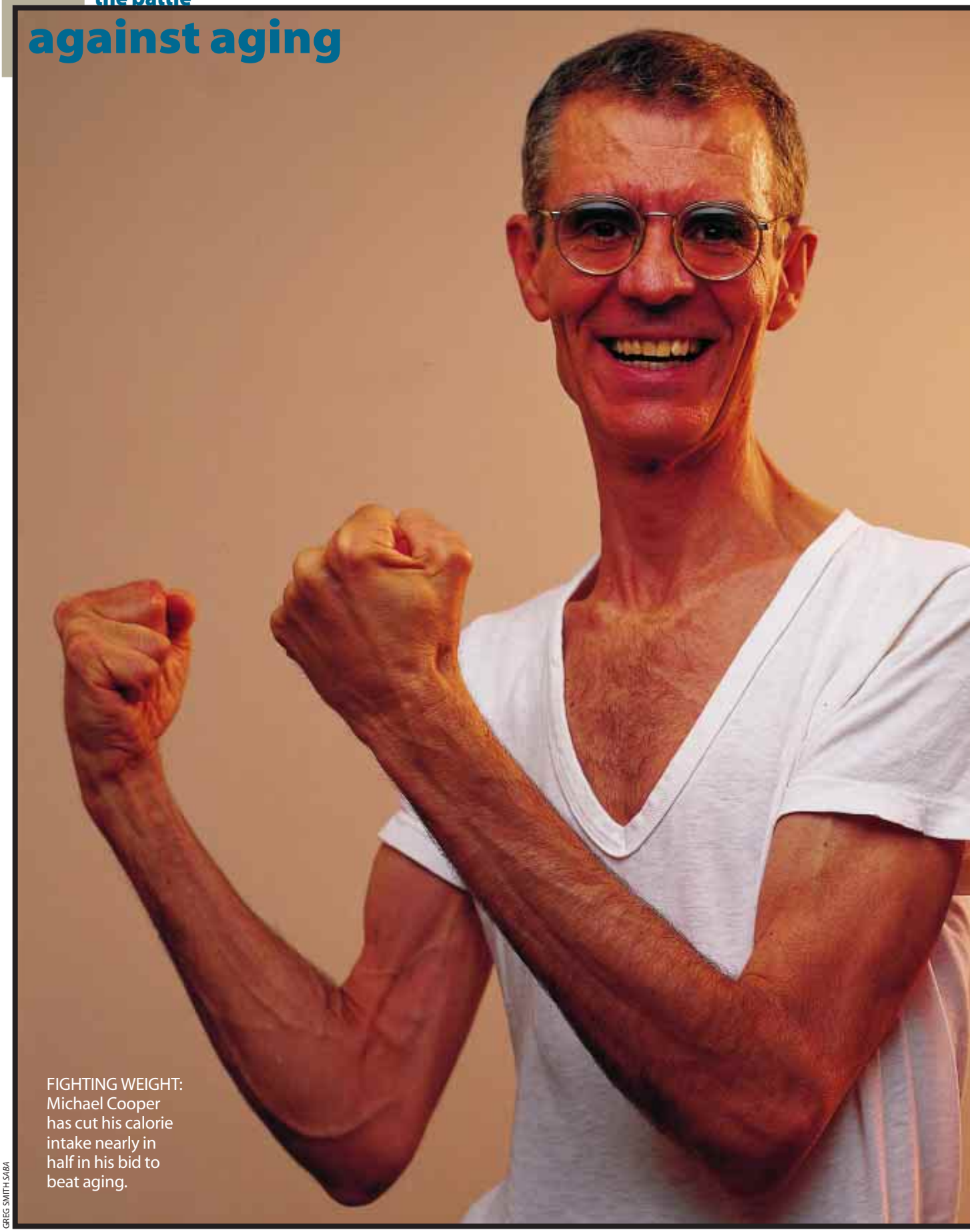
the battle
against aging



FIGHTING WEIGHT: Michael Cooper has cut his calorie intake nearly in half in his bid to beat aging.

