Caloric Restriction and Aging

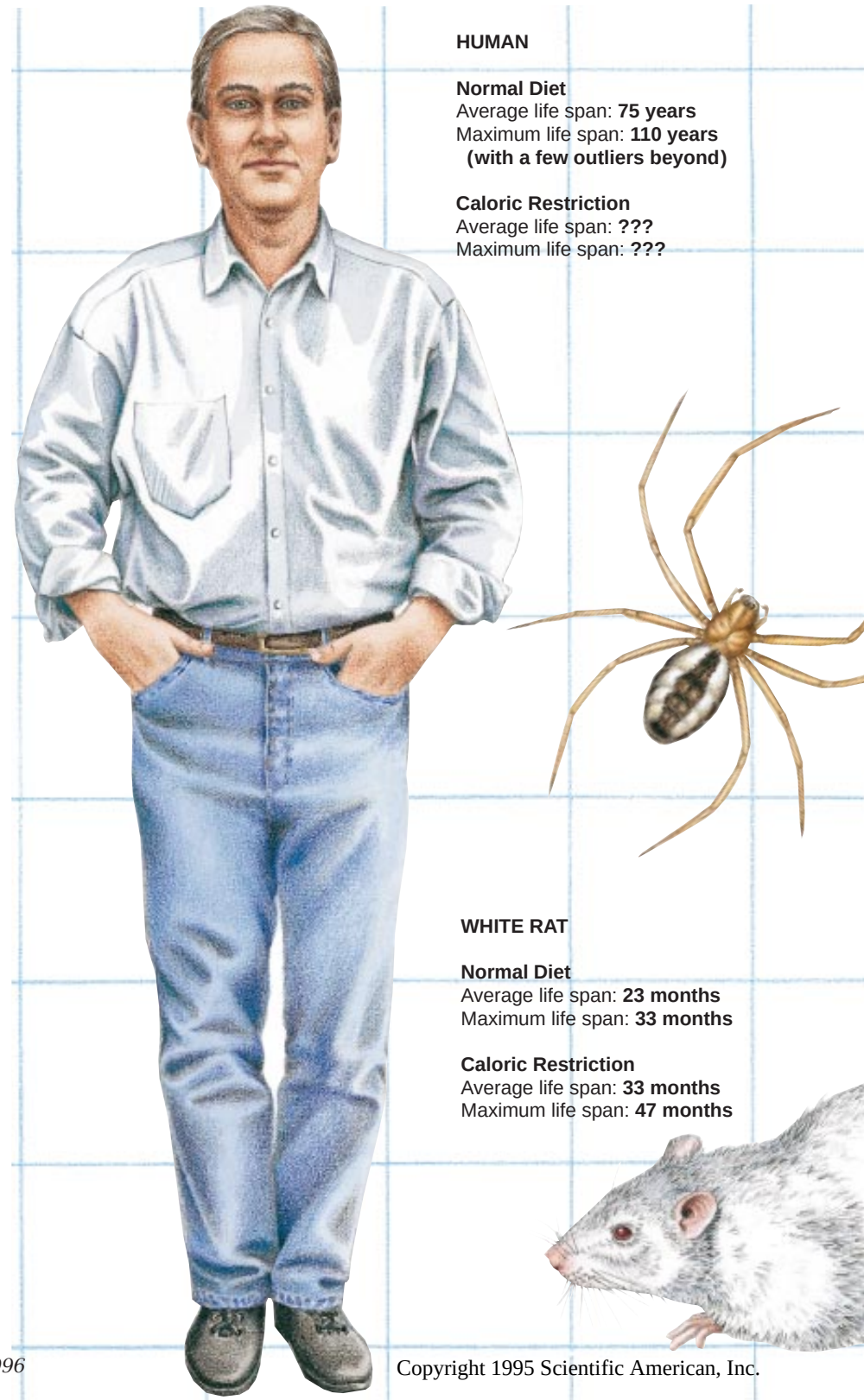
Eat less, but be sure to have enough protein, fat, vitamins and minerals. This prescription does wonders for the health and longevity of rodents. Might it help humans as well?

by Richard Weindruch

Sixty years ago scientists at Cornell University made an extraordinary discovery. By placing rats on a very low calorie diet, Clive M. McCay and his colleagues extended the outer limit of the animals' life span by 33 percent, from three years to four. They subsequently found that rats on low-calorie diets stayed youthful longer and suffered fewer late-life diseases than did their normally fed counterparts. Since the 1930s, caloric restriction has been the only intervention shown convincingly to slow aging in rodents (which are mammals, like us) and in creatures ranging from single-celled protozoans to roundworms, fruit flies and fish.

Naturally, the great power of the method raises the question of whether it can extend survival and good health in people. That issue is very much open, but the fact that the approach works in an array of organisms suggests the answer could well be yes. Some intriguing clues from monkeys and humans support the idea, too.

