with the mammalian body has extended life expectancy the way undernourishment has.

To researchers, dietary restriction is not just a matter of putting a mouse on a diet. It means dramatically cutting back the number of calories without squelching nutrition. In the rodent studies, a mouse's usual entree, consisting largely of crude protein and cornstarch, is cut by sometimes 60 to 70 percent and supplemented with twice the normal amount of vitamins and minerals. Undernutrition is not a synonym for malnutrition. As Richard Weindruch of the National Institute on Aging stresses, "The mice must be undernourished in a healthful way."

Scientists who have demonstrated that dietary restriction does indeed result in long-lived, skinny mice are directing their efforts toward a second question: What do calories have to do with aging?

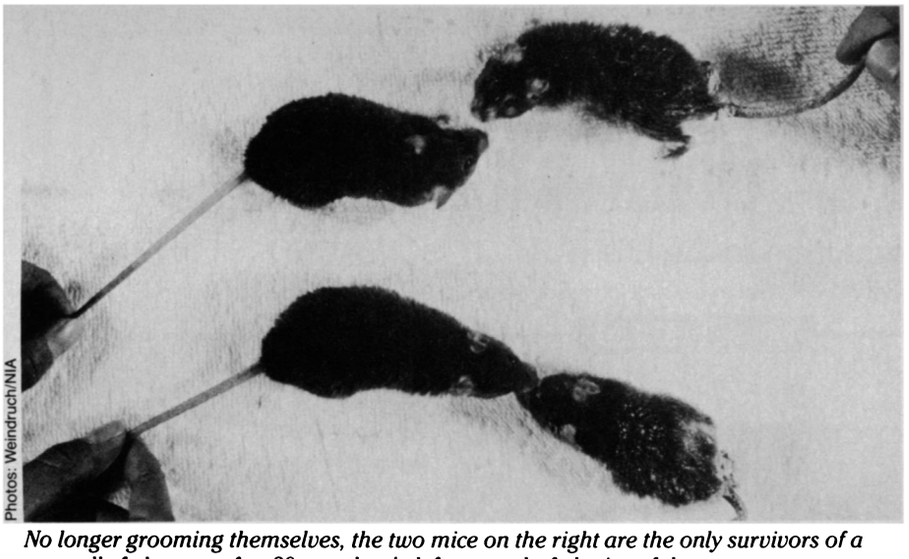
"The short answer to that is 'I don't know,'" says Weindruch.

The possible explanations of the phenomenon reflect another great unknown: the mechanism of aging itself. One diet/longevity theory is that the lack of food lowers a rat's metabolic rate, or the way it burns energy, thereby reducing wear and tear on the body. Another holds that a diet with fewer calories delays aging of the immune system, protecting the body from the diseases associated with old age. Still other scientists are investigating what happens to the neuroendocrine system when the body grows and lives on a severely restricted caloric intake. The way calories affect cellular aging processes, such as repairing damaged DNA to preserve protein synthesis, could also be a factor.

"The problem is we don't know what we're trying to explain," Weindruch says.

Since more than one process causes a body to age, these mechanisms need not be mutually exclusive. In fact, experiments with all the theories have led to an "embarrassment of riches," according to physiologist Edward Masoro of the University of Texas in San Antonio. Almost every mechanism studied seems to be at least partly responsible for the increased life expectancy of undernourished animals, he says.

Whether a metabolic mechanism could add years to life is a point of disagreement among some scientists. Masoro himself believes that when the metabolic measurements of the undernourished rats are adjusted for the animals' smaller size, "they do not have a lower metabolic rate [than the controls], but one that's slightly higher."



Photos: Weindruch/NIA

No longer grooming themselves, the two mice on the right are the only survivors of a normally fed group after 39 months. At left are underfed mice of the same age.

The reason for his criticism has to do with different ways of viewing the same data. Metabolic rate can be expressed in terms of oxygen consumption per gram of body weight, or in terms of oxygen consumption in a whole organism. After dietary restriction, rodents are smaller and without much body fat, and therefore use less oxygen overall. But when the animals are compared gram per gram (a standard normalization of the metabolic rate), the restricted rats show little difference from the controls, Masoro says.

Disagreeing with Masoro, Joseph Meites of Michigan State University in Lansing says the metabolic rate cannot be normalized for underfed rats when "these are not normal animals."

"I don't consider it normal when you have an animal that normally weighs 300 grams and it weighs 200," he says. "It's a debatable point."

Meites examines his rats, which are underfed by 50 percent, for what happens to the neuroendocrine system. One effect is that the endocrine organs secrete less hormone. Although his experiments are not yet complete, he has found that when undernourished rats are supplied thyroid hormones to make up for their deficiencies, the life-extension benefit of underfeeding tapers off.

Masoro believes one way dietary restriction slows aging is through its effects on the body's insulin/glucose system. He is investigating the theory of aging that says glucose attaches to certain proteins and alters their structure. Caloric restriction might indirectly delay this effect as it lowers the level of glucose in the blood. "Obviously, the data we have are early," he says.

Weindruch has long believed that the immune systems of skinny mice – especially the response of immune cells called T-lymphocytes – are much healthier than those of their normal counterparts, although there is no clear evidence to explain why. He and Roy Walford of the University of California, Los Angeles, reported in the April 1986 JOURNAL OF NUTRITION that mice underfed by at least 20 percent just after they were weaned had fewer incidences of several types of cancer.

Should scientists ever link fewer calories with longer lives in human beings, dietary restriction would be most practical to apply in adults. For this reason, some adult monkeys have been included in the National Institute on Aging study. While the overwhelming majority of rodent experiments have dealt with juvenile animals taken just after weaning, Walford and Weindruch have conducted one of the few experiments dealing with adult animals. Mice put on restricted diets after one year – the equivalent of middle-age in mouse years – still lived 10 to 20 percent longer than the controls, they reported in the March 12, 1982 SCIENCE.

Nutritionist Frederick Stare of Harvard School of Public Health cautions that even if fewer calories paved the path to a long life, people might be hesitant to give up their pork chops and Twinkies. "The only hitch," Stare maintains, "is that I think people wouldn't be very happy eating less. Eating is a nice pleasant experience in life."

While it's unlikely that dietary restriction will ever be universally accepted or lead to lives as long as Methuselah's, after more than 50 years it has endured as an unusual research tool. "It gives you a handle for looking at the mechanisms of aging," says Masoro. It's probable that several processes make people grow old, and that restricting calories may somehow affect them all.

On the other hand, he notes, dietary restriction "may be working on a single site, and none of us has been smart enough yet to find out what it is." □