GREG SMITH *SABA*

SEVERELY RESTRICTING DIET MAY INCREASE LIFE SPAN, BUT FEW WILL BE ABLE TO FOLLOW SUCH A HARSH REGIMEN

the famine of youth

BY GARY TAUBES

Despite the national propensity for fad diets and miracle health cures, despite the ubiquitous talk of "eating healthy"—a concept so mercurial that every decade brings a new definition—only a single dietary regime has ever been conclusively demonstrated to extend the life span and improve the health of laboratory animals, let alone humans. It is known in the scientific lingo as "caloric restriction" or "calorie restriction" and less technically as "eating considerably less than you might normally prefer"—perhaps 30 to even 50 percent less. In other words, an average-size human on a calorie-restricted diet might consume 1,500 calories a day, compared with the 2,100 calories of the typical American. It's four or five small meals a day, predominantly vegetables and fruits, and a life in which you are perpetually cold, painfully thin and constantly hungry. Calorie restriction, quite simply, is a Draconian diet and a lifelong one at that. "It requires a psychological profile only one person in 1,000 has," says Richard Miller, associate director for research at the University of Michigan Geriatrics Center.

Nevertheless, the study of calorie-restricted diets has lately become a hot-ticket item among longevity and nutrition researchers, who have taken to extolling its virtues with remarkably unrestrained enthusiasm. Their reasons are clear—the list of the beneficial effects of calorie restriction in laboratory animals reads like the packaging on a miracle cure. Calorie restriction will, for instance, increase both average and maximum life spans, and the fewer calories consumed, the greater the increase; it will reduce the occurrence of virtually all age-related diseases, including heart disease, diabetes and cancer. It will prevent kidney disease and cataracts as well as the development of Parkinson's and Alzheimer's diseases. It will lower blood cholesterol and forestall the age-related deterioration of the immune system. In mice, calorie restriction from an early age raises the maximum life span from 39 months to 56 months and at the same time preserves what passes for intellectual function: a three-year-old calorie-restricted mouse, for example, can negotiate a maze with the quickness and ease of a normally fed mouse of six months, which is the mouse version of salad days.

This harsh regime has been shown to work its life-extending magic on almost every species that's ever been tested—from paramecium and worms to spiders, insects, rodents and (although the data are still preliminary) primates. The two caveats are that the later in life the animals start on caloric restriction, the less the benefit, and that the diets must include plentiful amounts of vitamins and minerals. The an-

imals must be undernourished without being malnourished, as calorie-restriction researchers say.

All of this, though, leaves researchers struggling to answer three key questions: What exactly does calorie restriction do physiologically to extend longevity and fight off disease? Will it have the same effect in humans? And, if so, is there a way to get the benefits without the actual diet? "The purpose of studying calorie restriction," Miller says, "is not to develop yet another diet that people won't follow." Rather researchers would ideally like to concoct a pill or potion that will mimic the effects of calorie restriction and produce the benefits while allowing us to eat to our heart's content.

In the 65 years since Clive M. McKay of Cornell University first noticed that the regimen doubled the life span of his lab rats, and in the decade or so since calorie restriction moved from the fringes of longevity research to the mainstream, much of the laboratory work has been aimed at discerning the fundamental biology underlying the beneficial effects. What researchers generally agree on is that the response to calorie restriction in organisms seems to be an evolutionary adaptation to periods of scarcity. As food becomes hard to find, organisms evolve ways to "up-regulate" those defense mechanisms that increase life span and down-regulate reproductive mechanisms. That would keep the organisms alive long enough to find food, and at that point they could go back to reproducing and to a normal aging process, which is exactly what happens in the laboratory.

The question of how this might work is still open. The leading hypothesis is that calorie restriction reduces the amount of oxidative damage to the body. Oxidative damage is the foremost theory as to what causes the deterioration that comes with age. The concept is known in the business as the "oxygen paradox": we require oxygen to turn the food we eat into cellular fuel, but the side effects of this oxygen metabolism are detrimental to our health. The process takes place in cellular factories called mitochondria, where electrons are stripped from energy-rich substances—in particular, glucose—while converting them to the kind of fuel that cells can use.

