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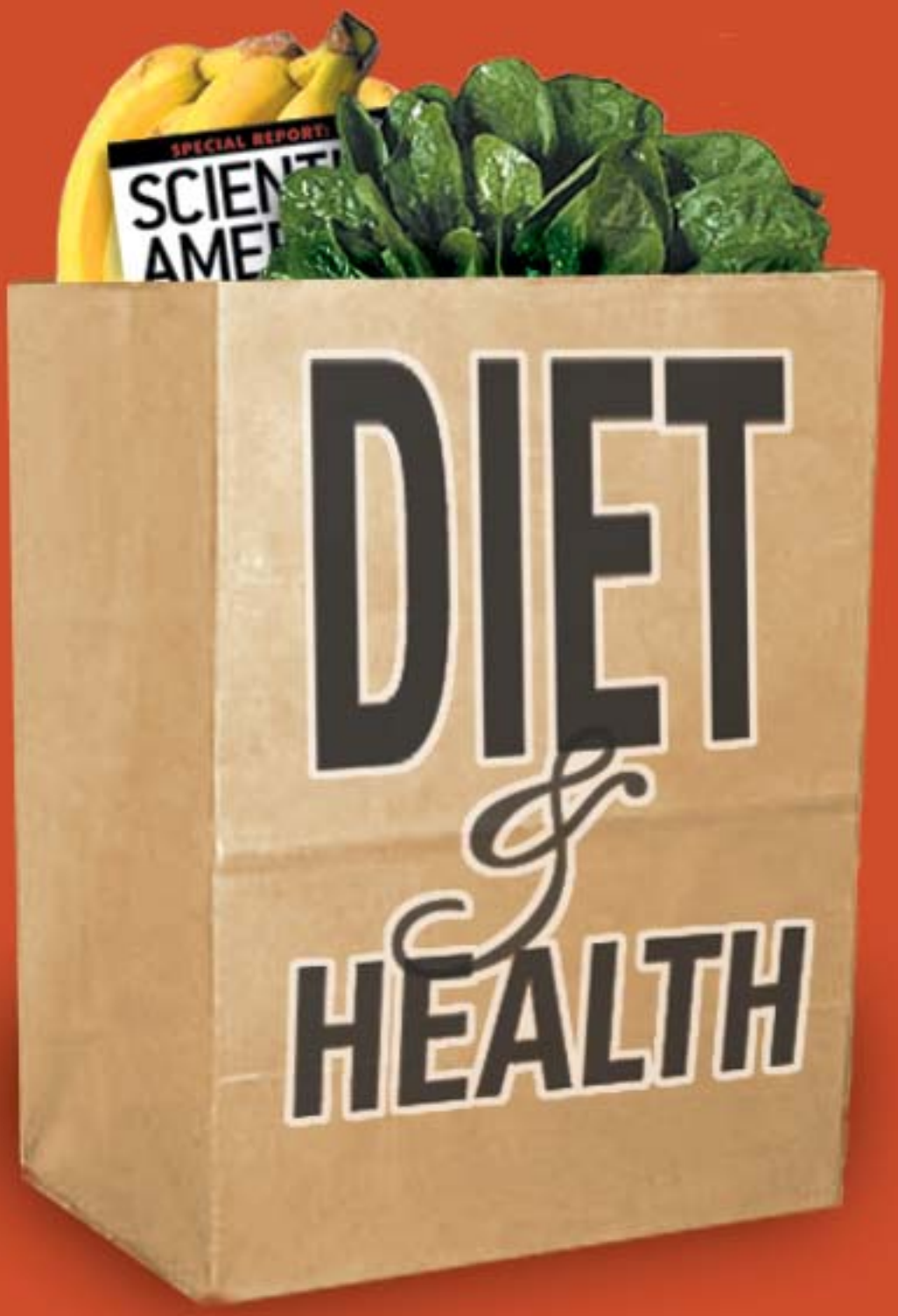

# DIET AND HEALTH

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If you're like many people, your New Year's resolution was to change your diet—whether by cutting back on quantity or improving quality, or both. In our fast-food era it is harder than ever to strike a healthy balance. And with new fad regimens springing up constantly, that balance is increasingly difficult to discern in the first place.

In this issue prominent researchers and journalists examine what we consume and how it affects us. Just how did our species find itself in such a nutritional predicament? Whatever happened to the food pyramid? Is moderate drinking good for you? Does caloric restriction actually promote longevity and youthfulness? Our authors tackle these questions and more. We think their writings will give you something to chew on. *—The Editors*

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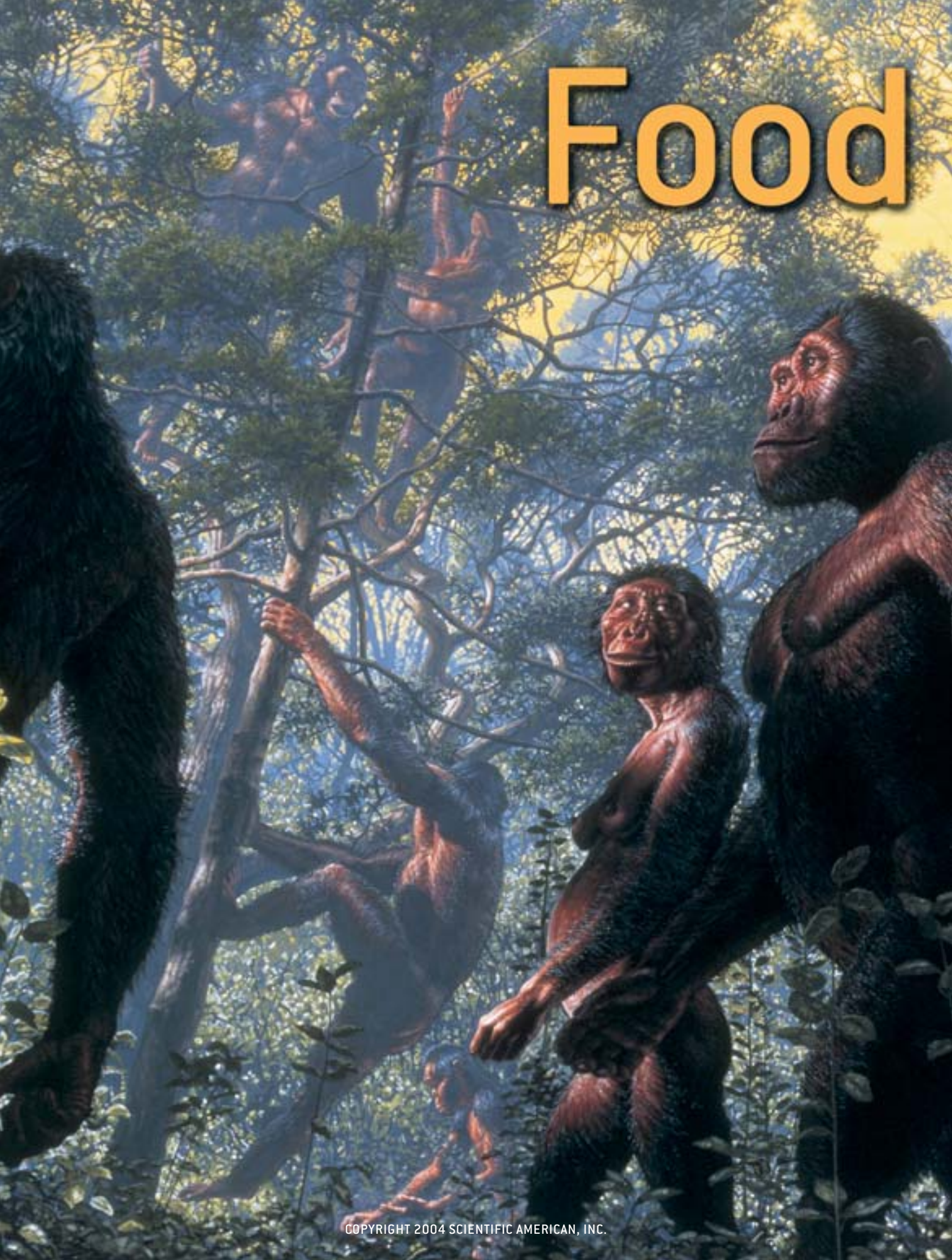