Of course, even if caloric austerity turns out to be a fountain of youth for humans, it might never catch on. After all, our track record for adhering to severe diets is poor. But scientists may one day develop drugs that will safely control our appetite over the long term or will mimic the beneficial influences of caloric control on the body's tissues. This last approach could enable people to consume fairly regular diets while still reaping the healthful effects of limiting their food intake. Many laboratories, including mine at the University of Wisconsin–Madison, are working to understand the cellular and molecular ba-



LIFE HAS BEEN EXTENDED, often substantially, by very low calorie diets in a range of animals, some of which are depicted here. Whether caloric restriction will increase survival in people remains to be seen. Such diets are successful only if the animals receive an adequate supply of nutrients.

sis of how caloric restriction retards aging in animals. Our efforts may yield useful alternatives to strict dieting, although at the moment most of us are focused primarily on understanding the aging process (or processes) itself.

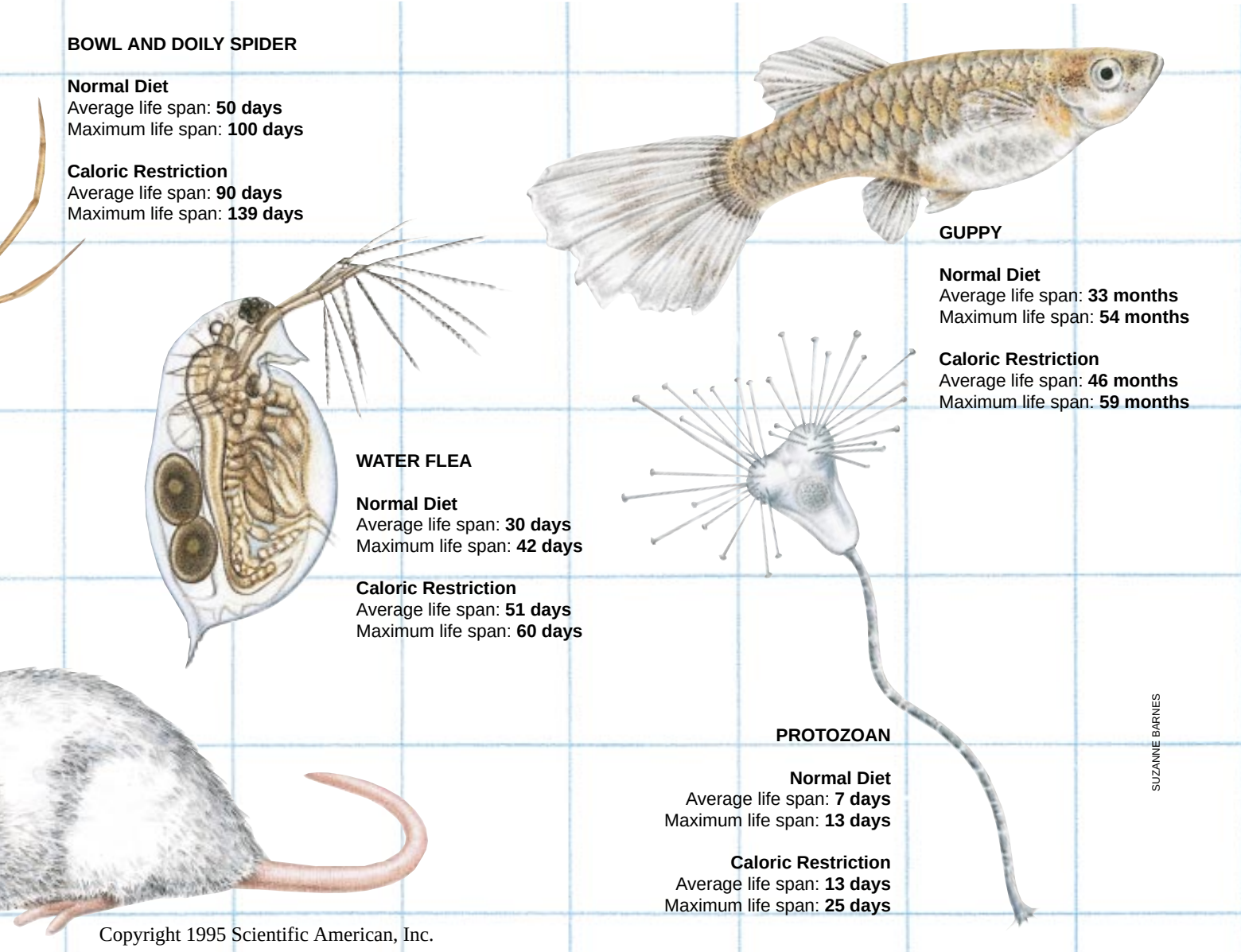
Less Is More for Rodents

Research into caloric restriction has now uncovered an astonishing range of benefits in animals—provided that the nutrient needs of the dieters are guarded carefully. In most studies the test animals, usually mice or rats, consume 30 to 50 percent fewer calories than are ingested by control subjects, and they weigh 30 to 50 percent less as well. At the same time, they receive enough protein, fat, vitamins and minerals to maintain efficient operation of their tissues. In other words, the animals follow an exaggerated form of a prudent diet, in which they consume minimal calories without becoming malnourished.

If the nutrient needs of the animals are protected, caloric restriction will consistently increase not only the average life span of a population but also the maximum span—that is, the lifetime of the longest-surviving members of the group. This last outcome means that caloric restriction tinkers with some basic aging process. Anything that forestalls premature death, such as is caused by a preventable or treatable disease or by an accident, will increase the average life span of a population. But one must truly slow the rate of aging in order for the hardiest individuals to surpass the existing maximum.