The electrons are then captured by oxygen atoms, which join with hydrogen to form water. But the process is inefficient, and the electrons often go astray, resulting in the formation of highly reactive molecules known as free radicals. Roy L. Walford, a gerontologist at the University of California at Los Angeles and a pioneer of calorie-restriction research, refers to free radicals as "great white sharks in the biochemical sea—short-lived but voracious agents [that] oxidize and damage tissues."

The oxidation that occurs in the human body is identical to the way in which rust is formed in metals, so it is not unreasonable to say that we will all eventually rust to death if given the opportunity. The free radicals damage the tissues but also seem to damage the genetic material, the DNA, that codes for the proteins required for the body's physiological functions. The primary candidate for most of this damage is the mitochondria themselves, which are not spared by the free radicals they produce. And once damaged, they produce even more free radicals.

Calorie restriction, by this theory, reduces the amount of fuel available for cells and the amount of oxygen needed by the mitochondria to convert the existing fuel into energy, and it makes the existing metabolic process more efficient. Not only do the mitochondria gen-

erate fewer damaging free radicals, but the lack of food also seems to up-regulate the production of enzymes that neutralize the free radicals.

In one of the more fascinating experiments in the field, Richard Weindruch and Tomas A. Prolla of the University of Wisconsin–Madison recently compared the expression of genes in young mice, normally fed aging mice and calorie-restricted aging mice. Weindruch, who has been studying calorie restriction since he was a U.C.L.A. graduate student in the mid-1970s with Walford, believes that the process lowers oxidative stress and damage to the mitochondria while having its effect predominantly in "critical target tissues" such as the brain and nerve cells and heart and skeletal muscle. "All these tissues depend heavily on mitochondrial energy metabolism to generate cellular energy, and all these tissues have fairly limited repair capabilities," he says.