# for THOUGHT

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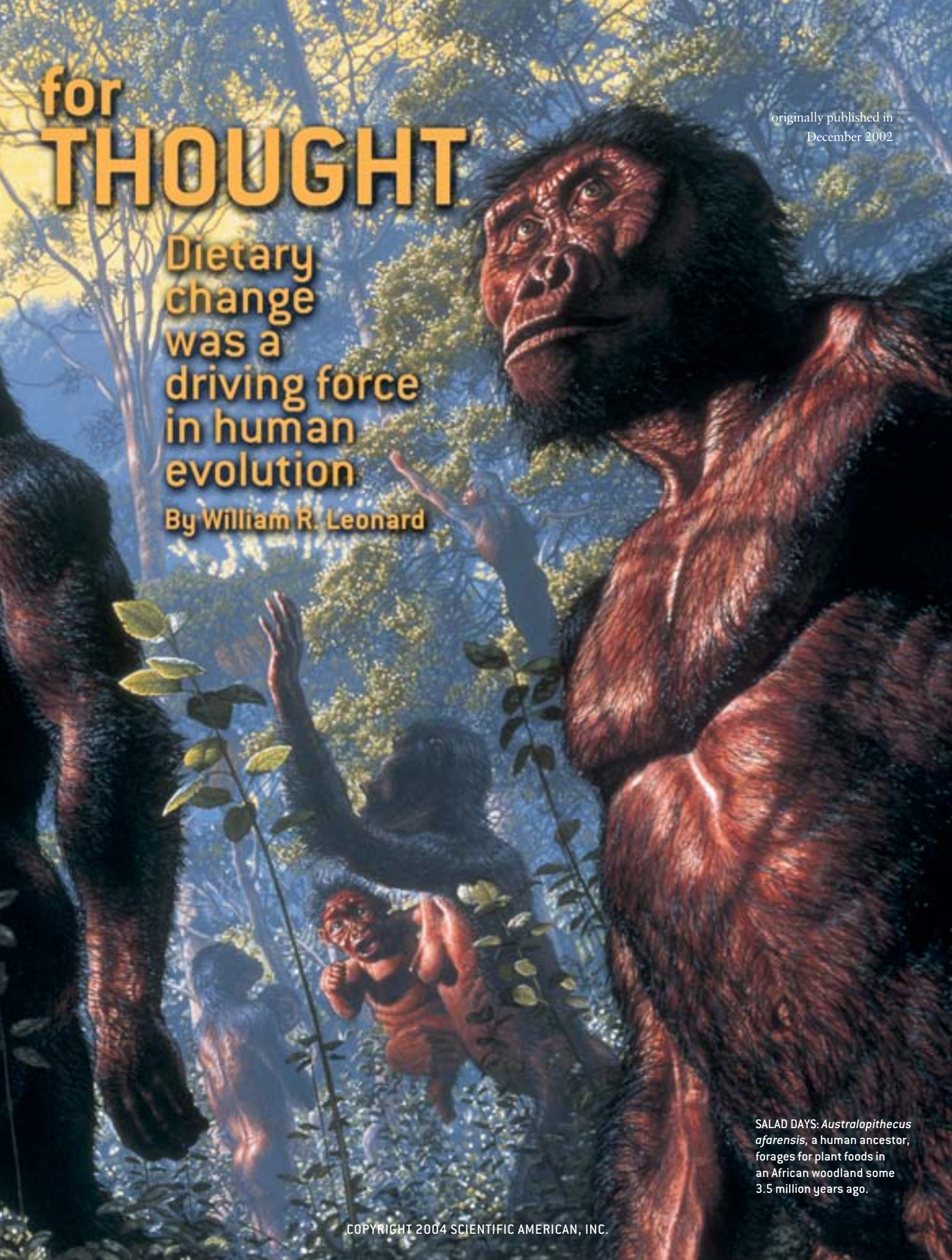
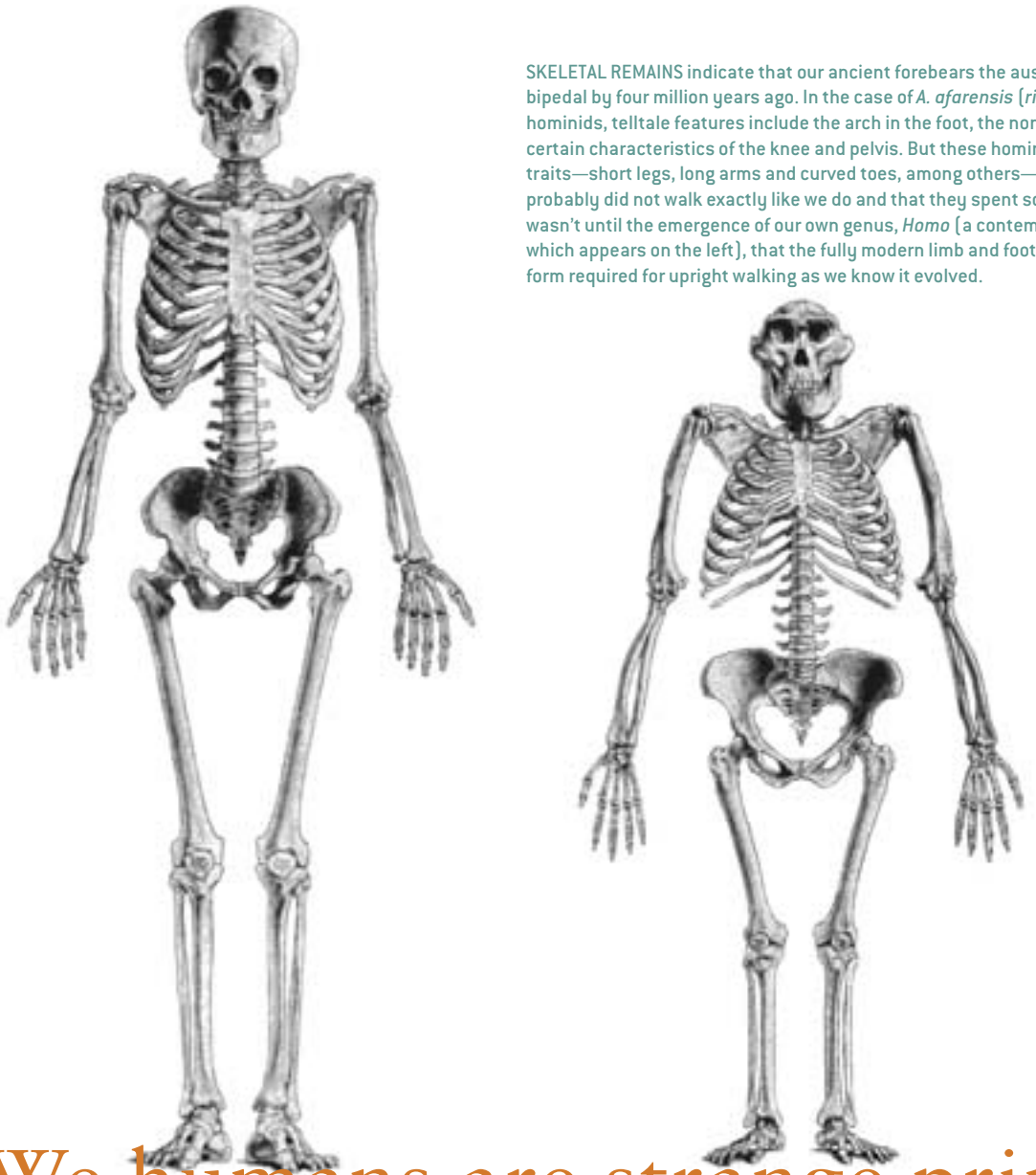
## Dietary change was a driving force in human evolution

By William R. Leonard



SALAD DAYS: *Australopithecus afarensis*, a human ancestor, forages for plant foods in an African woodland some 3.5 million years ago.



SKELETAL REMAINS indicate that our ancient forebears the australopithecines were bipedal by four million years ago. In the case of *A. afarensis* (*right*), one of the earliest hominids, telltale features include the arch in the foot, the nonopposable big toe, and certain characteristics of the knee and pelvis. But these hominids retained some apelike traits—short legs, long arms and curved toes, among others—suggesting both that they probably did not walk exactly like we do and that they spent some time in the trees. It wasn't until the emergence of our own genus, *Homo* (a contemporary representative of which appears on the left), that the fully modern limb and foot proportions and pelvis form required for upright walking as we know it evolved.

# We humans are strange primates.

We walk on two legs, carry around enormous brains and have colonized every corner of the globe. Anthropologists and biologists have long sought to understand how our lineage came to differ so profoundly from the primate norm in these ways, and over the years all manner of hypotheses aimed at explaining each of these oddities have been put forth. But a growing body of evidence indicates that these miscellaneous quirks of humanity in fact have a common thread: they are largely the result of natural selection acting to maximize dietary quality and foraging efficiency. Changes in food availability over time, it seems, strongly influenced our hominid ancestors. Thus, in an evolutionary sense, we are very much what we ate.

Accordingly, what we eat is yet another way in which we differ from our primate kin. Contemporary human populations the world over have diets richer in calories and nutrients than those of our cousins, the great apes. So when and how did our ancestors' eating habits diverge from those of other primates? Further, to what extent have modern humans departed from the ancestral dietary pattern?

Scientific interest in the evolution of human nutritional requirements has a long history. But relevant investigations started gaining momentum after 1985, when S. Boyd Eaton and Melvin J. Konner of Emory University published a seminal paper in the *New England Journal of Medicine* entitled "Paleolithic Nutrition." They argued that the prevalence in modern societies of many chronic diseases—obesity, hypertension, coronary heart disease and diabetes, among them—is the consequence of a mismatch between modern dietary patterns and the type of diet that our species evolved to eat as prehistoric hunter-gatherers. Since then, however, understanding of the evolution of human nutritional needs has advanced considerably—thanks in large part to new comparative analyses of traditionally living human populations and other primates—and a more nuanced picture has emerged. We now know that humans have evolved not to subsist on a single, Paleolithic diet but to be flexible eaters, an insight that has important implications for the current debate over what people today should eat in order to be healthy.

JOHN GURCHE (*preceding pages* and *above*)

To appreciate the role of diet in human evolution, we must remember that the search for food, its consumption and, ultimately, how it is used for biological processes are all critical aspects of an organism's ecology. The energy dynamic between organisms and their environments—that is, energy expended in relation to energy acquired—has important adaptive consequences for survival and reproduction. These two components of Darwinian fitness are reflected in the way we divide up an animal's energy budget. Maintenance energy is what keeps an animal alive on a day-to-day basis. Productive energy, on the other hand, is associated with producing and raising offspring for the next generation. For mammals like ourselves, this must cover the increased costs that mothers incur during pregnancy and lactation.

The type of environment a creature inhabits will influence the distribution of energy between these components, with harsher conditions creating higher maintenance demands. Nevertheless, the goal of all organisms is the same: to devote sufficient funds to reproduction to ensure the long-term success of the species. Thus, by looking at the way animals go about obtaining and then allocating food energy, we can better discern how natural selection produces evolutionary change.

## Becoming Bipeds

WITHOUT EXCEPTION, living nonhuman primates habitually move around on all fours, or quadrupedally, when they are on the ground. Scientists generally assume therefore that the last common ancestor of humans and chimpanzees (our closest living relative) was also a quadruped. Exactly when the last common ancestor lived is unknown, but clear indications of bipedalism—the trait that distinguished ancient humans from other apes—are evident in the oldest known species of *Australopithecus,* which lived in Africa roughly four million years ago. Ideas about why bipedalism evolved abound in the paleoanthropological literature. C. Owen Lovejoy of Kent State University proposed in 1981 that two-legged locomotion freed the arms to carry children and foraged goods. More recently, Kevin D. Hunt of Indiana University has posited that bipedalism emerged as a feeding posture that enabled access to foods that had previously been out of reach. Peter Wheeler of Liverpool John Moores University submits that moving upright allowed early humans to better regulate their body temperature by exposing less surface area to the blazing African sun.

The list goes on. In reality, a number of factors probably selected for this type of locomotion. My own research, conducted in collaboration with my wife, Marcia L. Robertson, suggests that bipedalism evolved in our ancestors at least in part because it is less energetically expensive than quadrupedalism. Our analyses of the energy costs of movement in living animals of all sizes have shown that, in general, the strongest predictors of cost are the weight of the animal and the speed at which it travels. What is striking about human bipedal movement is that it is notably more economical than quadrupedal locomotion at walking rates.