Beyond altering survival, low-calorie diets in rodents have postponed most major diseases that are common late in life [*see box on next page*], including cancers of the breast, prostate, immune system and gastrointestinal tract. Moreover, of the 300 or so measures of aging that have been studied, some 90 percent stay "younger" longer in calorie-restricted rodents than in well-fed ones. For example, certain immune responses decrease in normal mice at one year of age (middle age) but do not decline in slimmer but genetically identical mice until age two. Similarly, as rodents grow older they generally clear glucose, a simple sugar, from their blood less efficiently than they did in youth (a change that can progress to diabetes); they also synthesize needed proteins more slowly, undergo increased cross-linking (and thus stiffening) of long-lived proteins in tissues, lose muscle mass and learn less rapidly. In calorie-restricted animals, all these changes are delayed.

Not surprisingly, investigators have wondered whether caloric (energy) restriction per se is responsible for the advantages reaped from low-calorie diets or whether limiting fat or some other component of the diet accounts for the success. It turns out the first possibility is correct. Restriction of fat, protein or carbohydrate without caloric reduction does not increase the maximum life span of rodents. Supplementation



alone with multivitamins or high doses of antioxidants does not work, and neither does variation in the type of dietary fat, carbohydrate or protein.

The studies also suggest, heartteningly, that caloric restriction can be useful even if it is not started until middle age. Indeed, the most exciting discovery of my career has been that caloric restriction initiated in mice at early middle age can extend the maximum life span by 10 to 20 percent and can oppose the development of cancer. Further, although limiting the caloric intake to about half of that consumed by free-feeding animals increases the maximum life span the most, less severe restriction, whether begun early in life or later, also provides some benefit.

Naturally, scientists would be more confident that diet restriction could routinely postpone aging in men and women if the results in rodents could be confirmed in studies of monkeys (which more closely resemble people) or in members of our own species. To be most informative, such investigations would have to follow subjects for many years—an expensive and logistically difficult undertaking. Nevertheless, two major trials of monkeys are in progress.

Lean, but Striking, Primate Data

It is too early to tell whether low-calorie diets will prolong life or youthfulness in the monkeys over time. The projects have, however, been able to measure the effects of caloric restriction on so-called biomarkers of aging: attributes that generally change with age and may help predict the future span of health or life. For example, as primates grow older, their blood pressure and their blood levels of both insulin and glucose rise; at the same time, insulin sensitivity (the ability of cells to take up glucose in response to signals from insulin) declines. Postponement of these changes would imply that the experimental diet was probably slowing at least some aspects of aging.

One of the monkey studies, led by George S. Roth of the National Institute on Aging, began in 1987. It is examining rhesus monkeys, which typically live to about 30 years and sometimes reach 40 years, and squirrel monkeys, which rarely survive beyond 20 years.

Benefits of Caloric Restriction

Since 1900, advances in health practices have greatly increased the average life span of Americans (*inset in a*), mainly by improving prevention and treatment of diseases that end life prematurely. But those interventions have not substantially affected the maximum life span (*far right in a*), which is thought to be determined by intrinsic aging processes. (The curves and the data in the inset show projections for people born in the years indicated and assume conditions influencing survival do not change.) Caloric restriction, in contrast, has markedly increased the maximum as well as the average life span in rodents (*b*) and is, in fact, the only intervention so far shown to slow aging in mammals—a sign that aging in humans might be retarded as well.

Although severe diets extend survival more than moderate ones, a study of mice fed a reduced-calorie diet from early in life (three weeks of age) demonstrates that even mild restriction offers some benefit (*c*). This finding is potentially good news for people. Also encouraging is the discovery that caloric restriction in rodents does more than prolong life; it enables animals to remain youthful longer (*table*). The calorie-restricted mouse in the corner lived unusually long; most normally fed mice of her ilk die by 40 months. She was 53 months old when this photograph was taken and died of unknown causes about a month later.

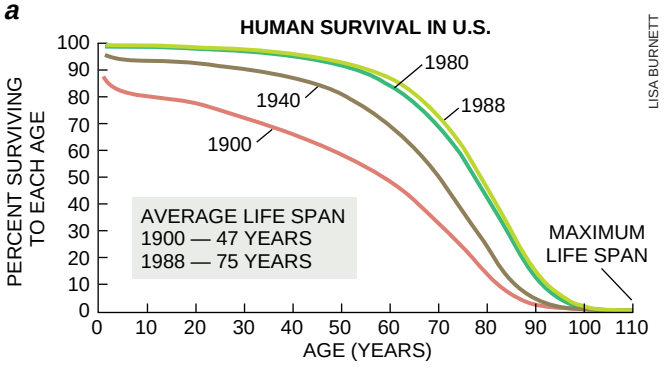
RESTRICTION IN RODENTS: SELECTED EFFECTS

Postpones age-related declines in:
Blood glucose control; female reproductive capacity; DNA repair; immunity; learning ability; muscle mass; protein synthesis

Slows age-related increases in:
Cross-linking of long-lived proteins; free-radical production by mitochondria; unrepaired oxidative damage to tissues

