

## Dieting Monkeys Offer Hope for Living Longer

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A long-awaited study of aging in rhesus monkeys suggests, with some reservations, that people could in principle fend off the usual diseases of old age and considerably extend their life span by following a special diet.

Known as caloric restriction, the diet has all the normal healthy ingredients but contains 30 percent fewer calories than usual. Mice kept on such a diet from birth have long been known to live up to 40 percent longer than comparison mice fed normally.

Would the same be true in people? More than 20 years ago, two studies of rhesus monkeys were begun to see if primates responded to caloric restriction the same way that rodents did. Since rhesus monkeys live an average of 27 years and a maximum of 40, these are experiments that require patience.

The results from one of the two studies, conducted by a team led by Ricki J. Colman and Richard Weindruch at the University of Wisconsin, were reported Thursday in *Science*. The researchers say that now, 20 years after the experiment began, the monkeys are showing many beneficial signs of caloric resistance, including significantly less diabetes, cancer, and heart and brain disease. "These data demonstrate that caloric restriction slows aging in a primate species," they conclude.

Some critics say this conclusion is premature. But in an interview, Dr. Weindruch called it "very good news."

"It says much of the biology of caloric restriction is translatable

into primates,” he said, “which makes it more likely it would apply to humans.”

In terms of deaths, 37 percent of the comparison monkeys have so far died in ways judged to be due to old age, compared with 13 percent of the dieting group.

Dr. Weindruch and his statistician, David Allison of the University of Alabama, Birmingham, said the dieting monkeys were expected to enjoy a life span extension of 10 percent to 20 percent, based on equivalent studies started in mice at the same age.

Few people can keep to a diet with 30 percent fewer calories than usual. So biologists have been looking for drugs that might mimic the effects of caloric restriction, conferring the gain without the pain. One of these drugs is resveratrol, a substance found in red wine, though in quantities too small to have any effect.

Dr. Weindruch said the study data offered “very encouraging” signs that resveratrol could duplicate in people some of the effects of caloric restriction.

Critics, however, are not yet ready to accept that the rhesus study proves caloric restriction works in primates.

If caloric restriction can delay aging, then there should have been significantly fewer deaths in the dieting group of monkeys than in the normally fed comparison group. But this is not the case. Though a smaller number of dieting monkeys have died, the difference is not statistically significant, the Wisconsin team reports.

The Wisconsin researchers say that some of the monkey deaths were not related to age and can properly be excluded. Some monkeys died under the anesthesia given while taking blood

samples. Some died from gastric bloat, a disease that can strike at any age, others from endometriosis. When the deaths judged not due to aging are excluded, the dieting monkeys lived significantly longer.

Some biologists think it is reasonable to exclude these deaths, but others do not. Steven Austad, an expert on aging at the University of Texas Health Science Center, said some deaths could have been due to caloric restriction, even if they did not seem to be related to aging. “Ultimately the results seem pretty inconclusive at this point,” Dr. Austad said. “I don’t know why they didn’t wait longer to publish.”

Leonard Guarente, a biologist who studies aging at the Massachusetts Institute of Technology, also had reservations about the findings. “The survival data needs to be fleshed out a little bit more before we can say that caloric restriction extends life in primates,” Dr. Guarente said. In mouse studies, people just count the number of dead animals without asking which deaths might be unrelated to aging, he said.

The second rhesus monkey study, being conducted by the National Institute on Aging, is not as advanced as the Wisconsin study. The researchers have not yet reported on the number of deaths in the dieting and normal monkey groups. But there are signs that the immune system is holding up better in the dieting group, said Julie Mattison, the leader of the institute’s study.

The outcome of the rhesus monkey studies bears strongly on the prospects of finding drugs that might postpone the aging process in people. Although people are similar to mice in many ways, they differ in other ways, notably in how many cancer treatments are effective in mice but do not work in people.

Even if caloric restriction extends longevity in people as well as in

mice, the extent of the effect remains unclear, though Dr. Weindruch believes the effects will be in the same general range. His monkeys were not started on the diet until 6 to 14 years of age, and seemed to be doing as well as mice that were started at equivalent ages. The most striking extensions of life span occur when the mice are put on the diet from birth.

Dietary restriction seems to set off an ancient strategy written into all animal genomes, that when food is scarce resources should be switched to tissue maintenance from breeding. In recent years biologists have had considerable success in identifying the mechanisms by which cells detect the level of nutrients available to the body. The goal is to find drugs that trick these mechanisms into thinking that famine is at hand. People could then literally have their cake and eat it, too, enjoying the health benefits of caloric restriction without the pain of forgoing rich foods.

Sirtris, a company based in Cambridge, Mass., is conducting clinical trials of resveratrol. It has developed several chemicals that mimic resveratrol and can be given in much smaller doses. On Wednesday, another such compound, the drug rapamycin, was reported to extend life span significantly in elderly mice, though it is not yet clear whether rapamycin sets off the same circuits as those that increase longevity in caloric restriction.

Dr. Weindruch joined the rhesus monkey experiment in 1990. He said he was used to being introduced as a man of incredible patience by biologists who study aging in laboratory roundworms, which live about three weeks. Dr. Weindruch will need the patience: he says he has another 15 years to go before the last monkey is expected to die.