Apes, in contrast, are not economical when moving on the ground. For instance, chimpanzees, which employ a peculiar form of quadrupedalism known as knuckle walking, spend some 35 percent more calories during locomotion than does a typical mammalian quadruped of the same size—a large dog, for example. Differences in the settings in which humans and apes evolved may help explain the variation in costs of movement. Chimps, gorillas and orangutans evolved in and continue to occupy dense forests where only a mile or so of trekking over the course of the day is all that is needed to find enough to eat. Much of early hominid evolution, on the other hand, took place in more open woodland and grassland, where sustenance is harder to come by. Indeed, modern human hunter-gatherers living in these environments, who provide us with the best available model of early human subsistence patterns, often travel six to eight miles daily in search of food.

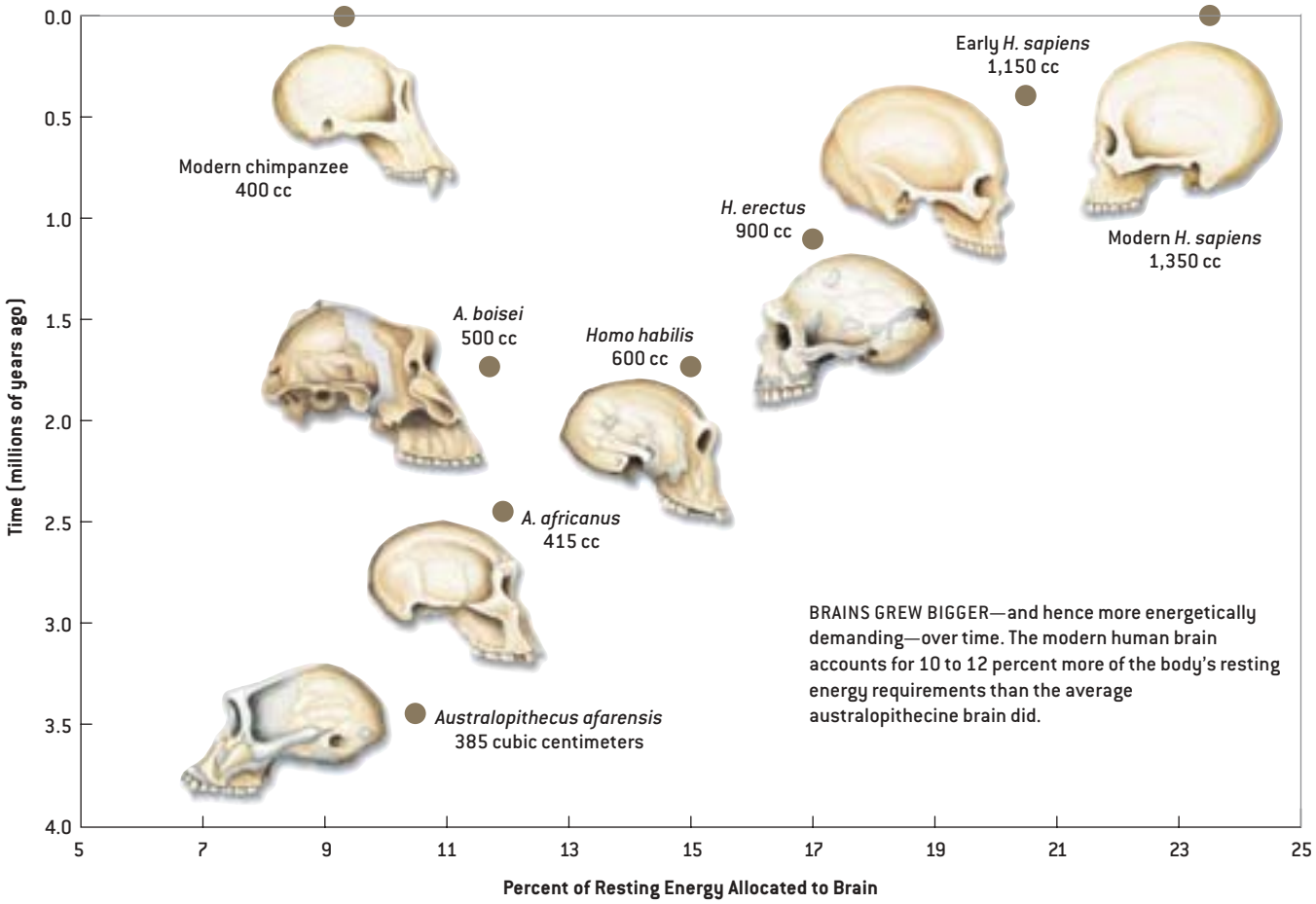
These differences in day range have important locomotor implications. Because apes travel only short distances each day, the potential energetic benefits of moving more efficiently are very small. For far-ranging foragers, however, cost-effective walking saves many calories in maintenance energy needs—calories that can instead go toward reproduction. Selection for energetically efficient locomotion is therefore likely to be more intense among far-ranging animals because they have the most to gain.

## Overview/*Diet and Human Evolution*

- The characteristics that most distinguish humans from other primates are largely the results of natural selection acting to improve the quality of the human diet and the efficiency with which our ancestors obtained food. Some scientists have proposed that many of the health problems modern societies face are consequences of a discrepancy between what we eat and what our Paleolithic forebears ate.
- Yet studies of traditionally living populations show that modern humans are able to meet their nutritional needs using a wide variety of dietary strategies. We have evolved to be flexible eaters. The health concerns of the industrial world, where calorie-packed foods are readily available, stem not from deviations from a specific diet but from an imbalance between the energy we consume and the energy we expend.

## Big Brains and Hungry Hominids

For hominids living between five million and 1.8 million years ago, during the Pliocene epoch, climate change spurred this morphological revolution. As the African continent grew drier, forests gave way to grasslands, leaving food resources patchily distributed. In this context, bipedalism can be viewed as one of the first strategies in human nutritional evolution, a pattern of movement that would have substantially reduced the number of calories spent in collecting increasingly dispersed food resources.




No sooner had humans perfected their stride than the next pivotal event in human evolution—the dramatic enlargement of the brain—began. According to the fossil record, the australopithecines never became much brainier than living apes, showing only a modest increase in brain size, from around 400 cubic centimeters four million years ago to 500 cubic centimeters two million years later. *Homo* brain sizes, in contrast, ballooned from 600 cubic centimeters in *H. habilis* some two million years ago up to 900 cubic centimeters in early *H. erectus* just 300,000 years later. The *H. erectus* brain did not attain modern human proportions (1,350 cubic centimeters on average), but it exceeded that of living nonhuman primates.

From a nutritional perspective, what is extraordinary about our large brain is how much energy it consumes—roughly 16 times as much as muscle tissue per unit weight. Yet although humans have much bigger brains relative to body weight than do other primates (three times larger than expected), the total resting energy requirements of the human body are no greater than those of any other mammal of the same size. We therefore use a much greater share of our daily energy budget to feed our voracious brains. In fact, at rest brain metabolism accounts for a whopping 20 to 25 percent of an adult human's energy needs—far more than the 8 to 10 percent observed in nonhuman primates, and more still than the 3 to 5 percent allotted to the brain by other mammals.

By using estimates of hominid body size compiled by Henry M. McHenry of the University of California at Davis, Robertson and I have reconstructed the proportion of resting energy needs that would have been required to support the brains of our ancient ancestors. Our calculations suggest that a typical, 80- to 85-pound australopithecine with a brain size of 450 cubic centimeters would have devoted about 11 percent of its resting energy to the brain. For its part, *H. erectus*, which weighed in at 125 to 130 pounds and had a brain size of some 900 cubic centimeters, would have earmarked about 17 percent of its resting energy—that is, about 260 out of 1,500 kilocalories a day—for the organ.

How did such an energetically costly brain evolve? One theory, developed by Dean Falk of Florida State University, holds that bipedalism enabled hominids to cool their cranial blood, thereby freeing the heat-sensitive brain of the temperature constraints that had kept its size in check. I suspect that, as with bipedalism, a number of selective factors were probably at work. But brain expansion almost certainly could not have occurred until hominids adopted a diet sufficiently rich in calories and nutrients to meet the associated costs.

Comparative studies of living animals support that assertion. Across all primates, species with bigger brains dine on richer foods, and humans are the extreme example of this correlation, boasting the

CORNELIA BLIK

largest relative brain size and the choicest diet [see "Diet and Primate Evolution," by Katharine Milton; SCIENTIFIC AMERICAN, August 1993]. According to recent analyses by Loren Cordain of Colorado State University, contemporary hunter-gatherers derive, on average, 40 to 60 percent of their dietary energy from animal foods (meat, milk and other products). Modern chimps, in comparison, obtain only 5 to 7 percent of their calories from these comestibles. Animal foods are far denser in calories and nutrients than most plant foods. For example, 3.5 ounces of meat provides upward of 200 kilocalories. But the same amount of fruit provides only 50 to 100 kilocalories. And a comparable serving of foliage yields just 10 to 20 kilocalories. It stands to reason, then, that for early *Homo,* acquiring more gray matter meant seeking out more of the energy-dense fare.

Fossils, too, indicate that improvements to dietary quality accompanied evolutionary brain growth. All australopithecines had skeletal and dental features built for processing tough, low-quality plant foods. The later, robust australopithecines—a dead-end branch of the human family tree that lived alongside members of our own genus—had especially pronounced adaptations for grinding up fibrous plant foods, including massive, dish-shaped faces; heavily built mandibles; ridges, or sagittal crests, atop the skull for the attachment of powerful chewing muscles; and huge, thickly enameled molar teeth. (This is not to say that australopithecines never ate meat. They almost certainly did on occasion, just as chimps do today.) In contrast, early members of the genus *Homo,* which descended from the gracile australopithecines, had much smaller faces, more delicate jaws, smaller molars and no sagittal crests—despite being far larger in terms of overall body size than their predecessors. Together these features suggest that early *Homo* was consuming less plant material and more animal foods.

As to what prompted *Homo*'s initial shift toward the higher-quality diet necessary for brain growth, environmental change appears to have once more set the stage for evolutionary change. The continued desiccation of the African landscape limited the amount and variety of edible plant foods available to hominids. Those on the line leading to the robust australopithecines coped with this problem morphologically, evolving anatomical specializations that enabled them to subsist on more widely available, difficult-to-chew foods. *Homo* took a different path. As it turns out, the spread of grasslands also led to an increase in the relative abundance of grazing mammals such as antelope and gazelle, creating opportunities for hominids capable of exploiting them. *H. erectus* did just that, developing the first hunting-and-gathering economy in which game animals became a significant part of the diet and resources were shared among members of the foraging groups. Signs of this behavioral revolution are visible in the archaeological record, which shows an increase in animal bones at hominid sites during this period, along with evidence that the beasts were butchered using stone tools.