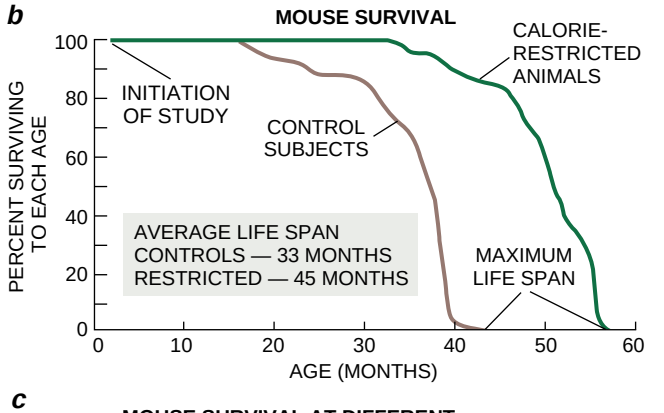
Delays onset of late-life diseases, including:
Autoimmune disorders; cancers; cataracts; diabetes; hypertension; kidney failure

a



SOURCE: U.S. Bureau of the Census; National Center for Health Statistics

b



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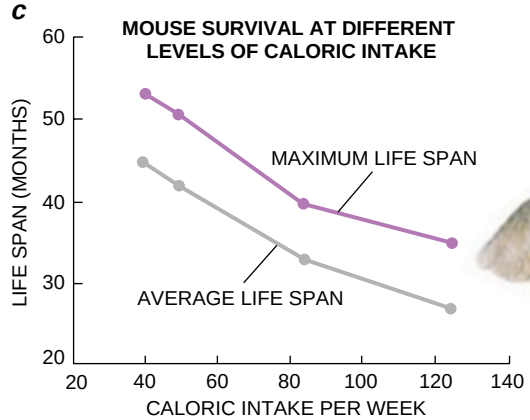


Some animals began diet restriction in youth (at one to two years), others after reaching puberty. The second project, involving only rhesus monkeys, was initiated in 1989 by William B. Ershler, Joseph W. Kemnitz and Ellen B. Roecker of the University of Wisconsin–Madison; I joined the team a year later. Our monkeys began caloric restriction as young adults, at eight to 14 years old. Both studies enforce a level of caloric restriction that is about 30 percent below the intake of normally fed controls.

So far the preliminary results are encouraging. The dieting animals in both projects seem healthy and happy, albeit eager for their meals, and their bodies seem to be responding to the regimen much as those of rodents do. Blood pressure and glucose levels are lower than in control animals, and insulin sensitivity is greater. The levels of insulin in the blood are lower as well.

No one has yet performed carefully controlled studies of long-term caloric restriction in average-weight humans over time. And data from populations forced by poverty to live on relatively few calories are uninformative, because such groups generally cannot attain adequate amounts of essential nutrients. Still, some human studies offer indirect evidence that caloric restriction could be of value. Consider the people of Okinawa, many of whom consume diets that are low in calories but provide needed nutrients. The incidence of centenarians there is high—up to 40 times greater than that of any other Japanese island. In addition, epidemiological surveys in the U.S. and elsewhere indicate that certain cancers, notably those of the breast, colon and stomach, occur less frequently in people reporting small caloric intakes.

Intriguing results were also obtained after eight people living in a self-contained environment—Biosphere 2, near Tucson, Ariz.—were forced to curtail their food intake sharply for two years because of poorer than expected yields from their food-producing efforts. The scientific merits of the overall project have been questioned, but those of us interested in the effects of low-calorie diets were fortunate that Roy L. Walford of the University of California at Los Angeles, who is an expert on caloric restriction and aging (and was my scientific mentor), was the team's physician. Walford helped his colleagues avoid malnutrition and monitored various aspects of the group's physiology. His analyses reveal that caloric restriction led to lowered blood pressure and glucose levels—just as it does in rodents and monkeys. Total serum cholesterol declined as well.

RICHARD WEINDRUCH

MICE ARE THE SAME AGE—40 months. Yet compared with the normally fed animal at the right, the one at the left, which has been reared on a low-calorie diet since 12 months of age (early middle age), looks younger and is healthier.

The results in monkeys and humans may be preliminary, but the rodent data show unequivocally that caloric restriction can exert a variety of beneficial effects. This variety raises something of a problem for researchers: Which of the many documented changes (if any) contribute most to increased longevity and youthfulness? Scientists have not yet reached a consensus, but they have ruled out a few once viable proposals. For instance, it is known that a low intake of energy retards growth and also shrinks the amount of fat in the body. Both these effects were once prime contenders as the main changes that lead to longevity but have now been discounted.

Several other hypotheses remain under consideration, however, and all of them have at least some experimental support. One such hypothesis holds that caloric restriction slows the rate of cell division in many tissues. Because the uncontrolled proliferation of cells is a hallmark of cancer, that change could potentially explain why the incidence of several late-life cancers is reduced in animals fed low-calorie diets. Another proposal is based on the finding that caloric restriction tends to lower glucose levels. Less glucose in the circulation would slow the accumulation of sugar on long-lived proteins and would thus moderate the disruptive effects of this buildup.