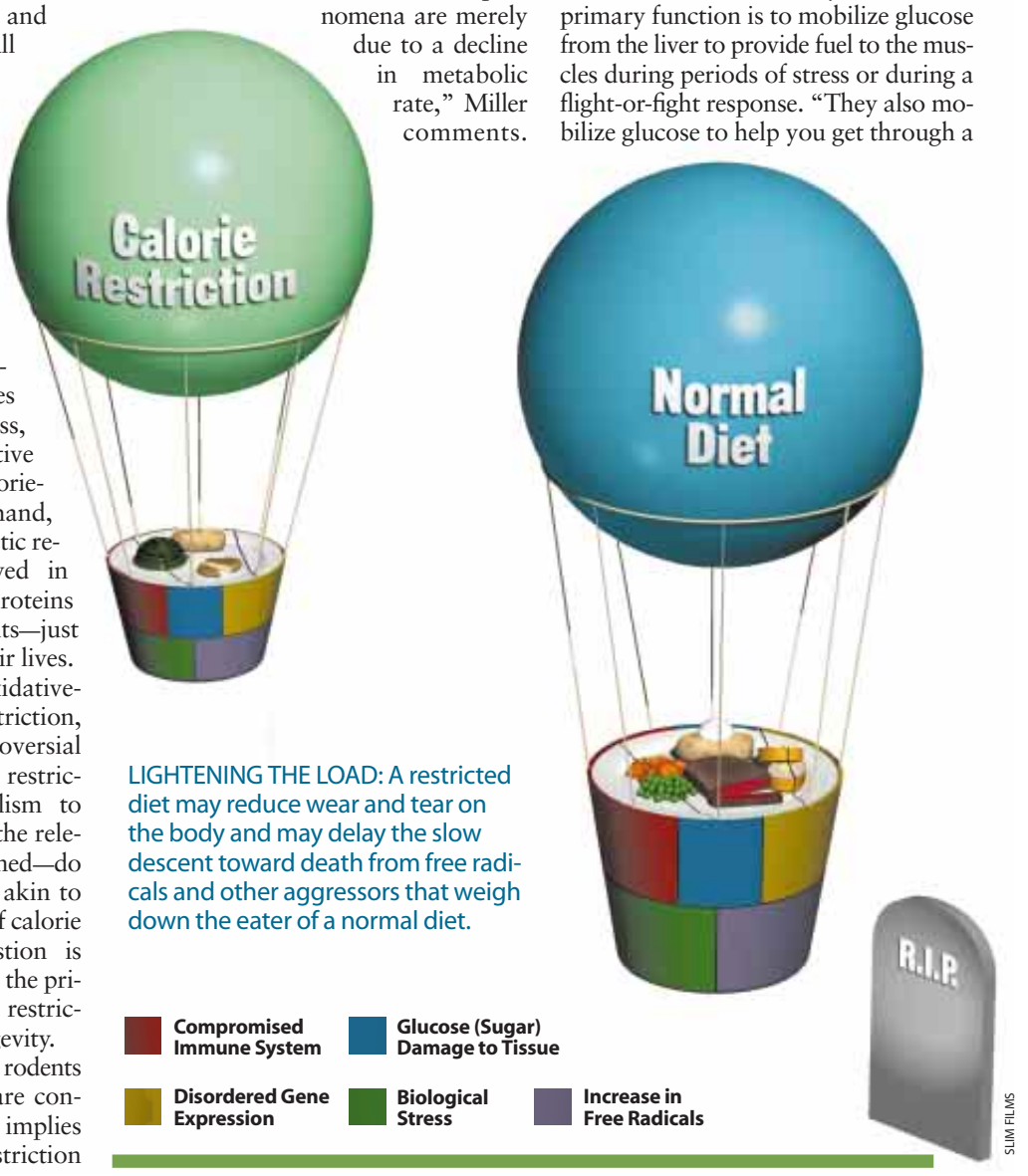
Weindruch and Prolla examined tissues from the calf muscles of mice and found that normally fed aging mice were putting most of their genetic effort into repairing genes and proteins damaged by stress, of which a good part is oxidative damage. The active genes of calorie-restricted mice, on the other hand, were much less involved in genetic repair and much more involved in biosynthesis—building new proteins and other cellular components—just like the mice in the prime of their lives.

Most researchers buy the oxidative-damage theory of calorie restriction, but they disagree on two controversial aspects. One is whether calorie restriction actually lowers metabolism to achieve its goal, in which case the relevance to humans might be lessened—do we have to go into something akin to hibernation to get the benefits of calorie restriction? The second question is whether lowering metabolism is the primary route that allows calorie restriction to achieve its effect on longevity.

The fact that calorie-restricted rodents have body temperatures that are considerably lower than normal implies that the benefits of calorie restriction come about because the less food eaten, the lower the metabolism and, hence, the lower the oxidative damage. "It's known that rodents can decrease their body temperature, their metabolic rate, and that [that] is how they survive famine periods," says Rajindar S. Sohal, a biologist at Southern Methodist University. "But mice and rats are not humans. We don't have that mechanism." Other researchers, however, disagree with this interpretation of the evidence, and the argument often comes down to a dispute about how best to measure metabolism in normally fed versus calorie-restricted animals. "It's a distinct oversimplification to say that the calorie-restriction phenomena are merely due to a decline in metabolic rate," Miller comments. "And many of the changes that occur in calorie-restricted rodents are hard to explain by the idea that fuel and oxygen consumption go down."