These changes in diet and foraging behavior did not turn our ancestors into strict carnivores; however, the addition of modest amounts of animal foods to the menu, combined with the sharing of resources that is typical of hunter-gatherer groups, would have significantly increased the quality and stability of hominid diets. Improved dietary quality alone cannot explain *why* hominid brains grew, but it appears to have played a critical role in enabling that change. After the initial spurt in brain growth, diet and

## A DIVERSITY OF DIETS

THE VARIETY OF SUCCESSFUL dietary strategies employed by traditionally living populations provides an important perspective on the ongoing debate about how high-protein, low-carbohydrate regimens such as the Atkins diet compare with those that underscore complex carbohydrates and fat restriction. The fact that both these schemes produce weight loss is not surprising, because both help people shed pounds through the same basic mechanism: limiting major sources of calories. When you create an energy deficit—that is, when you consume fewer calories than you expend—your body begins burning its fat stores and you lose weight.

The larger question about healthy weight-loss or weight-maintenance diets is whether they create eating patterns that are sustainable over time. On this point it appears that diets that severely limit large categories of foods (carbohydrates, for example) are much more difficult to sustain than are moderately restrictive diets. In the case of the Atkins-type regimen, there are also concerns about the potential long-term consequences of eating foods derived largely from feedlot animals, which tend to contain more fat in general and considerably more saturated fats than do their free-ranging counterparts.

In September the National Academy of Sciences's Institute of Medicine put forth new diet and exercise guidelines that mesh well with the ideas presented in this article. Not only did the institute set broader target ranges for the amounts of carbohydrates, fat and protein that belong in a healthy diet—in essence, acknowledging that there are various ways to meet our nutritional needs—the organization also doubled the recommended amount of moderately intense physical activity to an hour a day. By following these guidelines and balancing what we eat with exercise, we can live more like the Evenki of Siberia and other traditional societies—and more like our hominid ancestors. —*W.R.L.*

THE AUTHOR

*WILLIAM R. LEONARD* is a professor of anthropology at Northwestern University. He was born in Jamestown, N.Y., and received his Ph.D. in biological anthropology at the University of Michigan at Ann Arbor in 1987. The author of more than 80 research articles on nutrition and energetics among contemporary and prehistoric populations, Leonard has studied indigenous agricultural groups in Ecuador, Bolivia and Peru and traditional herding populations in central and southern Siberia.

## INTO THE FIRE

EATING MORE ANIMAL FOODS is one way of boosting the caloric and nutrient density of the diet, a shift that appears to have been critical in the evolution of the human lineage. But might our ancient forebears have improved dietary quality another way? Richard Wrangham of Harvard University and his colleagues recently examined the importance of cooking in human evolution. They showed that cooking not only makes plant foods softer and easier to chew, it substantially increases their available energy content, particularly for starchy tubers such as potatoes and manioc. In their raw form, starches are not readily broken down by the enzymes in the human body. When heated, however, these complex carbohydrates become more digestible, thereby yielding more calories.

The researchers propose that *Homo erectus* was probably the first hominid to apply fire to food, starting perhaps 1.8 million years ago. They argue that early cooking of plant foods (especially tubers) enabled this species to evolve smaller teeth and bigger brains than those of their predecessors. Additionally, the extra calories allowed *H. erectus* to start hunting—an energetically costly activity—more frequently.

From an energetics perspective, this is a logical enough line of reasoning. What makes the hypothesis difficult to swallow is the archaeological evidence Wrangham's team uses to make its case. The authors cite the East African sites of Koobi Fora and Chesowanja, which date to around 1.6 million and 1.4 million years ago, respectively, to indicate control of fire by *H. erectus*. These localities do indeed exhibit evidence of fires, but whether hominids were responsible for creating or harnessing the flames is a matter of some debate. The earliest unequivocal manifestations of fire use—stone hearths and burned animal bones from sites in Europe—are only some 200,000 years old.

Cooking was clearly an innovation that considerably improved the quality of the human diet. But it remains unclear when in our past this practice arose.

*—W.R.L.*

brain expansion probably interacted synergistically: bigger brains produced more complex social behavior, which led to further shifts in foraging tactics and improved diet, which in turn fostered additional brain evolution.

### A Movable Feast

THE EVOLUTION of *H. erectus* in Africa 1.8 million years ago also marked a third turning point in human evolution: the initial movement of hominids out of Africa. Until recently, the locations and ages of known fossil sites suggested that early *Homo* stayed put for a few hundred thousand years before venturing out of the motherland and slowly fanning out into the rest of the Old World. Earlier work hinted that improvements in tool technology around 1.4 million years ago—namely, the advent of the Acheulean hand ax—allowed hominids to leave Africa. But new discoveries indicate that *H. erectus* hit the ground running, so to speak. Rutgers University geochronologist Carl Swisher III and his colleagues have shown that the earliest *H. erectus* sites outside of Africa, which are in Indonesia and the Republic of Georgia, date to between 1.8 million and 1.7 million years ago. It seems that the first appearance of *H. erectus* and its initial spread from Africa were almost simultaneous.

The impetus behind this newfound wanderlust again appears to be food. What an animal eats dictates to a large extent how much territory it needs to survive. Carnivorous animals generally require far bigger home ranges than do herbivores of comparable size because they have fewer total calories available to them per unit area.

Large-bodied and increasingly dependent on animal foods, *H. erectus* most likely needed much more turf than the smaller, more vegetarian australopithecines did. Using data on contemporary primates and human hunter-gatherers as a guide, Robertson, Susan C. Antón of Rutgers University and I have estimated that the larger body size of *H. erectus*, combined with a moderate increase in meat consumption, would have necessitated an eightfold to 10-fold increase in home range size compared with that of the late australopithecines—enough, in fact, to account for the abrupt expansion of the species out of Africa. Exactly how far beyond the continent that shift would have taken *H. erectus* remains unclear, but migrating animal herds may have helped lead it to these distant lands.

As humans moved into more northern latitudes, they encountered new dietary challenges. The Neandertals, who lived during the last ice ages of Europe, were among the first humans to inhabit arctic environments, and they almost certainly would have needed ample calories to endure under those circumstances. Hints at what their energy requirements might have been come from data on traditional human populations that live in northern settings today. The Siberian reindeer-herding populations known as the Evenki, which I have studied with Peter Katzmarzyk of Queen's University in Ontario and Victoria A. Galloway of the University of Toronto, and the Inuit (Eskimo) populations of the Canadian Arctic have resting metabolic rates that are about 15 percent higher than those of people of similar size living in temperate environments. The energetically expensive activities associated with living in a northern climate ratchet their caloric cost of living up further still. Indeed, whereas a 160-pound American male with a typical urban way of life requires about 2,600 kilocalories a day, a diminutive, 125-pound Evenki man needs more than 3,000 kilocalories a day to sustain himself. Using these modern northern popu-

lations as benchmarks, Mark Sorensen of Northwestern University and I have estimated that Neandertals most likely would have required as many as 4,000 kilocalories a day to survive. That they were able to meet these demands for as long as they did speaks to their skills as foragers [*see box on this page*].

## Modern Quandaries

JUST AS PRESSURES to improve dietary quality influenced early human evolution, so, too, have these factors played a crucial role in the more recent increases in population size. Innovations such as cooking, agriculture and even aspects of modern food technology can all be considered tactics for boosting the quality of the human diet. Cooking, for one, augmented the energy available in wild plant foods [*see box on page 8*]. With the advent of agriculture, humans began to manipulate marginal plant species to increase their productivity, digestibility and nutritional content—essentially making plants more like animal foods. This kind of tinkering continues today, with genetic modification of crop species to make "better" fruits, vegetables and grains. Similarly, the development of liquid nutritional supplements and meal replacement bars is a continuation of the trend that our ancient ancestors started: gaining as much nutritional return from our food in as little volume and with as little physical effort as possible.

Overall, that strategy has evidently worked: humans are here today and in record numbers to boot. But perhaps the strongest testament to the importance of energy- and nutrient-rich foods in human evolution lies in the observation that so many health concerns facing societies around the globe stem from deviations from the energy dynamic that our ancestors established. For children in rural populations of the developing world, low-quality diets lead to poor physical growth and high rates of mortality during early life. In these cases, the foods fed to youngsters during and after weaning are often not sufficiently dense in energy and nutrients to meet the high nutritional needs associated with this period of rapid growth and development. Although these children are typically similar in length and weight to their U.S. counterparts at birth, they are much shorter and lighter by the age of three, often resembling the smallest 2 to 3 percent of American children of the same age and sex.

In the industrial world, we are facing the opposite problem: rates of childhood and adult obesity are rising because the energy-rich foods we crave—notably those packed with fat and sugar—have become


LAURIE GRACE (*map*)

AFRICAN EXODUS began as soon as *H. erectus* evolved, around 1.8 million years ago, probably in part because it needed a larger home range than that of its smaller-bodied predecessors.

## NEANDERTAL HUNTERS

TO RECONSTRUCT what early humans ate, researchers have traditionally studied features on their fossilized teeth and skulls, archaeological remains of food-related activities, and the diets of living humans and apes. Increasingly, however, investigators have been tapping another source of data: the chemical composition of fossil bones. This approach has yielded some especially intriguing findings with regard to the Neandertals.

Michael Richards, now at the University of Bradford in England, and his colleagues recently examined isotopes of carbon ($^{13}C$) and nitrogen ($^{15}N$) in 29,000-year-old Neandertal bones from Vindija Cave in Croatia. The relative proportions of these isotopes in the protein part of human bone, known as collagen, directly reflect their proportions in the protein of the individual's diet. Thus, by comparing the isotopic "signatures" of the Neandertal bones to those of other animals living in the same environments, the authors were able to determine whether the Neandertals were deriving the bulk of their protein from plants or from animals.