A Radical Explanation

The view that has so far garnered the most convincing support, though, holds that caloric restriction extends survival and vitality primarily by limiting injury of mitochondria by free radicals. Mitochondria are the tiny intracellular structures that serve as the power plants of cells. Free radicals are highly reactive molecules (usually derived from oxygen) that carry an unpaired electron at their surface. Molecules in this state are prone to destructively oxidizing, or snatching electrons from, any compound they encounter. Free radicals have been suspected of contributing to aging since the 1950s, when Denham Harman of the University of Nebraska Medical School suggested that their generation in the course of normal metabolism gradually disrupts cells. But it was not until the 1980s that scientists began to realize that mitochondria were probably the targets hit hardest.

The mitochondrial free-radical hypothesis of aging derives in part from an understanding of how mitochondria produce ATP (adenosine triphosphate)—the molecule that provides the energy for most cellular processes, such as pumping ions across cell membranes, contracting muscle fibers and constructing proteins. ATP synthesis occurs by a very complicated sequence of reactions, but essentially it involves activity by a series of molecular complexes embedded in an internal membrane—the inner membrane—of mitochondria. With help from oxygen, the complexes extract energy from nutrients and use that energy to manufacture ATP.

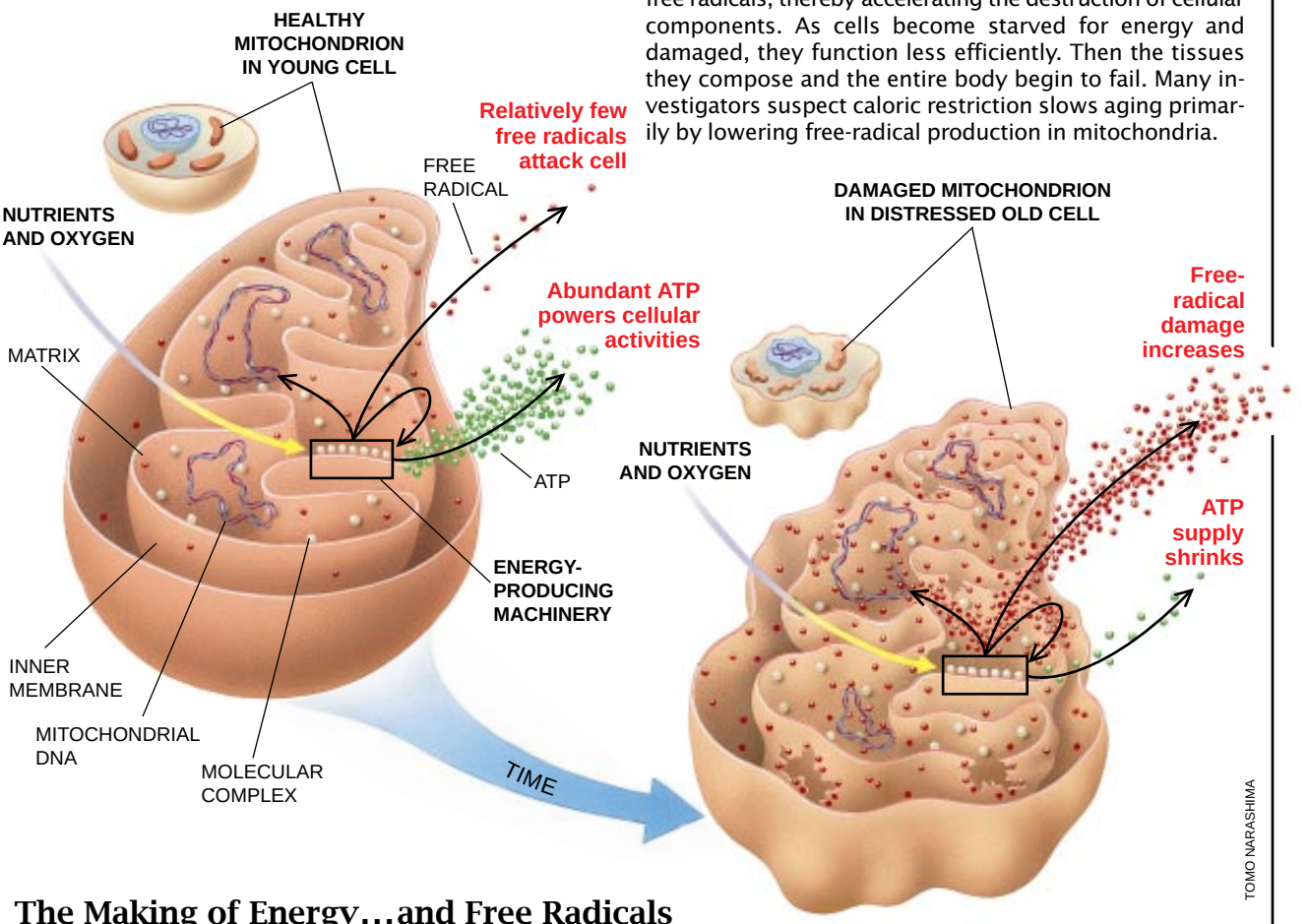
Unfortunately, the mitochondrial machinery that draws energy from nutrients also produces free radicals as a by-product. Indeed, mitochondria are thought to be responsible for creating most of the free radicals in cells. One such by-product is the superoxide radical ($O_2^{\cdot -}$). (The dot in the formula represents the unpaired electron.) This renegade is destructive in its own right but can also be converted into hydrogen peroxide (H_2O_2), which technically is not a free radical but can readily form the extremely aggressive hydroxyl free radical ($OH^{\cdot -}$).