A Shot of Hormones

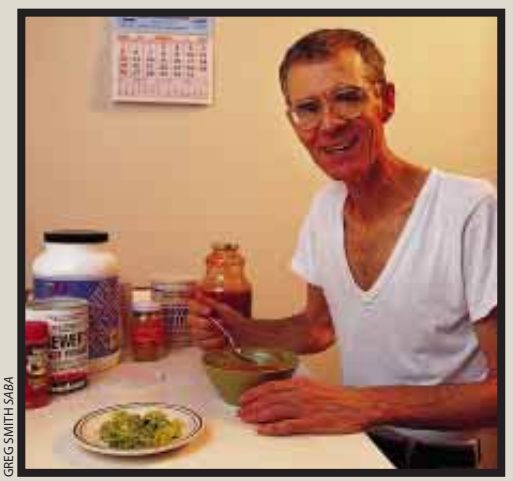
That there is more going on is suggested by the work of James F. Nelson, a physiologist at the University of Texas Health Science Center at San Antonio. Nelson and his colleagues have shown that calorie restriction subtly raises the levels of hormones called glucocorticoids. These hormones do "probably a zillion different things" in an organism, Nelson says, of which researchers have nailed down only a few. Their primary function is to mobilize glucose from the liver to provide fuel to the muscles during periods of stress or during a flight-or-fight response. "They also mobilize glucose to help you get through a



LIGHTENING THE LOAD: A restricted diet may reduce wear and tear on the body and may delay the slow descent toward death from free radicals and other aggressors that weigh down the eater of a normal diet.

four square
snacks a day

Michael Cooper, suffice it to say, is obsessed with the problem of aging and has been since he was a boy. He recalls looking at his seventh-grade teacher, a balding man in his 50s, and thinking, "I don't want to be like him," and, he says, "Those thoughts never left my mind." Now Cooper is 51, a former electrical engineer who recently went back to school to study biology at Southern Methodist University. Since the mid-1970s he has been reading voraciously about longevity, nutrition and health. And in February 1986 he began practicing calorie restriction, hoping to extend his life well beyond the biblical three score and 10 years. The 6'2" Cooper has reduced his daily calorie intake from 2,800 to 1,500, and his weight has dropped over a seven-year period from 160 pounds to a feather-light 120.



GREG SMITH *SABA*

THE SKINNY ON AGING: Michael Cooper consumes a 350-calorie lunch that includes whey protein, brewer's yeast and broccoli.

Cooper would have gone lower, but he found plenty of reasons to convince him otherwise. "For one thing," he points out, "if I was any thinner I would probably freeze to death. I wear long thermal underwear year-round in Texas, and I can't generate any body heat. If I sit still, I get cold even in a warm room. I have a little bit of digestive trouble, probably related to consuming too few calories. And my bones are quite vulnerable. They're more sensitive to sitting. I have to sit on a pillow. And my feet don't have any pad on the bottom. So I have to extra-pad my shoes. It's not a big deal; I get along just fine."

As for his daily diet, he explains, it's basically the equivalent of a handful of snacks a day: "Most wouldn't consider it very tasteful, but I like it a lot. In the morning, for instance, I mix up wheat bran and solid protein, and I put some canned pumpkin in it, a little bit of spices and occasionally half a cup of yogurt. For lunch I have vegetables. For supper I have two meals, one at about 5:00, which is just vegetables, maybe three different kinds. And around 7:30 I have what I call dessert, which might be berries mixed up with whey protein."

So far Cooper sees little evidence that his severe diet has slowed the aging process, and it certainly hasn't diminished the unaesthetic side effects, although he remains relentlessly optimistic. "My hair is thinner," he notes, "and when you're thinner you look older. Wrinkles show up more. On the other hand, if I weren't doing this I might already be in decrepit condition. I have no way of knowing. And even if I come down with a disease like cancer or heart disease and I know I'm going to die, I figure I've probably gained a few years by doing what I've done." —*G.T.*

fasting stage, to keep blood sugar high enough so you can keep going to your next meal," he says. These hormones, too, serve to fight inflammation, hinting that they play a direct role in the survival of the organism. And glucocorticoids are only one of a host of hormones in laboratory animals that seem to be affected by calorie restriction.

The Human Question

Nelson and his colleagues are currently testing lab animals to find out if the hormonal changes in calorie-restricted animals are a side effect of calorie restriction or a mechanism that directly leads to longevity. In one experiment, for instance, Nelson's laboratory is spiking the drinking water of lab mice with glucocorticoids to determine if the mice live longer. "The next thing would be to see if any of these effects are translatable to humans," he asserts.