The analyses show that the Vindija Neandertals had $^{15}N$ levels comparable to those seen in northern carnivores such as foxes and wolves, indicating that they obtained almost all their dietary protein from animal foods. Earlier work hinted that inefficient foraging might have been a factor in the subsequent demise of the Neandertals. But Richards and his collaborators argue that in order to consume as much animal food as they apparently did, the Neandertals had to have been skilled hunters. These findings are part of a growing body of literature that suggests Neandertal subsistence behavior was more complex than previously thought [see "Who Were the Neandertals?" by Kate Wong; SCIENTIFIC AMERICAN, April 2000]. —*W.R.L.*

| Population | Energy Intake (kilocalories/day) | Energy from Animal Foods (%) | Energy from Plant Foods (%) | Total Blood Cholesterol (milligrams/deciliter) | Body Mass Index (weight/height squared) |
|---|---|---|---|---|---|
| HUNTER-GATHERERS | | | | | |
| !Kung (Botswana) | 2,100 | 33 | 67 | 121 | 19 |
| Inuit (North America) | 2,350 | 96 | 4 | 141 | 24 |
| PASTORALISTS | | | | | |
| Turkana (Kenya) | 1,411 | 80 | 20 | 186 | 18 |
| Evenki (Russia) | 2,820 | 41 | 59 | 142 | 22 |
| AGRICULTURALISTS | | | | | |
| Quechua (Highland Peru) | 2,002 | 5 | 95 | 150 | 21 |
| INDUSTRIAL SOCIETIES | | | | | |
| U.S. | 2,250 | 23 | 77 | 204 | 26 |

*Note: Energy intake figures reflect the adult average (males and females); blood cholesterol and body mass index (BMI) figures are given for males. Healthy BMI = 18.5–24.9; overweight = 25.0–29.9; obese = 30 and higher.*

VARIOUS DIETS can satisfy human nutritional requirements. Some populations subsist almost entirely on plant foods; others eat mostly animal foods. Although Americans consume less meat than do a number of the traditionally living people described here, they have on average higher cholesterol levels and higher levels of obesity (as indicated by body mass index) because they consume more energy than they expend and eat meat that is higher in fat.

widely available and relatively inexpensive. According to recent estimates, more than half of adult Americans are overweight or obese. Obesity has also appeared in parts of the developing world where it was virtually unknown less than a generation ago. This seeming paradox has emerged as people who grew up malnourished move from rural areas to urban settings where food is more readily available. In some sense, obesity and other common diseases of the modern world are continuations of a tenor that started millions of years ago. We are victims of our own evolutionary success, having developed a calorie-packed diet while minimizing the amount of maintenance energy expended on physical activity.

The magnitude of this imbalance becomes clear when we look at traditionally living human populations. Studies of the Evenki reindeer herders that I have conducted in collaboration with Michael Crawford of the University of Kansas and Ludmila Osipova of the Russian Academy of Sciences in Novosibirsk indicate that the Evenki derive almost half their daily calories from meat, more than 2.5 times the amount consumed by the average American. Yet when we compare Evenki men with their U.S. peers, they are 20 percent leaner and have cholesterol levels that are 30 percent lower.

These differences partly reflect the compositions of the diets. Although the Evenki diet is high in meat, it is relatively low in fat (about 20 percent of their dietary energy comes from fat, compared with 35 percent in the average U.S. diet), because free-ranging animals such as reindeer have less body fat than cattle and other feedlot animals do. The composition of the fat is also different in free-ranging animals, tending to be lower in saturated fats and higher in the polyunsaturated fatty acids that protect against heart disease. More important, however, the Evenki way of life necessitates a much higher level of energy expenditure.

Thus, it is not just changes in diet that have created many of our pervasive health problems but the interaction of shifting diets and changing lifestyles. Too often modern health problems are portrayed as the result of eating "bad" foods that are departures from *the* natural human diet—an oversimplification embodied by the current debate over the relative merits of a high-protein, high-fat Atkins-type diet or a low-fat one that emphasizes complex carbohydrates. This is a fundamentally flawed approach to assessing human nutritional needs. Our species was not designed to subsist on a single, optimal diet. What is remarkable about human beings is the extraordinary variety of what we eat. We have been able to thrive in almost every ecosystem on the earth, consuming diets ranging from almost all animal foods among populations of the Arctic to primarily tubers and cereal grains among populations in the high Andes. Indeed, the hallmarks of human evolution have been the diversity of strategies that we have developed to create diets that meet our distinctive metabolic requirements and the ever increasing efficiency with which we extract energy and nutrients from the environment. The challenge our modern societies now face is balancing the calories we consume with the calories we burn. SA

## MORE TO EXPLORE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originally published in
August 2000

# Birth of the Modern Diet

*Ever wonder why dessert is served after dinner? The origins of modern Western cooking can be traced to ideas about diet and nutrition that arose during the 17th century*

by Rachel Laudan

Were we to attend a 16th-century court banquet in France or England, the food would seem strange indeed to anyone accustomed to traditional Western cooking. Dishes might include blancmange—a thick puree of rice and chicken moistened with milk from ground almonds, then sprinkled with sugar and fried pork fat. Roast suckling pig might be accompanied by a cameline sauce, a side dish made of sour grape juice thickened with bread crumbs, ground raisins and crushed almonds, and spiced with cinnamon and cloves. Other offerings might consist of fava beans cooked in meat stock and sprinkled with chopped mint or quince paste, a sweetmeat of quinces and sugar or honey. And to wash it all down, we would probably drink hypocras, a mulled red wine seasoned with ground ginger, cinnamon, cloves and sugar.

Fast-forward 100 years, though, and the food would be reassuringly familiar. On the table might be beef bouillon, oysters, anchovies and a roast turkey with gravy. These dishes might be served alongside mushrooms cooked in cream and parsley, a green salad with a dressing of oil and vinegar, fresh pears, lemon sherbet, and sparkling white wine.

Before 1650, the elite classes throughout the Islamic and Christian worlds from Delhi to London shared pretty much the same diet: thick purees, lots of spices, sweet and sour sauces, cooked vegetables, and warmed wines. Sugar was ubiquitous as a seasoning in savory dishes. But in the middle of the 17th century, the northern European diet began to change. This new regimen relied on fewer spices, based its sauces on fats such as butter and olive oil, and incorporated raw fruits and vegetables. Sugar appeared only at the end of a meal.

What happened? Economic considerations cannot account for the difference: for the upper class, money was no object. For the poor, both meals would have been far out of reach. Well into the 19th century, they subsisted on vegetable soups and gruels with bread or porridge. Novel foodstuffs from the New World do not explain the shift in diet either, because with the exception of turkey, the dishes at the second banquet depended not on new ingredients but on new uses of long familiar ones. The clue to this transformation in eating habits between the 16th and 17th centuries must be sought instead in evolving ideas about diet and nutrition—which is to say, in the history of chemistry and medicine.

## Medicine in the 16th Century

Eating healthy food was extremely important to people of earlier eras, perhaps even more so than it is today. Activity in the kitchen mattered so much because physicians had so few other options. To avoid resorting to unpleasant therapies such as purging or bloodletting, doctors carefully monitored their wealthy patients' daily habits: their emotional state, for example, or how much sleep, exercise and fresh air they got. Most crucially, doctors advised their patients on the food and drink they should consume. Every court had a bevy of physicians who were schooled in the physiology of digestion, the nutritive properties of foodstuffs and the nature of a healthy meal. Offering dietary advice to their affluent patrons was a major part of their work.

The actual task of transforming abstract dietary theory into dishes appropriate for the courtly table fell to the head chefs, or majordomos, as they were often called. In a popular medical text written in 1547, *Breviary of Health,* author Andrew Boorde noted, "A good coke is halfe a physycyon." Sixteenth-century cooks, physicians and their patrons shared a common notion of diet and nutrition that can be traced to classical antiquity. First formulated around 400 B.C. as part of the Hippocratic Collection, the ideas were systematized by the great Roman doctor Galen in the early second century A.D. After the collapse of classical civilization, Islamic intellectuals eagerly took up these notions (along with many other scientific theories of the ancient world).

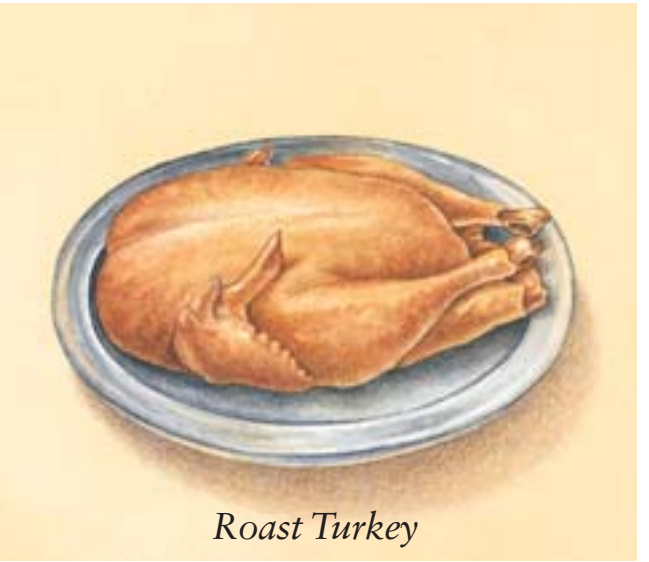
By the 12th century, European scholars had translated key Arabic texts into Latin; teachers at the major medical schools, such as Montpellier in the south of France, relied extensively on these texts. In the late 15th century, experts began translating newly discovered Greek manuscripts as well as retranslating known texts. These documents formed the basis of a host of popular manuals and mnemonic jingles. Particularly well liked were the numerous vernacular variations on a Latin poem, the *Regimen Sanitatis Salernitanum,* apparently composed around the end of the 11th cen-

**SUMPTUOUS SPREAD from the 16th century might have included blancmange (a puree of rice and chicken) and a side dish of cameline sauce (made of crushed almonds, bread crumbs and spices moistened with sour grape juice), accompanied by mulled red wine, or hypocras. By the 17th century the foods looked more familiar to the modern eye: roast turkey, green salad with oil and vinegar dressing, and sparkling white wine.**