Once formed, free radicals can dam-

A Theory of Aging

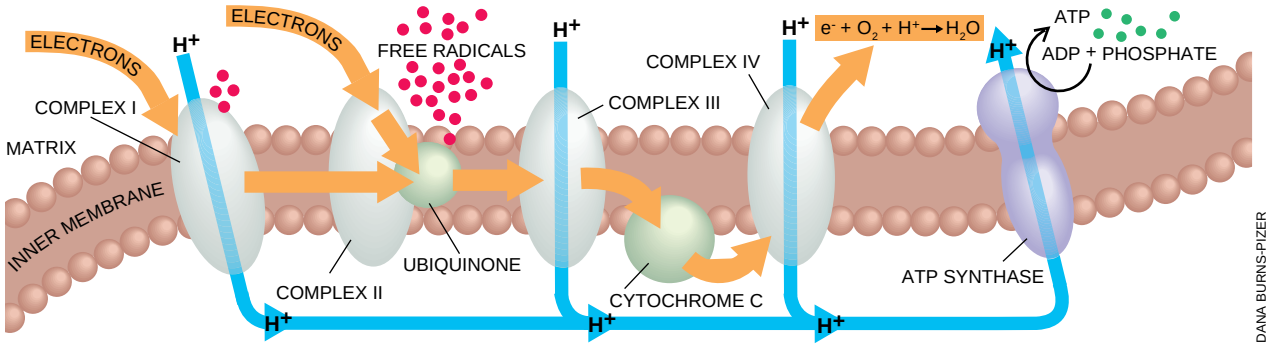
A leading explanation for why we age places much of the blame on destructive free radicals (*red*) generated in mitochondria, the cell's energy factories. The radicals form (*left*) when the energy-producing machinery in mitochondria (*boxed in black*) uses oxygen and nutrients to synthesize ATP (adenosine triphosphate)—the molecule (*green*) that powers most other activities in cells. Those radicals attack, and may permanently injure, the machinery itself and the mitochondrial DNA that is needed to construct parts of it. They can also harm other components of mitochondria and cells.

The theory suggests that over time (*right*) the accumulated damage to mitochondria precipitates a decline in ATP production. It also engenders increased production of free radicals, thereby accelerating the destruction of cellular components. As cells become starved for energy and damaged, they function less efficiently. Then the tissues they compose and the entire body begin to fail. Many investigators suspect caloric restriction slows aging primarily by lowering free-radical production in mitochondria.



The Making of Energy…and Free Radicals

The energy-producing machinery in mitochondria consists mainly of the electron-transport chain: a series of four large (*gray*) and two smaller (*light green*) molecular complexes. Complexes I and II (*far left*) take up electrons (*gold arrows*) from food and relay them to ubiquinone, the site of greatest free-radical (*red*) generation. Ubiquinone sends the electrons down the rest of the chain to complex IV, where they interact with oxygen and hydrogen to form water. The electron flow induces protons (H+) to stream (*blue arrows*) to yet another complex—ATP synthase (*purple*)—which draws on energy supplied by the protons to manufacture ATP (*dark green*). Free radicals form when electrons escape from the transport chain and combine with oxygen in their vicinity.



age proteins, lipids (fats) and DNA anywhere in the cell. But the components of mitochondria—including the ATP-synthesizing machinery and the mitochondrial DNA that gives rise to some of that machinery—are believed to be most vulnerable. Presumably they are at risk in part because they reside at or near the "ground zero" site of free-radical generation and so are constantly bombarded by the oxidizing agents. Moreover, mitochondrial DNA lacks the protein shield that helps to protect nuclear DNA from destructive agents. Consistent with this view is that mitochondrial DNA suffers much more oxidative damage than does nuclear DNA drawn from the same tissue.

Proponents of the mitochondrial free-radical hypothesis of aging suggest that damage to mitochondria by free radicals eventually interferes with the efficiency of ATP production and increases the output of free radicals. The rise in free radicals, in turn, accelerates the oxidative injury of mitochondrial components, which inhibits ATP production even more. At the same time, free radicals attack cellular components outside the mitochondria, further impairing cell functioning. As cells become less efficient, so do the tissues and organs they compose, and the body itself becomes less able to cope with challenges to its stability. The body does try to counteract the noxious effects of the oxidizing agents. Cells possess antioxidant enzymes that detoxify free radicals, and they make other enzymes that repair oxidative damage. Neither of these systems is 100 percent effective, though, and so such injury is likely to accumulate over time.

Experimental Support

The proposal that aging stems to a great extent from free-radical-induced damage to mitochondria and other cellular components has recently been buttressed by a number of findings. In one striking example, Rajindar S. Sohal, William C. Orr and their colleagues at Southern Methodist University in Dallas investigated rodents and several other organisms, including fruit flies, houseflies, pigs and cows. They noted increases with age in free-radical generation by mitochondria and in oxidative changes to the inner mitochondrial membrane (where ATP is synthesized) and to mitochondrial proteins and DNA. They also observed that greater rates of free-radical production correlate with shortened average and maximum life spans in several of the species.