The human question is the big one. The existing data on humans are very thin. Most human populations that are forced to survive on low-calorie diets are also malnourished and are as likely as not to die prematurely from vitamin and mineral deficiencies. The only known exception is on the Japanese island of Okinawa, Walford notes: "The Okinawans have about 70 percent of the calorie intake of the rest of Japan. They eat mainly fish and vegetables. They have as much as 40 times the incidence of people over 100. They have less diabetes, tumors and so forth than the rest of Japan."

On the other hand, he adds, there could be numerous other factors that contribute to the Okinawans' longevity. Doing a controlled trial of calorie-restricted humans is impractical for what David B. Allison, an obesity researcher at St. Luke's-Roosevelt Hospital Center in New York City, calls "the obvious reasons": researchers would have to convince hundreds or thousands of humans to spend the better part of their lifetime living on an extreme diet, without being able to promise them benefits. And the trial would, by definition, take the better part of a century to complete.

Instead the National Institute on Aging (NIA), in collaboration with Wein-

DAVE BARTRUFF *Corbis*

druch and his colleagues, is testing the calorie-restriction proposition on rhesus and squirrel monkeys, assuming that if it works for any primates, it's a good bet it would work for humans. They now have some 200 monkeys in the trial, half on a calorie-restricted diet and half eating normally. Even these monkeys are likely to live 30 or 40 years, so the study is a long-term endeavor. But the calorie-restricted monkeys are already showing signs of unnaturally robust health.

With so little information on whether calorie restriction will benefit humans, researchers have barely touched on how to mimic its effect without going on a diet that could take the fun out of living, and certainly out of eating, for almost anyone willing to try it. One possibility, Allison says, is to give all people, not just the excessively overweight, anti-obesity drugs. This would suppress appetite, but a healthy *un*satisfied appetite may be a necessary factor in convincing an organism that famine has arrived and thus stimulate the beneficial effects. "That this might lengthen life is real speculation, and it goes far beyond any data," Allison observes. "We've never demonstrated in humans that antiobesity drugs even make the obese live longer, let alone the average-weight person."

At the NIA, George S. Roth, Donald K. Ingram and Mark P. Mattson are trying another tack—fooling cells into thinking they've been fed when they haven't. They're using a compound called 2-deoxy-D-glucose, which is virtually identical to glucose but lacks two oxygen atoms. Once inside the body, it goes where glucose would normally go, but it can't be metabolized by the cells. The compound is synthetic, relatively inexpensive and has been used in research laboratories for years. It's also mildly toxic in high enough doses, however, which makes it a debatable intervention for humans even if it works.

UNCONTROLLED EXPERIMENT: Okinawans, with 70 percent of the calorie intake of other Japanese, count among their number up to 40 times as many centenarians as their countrymen do.

The researchers gave moderate doses to rats for six months—not long enough to establish whether the compound increased longevity but long enough to see if it might. With the 2-deoxy-D-glucose added to their diet, the rats continued to eat the same amount of calories, and yet they lost weight and their body temperature dropped, as it would have had they been dieting. Their insulin levels also dropped, another hallmark of calorie restriction. This convinced the NIA researchers that 2-deoxy-D-glucose was worth testing for the lifetime of the rats, a study that's ongoing. If the rats do indeed live longer, the NIA researchers will at least have proved that the mimetic phenomenon, as they call this calorie-restriction mimicry, has promise. "Then we'll look for other kinds of compounds that exert the same effects without any toxicity," Roth says. That would mark a big step toward the ultimate goal of letting people have their cake and live longer, too.

Gary Taubes *is a California-based science writer.*

Further Information

Caloric Restriction and Aging. Richard Weindruch in *Scientific American,* Vol. 274, No. 1, pages 32–38; January 1996.

Roy Walford, the gerontologist who is observing a calorically restricted diet, maintains a site at www.walford.com on the World Wide Web.