*Before 1650*

*After 1650*

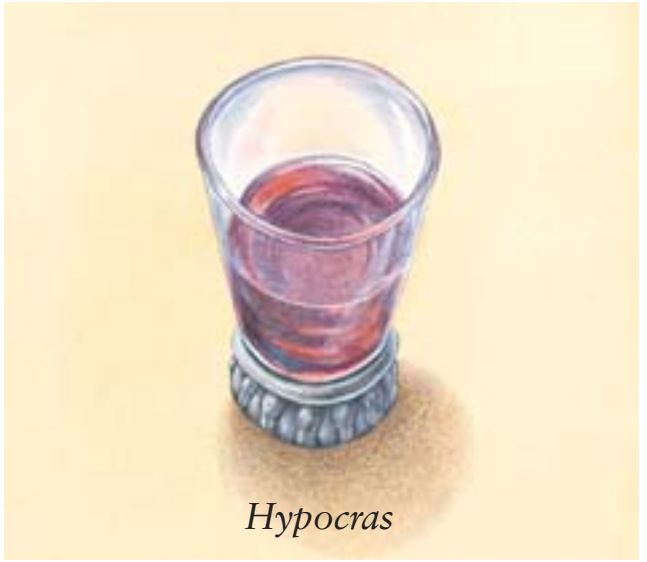
*Blancmange*



*Roast Turkey*

*Cameline Sauce*

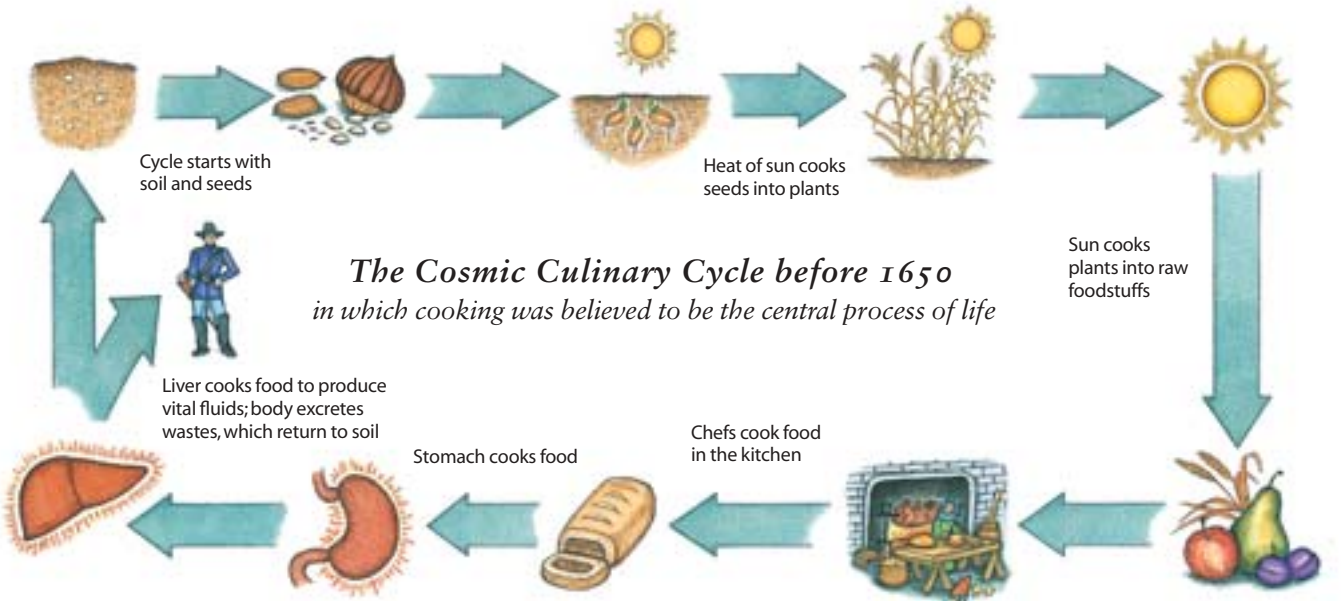
*Salad*



*Hypocras*

*Sparkling Wine*

HEIDI NOLAND




## *The Cosmic Culinary Cycle before 1650*

*in which cooking was believed to be the central process of life*

tury but still widely circulated in the 16th and even 17th centuries:

*Peaches, apples, pears, milk,*
*cheese, and salted meat,*
*Deer, hare, goat, and veal,*
*These engender black bile and are*
*enemies of the sick*

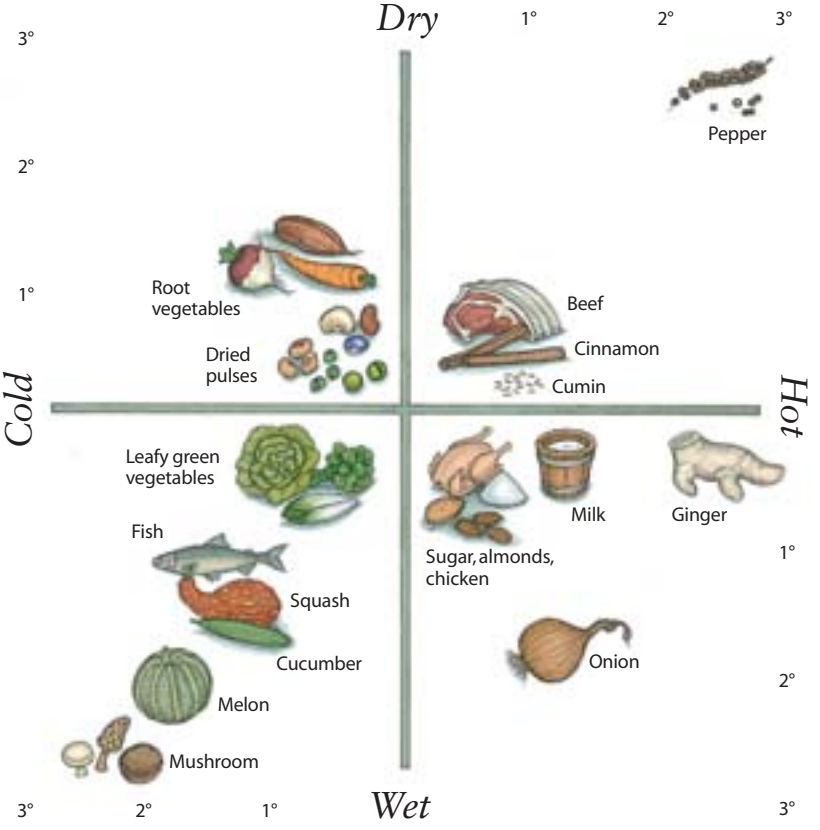
The prevailing dietary wisdom of the 16th century, as presented in these medical guidebooks, relied on two assumptions: first, that the process of digesting foods was actually a form of cooking. Indeed, cooking stood as the basic metaphor for the systems that sustained all life. Seeds were cooked into plants; when the plants appeared above the ground, the heat of the sun cooked them into ripe fruits and grains. If humans gathered these foodstuffs, they could cook them further to create edible dishes. Finally, the internal heat of the body turned the food into blood. The body then expelled as feces what was not digestible. Excrement joined putrefying dead animals and plants to begin the life cycle again.

The second assumption about food and health in this scenario involved maintaining a proper equilibrium of bodily fluids by eating a suitably balanced diet. Doctors and chefs of the time believed that four fluids, or humors, circulated in the body: blood, phlegm, yellow bile and black bile. These humors corresponded to the four Aristotelian elements—air, water, fire and earth. Because blood was hot and moist, it corresponded to air; phlegm was cold and moist and thus resembled water; yellow bile was hot and dry, similar to fire; black bile was cold and dry, connected to earth.

Ideally, the human body was slightly warm and slightly moist, although in practice the exact balance varied from individual to individual, depending on variables such as age, sex and geographic location. Older people were believed to be colder and drier than younger ones; menstruating women colder and wetter than men; southern Europeans more hot-blooded than their neighbors to the north. The perfect meal, like the perfect human temperament, was slightly warm and slightly moist, but combinations away from this center could be used as mild dietary correctives to warm and moisten the elderly, dry out the moister sex, and calm down the southerner or perk up the northerner.

## *Classification System of the 16th Century*

*in which foods were assigned degrees of*
*heat, coldness, wetness and dryness*

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The majordomo, then, had the challenge of selecting and preparing meals adjusted to the temperament of the eater. The properties of any given food item were common knowledge: pepper, for example, was hot and dry in the third degree, and vinegar was cold and wet in the second degree. Root vegetables such as turnips were by nature earthy—dry and cold—and thus better left to peasants. If chefs should decide to prepare them, however, they would make sure to stew them, thereby adding warmth and moisture. In contrast, chard, marrow (a watery, squashlike vegetable) and especially onions were very wet and had to be fried.

Other foods were completely unacceptable: Guy Patin, a doctor at the University of Paris and author of *Treatise on the Conservation of Health,* published in 1632, cautioned that mushrooms, being cold and wet, should be avoided entirely. Melons and other fresh fruit were not much better, being very moist and liable to putrefy. In general, though, cooking not only helped achieve proper culinary balance—dry foods were boiled, wet foods fried or roasted—but the process also, in effect, partially predigested the foods, making them easier for the body to assimilate.

According to these medical theories, the blancmange on our 16th-century table was close to perfect. The wise chef had combined chicken, rice and almond milk, all slightly warm and moist, and the sugar on top—also warm and moist—was the crowning touch. The naturally moist suckling pig had been roasted. The cameline sauce balanced cool, moist vinegar with the warmth of raisins and hot, dry spices. The chef was careful not to serve quinces and grapes fresh, and hence dangerously cold and moist, but instead offered them dried or cooked with added sugar (in the quince paste).

Health experts viewed wine with a meal as an ideal nutrient—provided, of course, that diners did not drink to excess. *The Book of Wine,* written around 1310, printed in 1478 and widely attributed to Arnald of Villanova (a leading medical writer and physician to James II of Aragon), had only high praise for the beverage: besides being good for flatulence and infertility, wine "fortifies the brain and the natural strength … causes foods to be digested and produces good blood." Even so, because red wine tended to be cold and dry, chefs often served it warm with added sugar and spices, creating hypocras. With these options before them, the members of the 16th-century court could rest assured that they were getting a healthy meal.