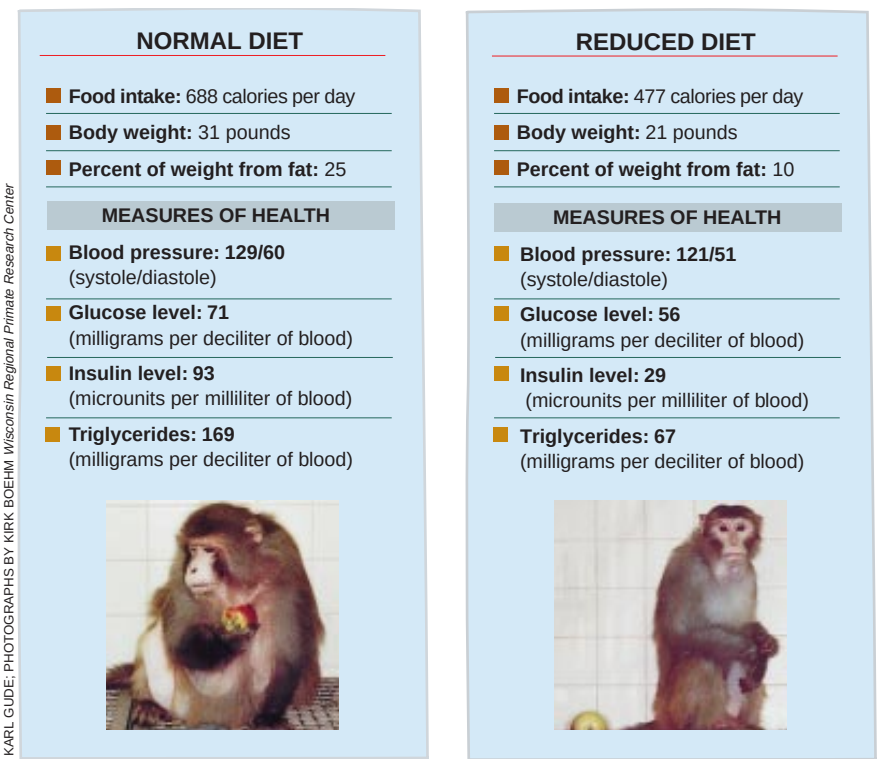
It turns out, too, that ATP manufacture decreases with age in the brain, heart and skeletal muscle, as would be expected if mitochondrial proteins and DNA in those tissues were irreparably impaired by free radicals. Similar decreases also occur in human tissues and may help explain why degenerative diseases of the nervous system and heart are common late in life and why muscles lose mass and weaken.

Some of the strongest support for the proposition that caloric restriction retards aging by slowing oxidative injury of mitochondria comes from Sohal's group. When the workers looked at mitochondria harvested from the brain, heart and kidney of mice, they discovered that the levels of the superoxide radical and of hydrogen peroxide were markedly lower in animals subjected to long-term caloric restriction than in normally fed controls. In addition, a significant increase of free-radical production with age seen in the control groups was blunted by caloric restriction in the experimental group. This blunted increase was, moreover, accompanied by lessened amounts of oxidative insult to mitochondrial proteins and DNA. Other work indicates that caloric restriction helps to prevent age-related changes in the activities of some antioxidant enzymes—although many investigators, including me, suspect that strict dieting ameliorates oxidative damage mainly through slowing free-radical production.

By what mechanism might caloric restriction reduce the generation of free radicals? No one yet knows. One proposal holds that a lowered intake of calories may somehow lead to slower consumption of oxygen by mitochondria—either overall or in selected cell types. Alternatively, low-calorie diets may increase the efficiency with which mitochondria use oxygen, so that fewer free radicals are made per unit of oxygen consumed. Less use of oxygen or more efficient use would presumably result in the formation of fewer free radicals. Recent findings also intimate that caloric control may minimize free-radical generation in mitochondria by reducing levels of a circulating thyroid hormone known as triiodothyronine, or T_3, through unknown mechanisms.

Applications to Humans?

Until research into primates has progressed further, few scientists would be prepared to recommend that large numbers of people embark on a severe caloric-restriction regimen. Nevertheless, the accumulated findings do offer



KARL GUDE; PHOTOGRAPHS BY KIRK BOEHM *Wisconsin Regional Primate Research Center*

RESULTS FROM ONGOING TRIAL of caloric restriction in rhesus monkeys cannot yet reveal whether limiting calories will prolong survival. But comparison of a control group (*left*) with animals on a strict diet (*right*) after five years indicates that at least some biological measures that typically rise with age are changing more slowly in the test animals. Blood pressure is only slightly lower in the restricted group now, but has been markedly lower for much of the study period.

some concrete lessons for those who wonder how such programs might be implemented in humans.

One implication is that sharp curtailment of food intake would probably be detrimental to children, considering that it retards growth in young rodents. Also, because children cannot tolerate starvation as well as adults can, they would presumably be more susceptible to any as yet unrecognized negative effects of a low-calorie diet (even though caloric restriction is not equivalent to starvation). An onset at about 20 years of age in humans should avoid such drawbacks and would probably provide the greatest extension of life.

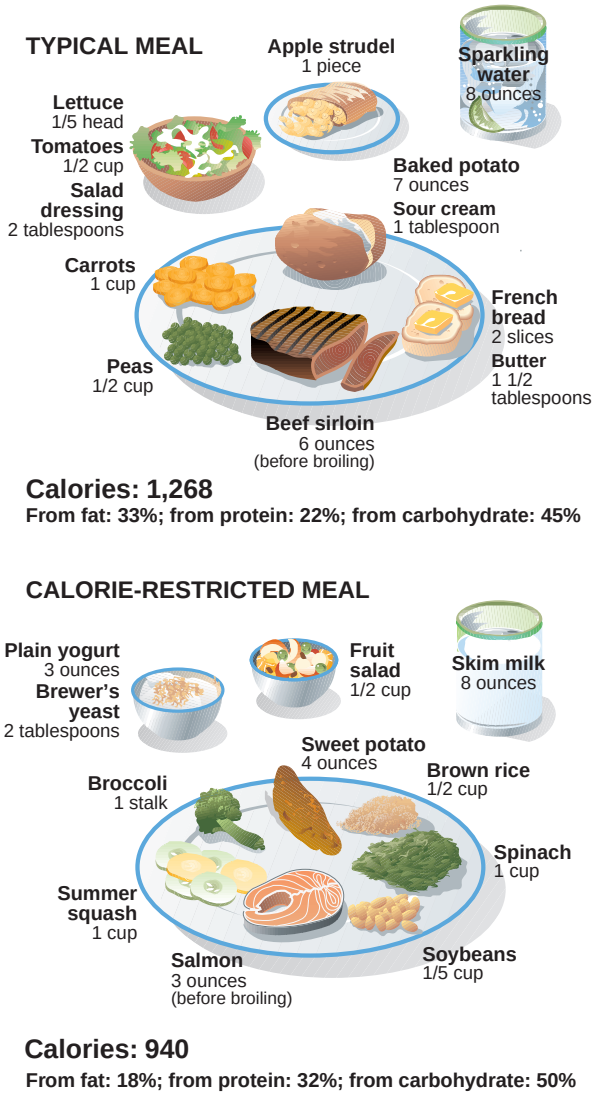
The speed with which calories are reduced needs to be considered, too. Early researchers were unable to prolong survival of rats when diet control was instituted in adulthood. I suspect the failure arose because the animals were put on the regimen too suddenly or were given too few calories, or both. Working with year-old mice, my colleagues and I have found that a gradual tapering of calories to about 65 percent of normal did increase survival.

How might one determine the appropriate caloric intake for a human being? Extrapolating from rodents is difficult, but some findings imply that many people would do best by consuming an amount that enabled them to weigh 10 to 25 percent less than their personal set point. The set point is essentially the weight the body is "programmed" to maintain, if one does not eat in response to external cues, such as television commercials. The problem with this guideline is that determining an individual's set point is tricky. Instead of trying to identify their set point, dieters (with assistance from their health advisers) might engage in some trial and error to find the caloric level that reduces the blood glucose or cholesterol level, or some other measures of health, by a predetermined amount.

The research in animals further implies that a reasonable caloric-restriction regimen for humans might involve a daily intake of roughly one gram (0.04 ounce) of protein and no more than about half a gram of fat for each kilogram (2.2 pounds) of current body weight. The diet would also include enough complex carbohydrate (the long chains of sugars abundant in fruits and vegetables) to reach the desired level of calories. To attain the standard recommended daily allowances for all essential nutrients, an individual would have to select foods with extreme care and probably take vitamins or other supplements.

Anyone who contemplated following a caloric-restriction regimen would also have to consider potential disadvantages beyond hunger pangs and would certainly want to undertake the program with the guidance of a physician. Depending on the severity of the diet, the weight loss that inevitably results might impede fertility in females. Also, a prolonged anovulatory state, if accompanied by a diminution of estrogen production, might increase the risk of osteoporosis (bone loss) and loss of muscle mass later in life. It is also possible that caloric restriction will compromise a person's ability to withstand stress, such as injury, infection or exposure to extreme temperatures. Oddly enough, stress resistance has been little studied in rodents on low-calorie diets, and so they have little to teach about this issue.

It may take another 10 or 20 years before scientists have a firm idea of whether caloric restriction can be as beneficial for humans as it clearly is for rats, mice and a variety of other creatures. Meanwhile investigators studying this intervention are sure to learn much about the nature of aging and to gain ideas about how to slow it—whether through caloric restriction, through drugs that reproduce the effects of dieting or by methods awaiting discovery.



KARL GUDE; SOURCE: ROY L. WALFORD *University of California, Los Angeles*

DINNER of a person on a roughly 2,000-calorie diet (*top*) might be reduced considerably—by about a third of the calories (*bottom*)—for someone on a caloric-restriction regimen. To avoid malnutrition, people on such programs would choose nutrient-dense foods such as those shown.

The Author

RICHARD WEINDRUCH, who earned his Ph.D. in experimental pathology at the University of California, Los Angeles, is associate professor of medicine at the University of Wisconsin–Madison, associate director of the university's Institute on Aging and a researcher at the Veterans Administration Geriatric Research, Education and Clinical Center in Madison. He has devoted his career to the study of caloric restriction and its effects on the body and practices mild restriction himself. He has not, however, attempted to put his family or his two cats on the regimen.

Further Reading

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