## *Typical Pre-17th-Century Recipes*

### *Cameline Sauce*

*"To make an excellent cameline sauce, take skinned almonds and pound and strain them; take raisins, cinnamon, cloves and a little crumb of bread and pound everything together, and moisten with verjuice*; and it is done."*

**sour juice of unripe grapes*

### *Blancmange*

*"Take cooked breasts of chicken and put them on a table and shred them into the finest fibers you can. Then wash the rice and dry it, and make it into flour, and put it through a sieve; then moisten this rice flour with goat's, sheep's or almond milk, and boil it in a well-washed and clean pan; and when it begins to boil, add those shredded breasts, with white sugar and fried white pork fat; and keep it away from the smoke, and let it boil gently without excessive fire, so that it becomes as thick as the rice should be. And when you serve it, top it with crushed or pounded sugar, and fried pork fat."*

### *Hypocras*

*"To make a lot of good hypocras, take an once of cinamonde, known as long tube cinnamon, a knob of ginger, and an equal amount of galangal,* pounded well together, and then take a livre of good sugar; pound this all together and moisten it with a gallon of the best Beaune wine you can get; and let it steep for an hour or two. Then strain it through a cloth bag several times so it will be very clear."*

**a root in the ginger family*

*SOURCE:* The Medieval Kitchen: Recipes from France and Italy. *University of Chicago Press, 1998.*

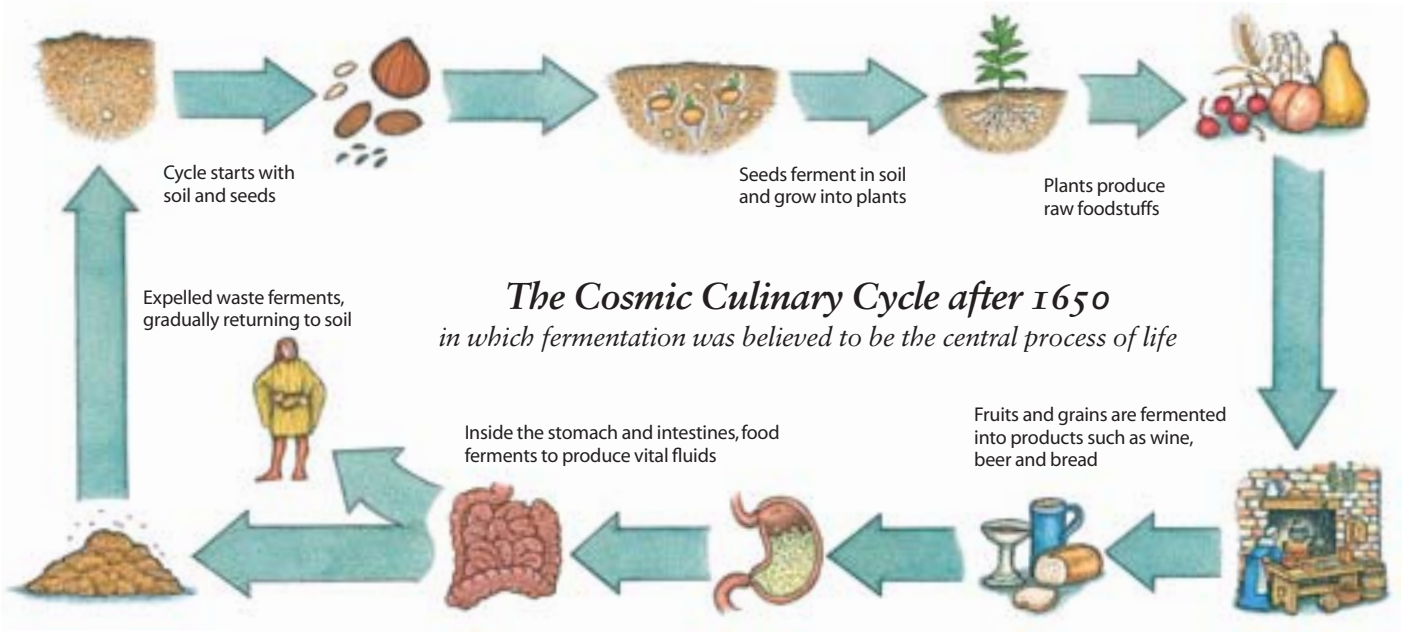
### 17th-Century Cooking

By the middle of the 17th century, however, physicians of a quite different persuasion began to join the courts of northern Europe. These scholars derived their ideas from Paracelsus, an itinerant doctor from Germany who, in the 1520s, began to mock the structure of classical medicine. Paracelsus's abrasive personality and radical religious beliefs gave him a dreadful reputation, so few physicians admitted to this heritage. But acknowledged or not, the link was clear: these court doctors argued, as Paracelsus had, that the idea of a cosmic life cycle based on cooking and the Aristotelian elements was wrong and had to be revised.

Historians of science still debate the causes of this shift, but the technology of distillation seems to have contributed to it. As the practice became more important from the late Middle Ages on, chemists experimented with heating a great variety of natural substances, many of them edible, such as fennel, nutmeg and cloves. They noted that in every case the original material separated into three parts: a volatile, or "spirituous," fluid; an oily substance; and a solid residue.

Drawing on such observations, these chemists proposed three new elements in place of Aristotle's four: mercury (the essence of the vaporous fluids; not related to the toxic chemical of the same name), sulfur (the essence of the oily substances; again, unrelated to the chemical) and salt (the essence of the solids; not the same as modern table salt). In such a scheme, salt dictated the taste and consistency of foods. Mercury was the source of smells and aromas. Sulfur, or oil, carried the properties of moistness and sweetness; it also bound together the other two, normally antagonistic, elements.

Physicians of this era also believed that digestion involved fermentation rather than cooking, and they began to investigate the familiar yet mysterious process more closely. Because fermentation included gentle heat and the production of vapors, it seemed to resemble (or was possibly the same as) putrefaction, distillation, and the interaction of acids and salts. Vapors, spirits or airs (soon to be dubbed "gases" by Dutch scientist and mystic Johannes Baptista van Helmont)




excited chemists of the time, as they appeared to be the very essence of the substance from which they originated.

Several prominent physicians of the 17th century advocated this new understanding of digestion, among them van Helmont, Franciscus Sylvius, a physician at the University of Leiden, and Thomas Willis, then the best-known doctor in England and a founding member of the Royal Society of London. According to this view, digestion involved the fermenting, rather than the cooking, of foodstuffs. Gastric juices, considered acid and sharp, acted on foods to turn them into a white, milky fluid, which then mixed with alkaline bile in the digestive tract. The mixture fermented and bubbled, producing a salty substance that the body could transform into blood and other fluids.

Like their 16th-century predecessors, these later physicians presented a cosmic cycle of life that reflected their view of digestion. Seeds became plants as a result of the "ferments of the earth," in the words of John Evelyn, a keen horticulturist who spoke before the Royal Society in 1675. Fermentation turned grains and fruits into bread, beer and wine, which the digestive system could ferment further. Putrefaction of waste material started the cycle all over again. "Vegetable putrefaction resembles very much Animal Digestion," stated John Arbuthnot, member of the Royal Society and physician to Queen Anne, in a popular handbook on foodstuffs that appeared in 1732. The cosmos was still a kitchen but was now equipped with brewers' vats, and the human body held miniature copies of that equipment.

These changes in the understanding of the digestive process put 17th-century chefs on guard. Alert cooks seized the opportunity to establish their good reputations by thinking up dishes that were healthful by the new standards—and, of course, also tasty. For instance, chefs welcomed oysters, anchovies, green vegetables, mushrooms and fruits because they fermented so readily and thus did not need complicated preparation in the kitchen to be predigested. As cooks began to incorporate fresh produce into many of their dishes, horticulture and botanical gardens became the rage. Scientists and scholarly gentlemen exchanged seeds, translated gardening books and developed hothouses for tender vegetables. They began cultivating mushrooms on beds of putrefying dung. In England, the well-to-do put even such previously distasteful dishes as eggplant on their tables.

## The First Restaurants

Substances rich in oil, such as butter, lard or olive oil, all with the useful property of binding the components of salt and mercury, became the basis of a variety of sauces. They were combined with ingredients containing the element salt, such as flour and table salt, and others high in mercury, such as vinegar, wine, spirits, and essences of meat or fish. The first recipe for roux, a combination of fat and flour moistened with wine or stock to produce a single delicious taste, appeared in the cookbook *The French Chef,* written in 1651 by François Pierre de la Varenne. Salads, which combined oil-based dressings and readily digestible greens, also became quite fashionable. (Evelyn promoted vinaigrette salad dressing in his *Acetaria: A Discourse of Sallets,* published in 1699.)

As fruits, herbs and vegetables assumed a more prominent place in the main meal, sugar, formerly lauded as a panacea, came in for rough treatment at the hands of the chemical physicians. Some wanted to banish it altogether. "Under its whiteness," hissed Joseph Duchesne, physician to Henry IV of France, in 1606, "sugar hides a great blackness"—doctors knew that it blackened the teeth—"and under its sweetness a very great acrimony, such that it equals agua fortis [nitric acid]."

British physician Willis, who had noticed the sugary urine of patients suffering from what doctors later termed diabetes, concurred. "Sugar, distilled by itself, yields a liquor scarcely inferior to aqua fortis.... Therefore it is very probable that mixing sugar with almost all our food, and taken to so great a degree, from its daily use, renders the blood and humours salt and acrid; and consequently scorbutic."

The moral was clear: sugar was dangerous, perhaps even a poison. Such dire warnings would surely have given any chef second thoughts about sprinkling it over the main dishes of the meal, leaving the diner no choice but to eat it. Thus, sugar moved to the periphery of the menu, served only in desserts, which were prepared in a separate kitchen. Sugar became the subject of a distinct genre of books dedicated to its decorative, not medical, properties.

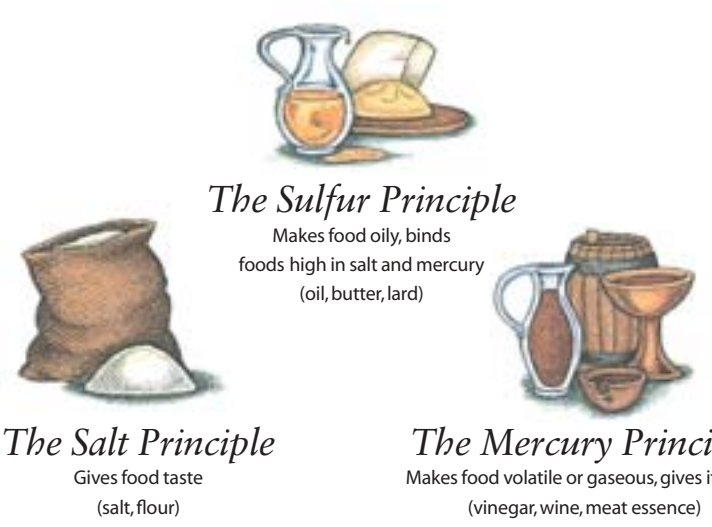
Physicians regarded alcoholic spirits and other distilled essences as useful medicines. They and their patients, though, considered a cordial or an eau-

ILLUSTRATIONS BY PATRICIA J. WYNNE

de-vie fine for the occasional sip but too strong for everyday use. Less powerful extractions, made from nutritive foods such as meats that had been concentrated by boiling or fermenting, could be more easily digested. Sometimes the concentrated goodness of a food even showed up as desirable gas bubbles that nourished the brain. Sparkling mineral waters gained immense popularity as spas opened across Europe. At the table, hot and spicy hypocras yielded to cool wines, even to sparkling champagne, which was most likely first produced in the late 17th century.

Chefs made essences of meat or fish from the "musculous Flesh, which is of all [parts of the animal] the most nourishing, that which produces the best juice," and then served this healthy fare in the form of stock, bouillon or jellies made from these liquids. Land animals had more nutritious juices than fish or birds did, and of the land animals, beef produced the most restorative ones. By 1733 Vincent la Chapelle, a French chef who worked for the earl of Chesterfield in England, had a variety of recipes for delicately garnished beef bouillon in his book *The Modern Cook*, which was quickly translated into French. Before long, entrepreneurs saw an opportunity in this new cuisine, selling "restaurants"—which is French for "restoratives"—to those who could not afford their own chefs.

Eventually Europe's middle classes emulated the aristocracy, developing a taste not only for restaurants but for all the new cuisine. Such foods seemed to offer a certain refinement, not just in the sense of good taste but also in a chemical sense, as the meals represented the most enhanced form of food. As the authors of the gastronomic treatise *The Gifts of Comus,* published in Paris in 1739, put it: "Modern cookery is a kind of chemistry. The cook's science consists today of analyzing, digesting, and extracting the quintessence of foods, drawing out the light and nourishing juices, mingling and blending them together."




This new diet gradually spread across Europe as it simultaneously made its way down the social scale. By the mid- to late 19th century it had become the standard for the English- and French-speaking worlds in Europe, the U.S., Canada and Australia. Other regions, however—the Islamic world and Spanish-speaking parts of the Americas, for example—remained isolated from the chemistry derived from Paracelsus and adopted neither the dietary theory nor the resultant cuisine. (The modern curries of India and moles of Mexico, for instance, resemble the cuisine of pre-Paracelsian northern Europe.)

The Western cuisine born in the 17th century long outlived the dietary theory that inspired it. By the end of the 18th century, chemists and physicians had embarked on the research that was to lead to the modern theories of the role of calories, carbohydrates, proteins, vitamins and minerals in the biochemical processes of digestion. Notably, during the 19th and early 20th centuries, when most of these studies were carried out, nutritionists focused on developing a cheap but adequate diet for factory workers, soldiers and other less affluent people. The shift of emphasis in the medical community from the rich to the poor, though, meant that chefs catering to the well-heeled continued to develop Western cuisine along the lines established in the 17th century.

Now that almost everyone in the West can afford the cuisine formerly restricted to the wealthy, we have come to realize that its dietary foundations are a mixed blessing. Although fresh fruit and vegetables score high marks, the centrality of fat in our diets (a result of the importance given to meat and fat-based sauces) is blamed for the high rates of obesity in most developed nations. In response, everyone from physicians to chefs has returned attention to the age-old problem of developing a new cuisine, at once delicious and in line with the latest findings in physiology and nutrition. SA

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### The Author

RACHEL LAUDAN received her doctorate in history and philosophy of science from the University of London. She has taught history of science and technology at Carnegie Mellon University, the University of Pittsburgh, Virginia Polytechnic Institute and State University, and the University of Hawaii. Laudan is the author of *From Mineralogy to Geology: The Foundations of a Science 1650–1830* (University of Chicago Press, 1987) and winner of the Jane Grigson prize for food scholarship of the Julia Child Cookbook Awards. She now lives in Mexico, where she is working on a book about the history of diet, to be published by the University of Chicago Press.


### Further Information


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By Walter C. Willett
and Meir J. Stampfer

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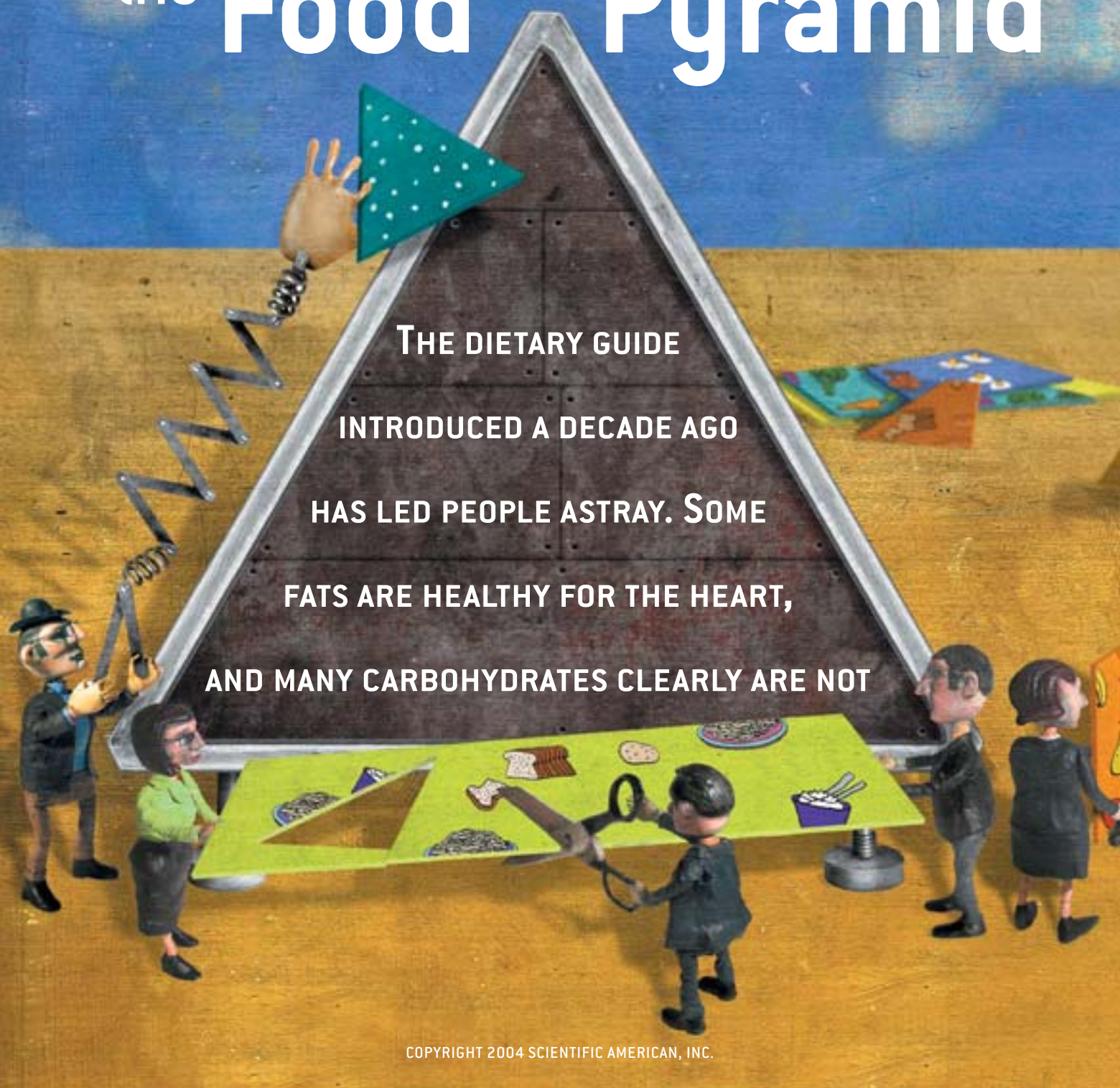
# REBUILD the Food Pyramid



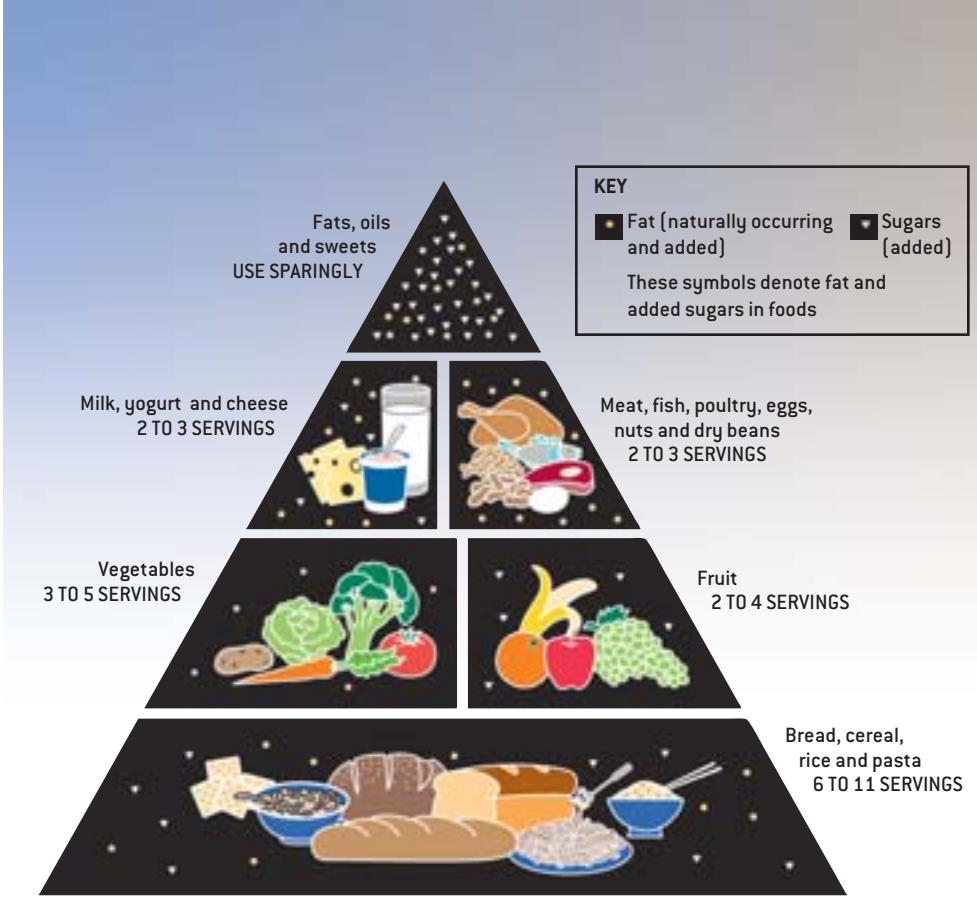
THE DIETARY GUIDE INTRODUCED A DECADE AGO HAS LED PEOPLE ASTRAY. SOME FATS ARE HEALTHY FOR THE HEART, AND MANY CARBOHYDRATES CLEARLY ARE NOT

# In 1992

the U.S. Department of Agriculture officially released the Food Guide Pyramid, which was intended to help the American public make dietary choices that would maintain good health and reduce the risk of chronic disease. The recommendations embodied in the pyramid soon became well known: people should minimize their consumption of fats and oils but should eat six to 11 servings a day of foods rich in complex carbohydrates—bread, cereal, rice, pasta and so on. The food pyramid also recommended generous amounts of vegetables (including potatoes, another plentiful source of complex carbohydrates), fruit and dairy products, and at least two servings a day from the meat and beans group, which lumped together red meat with poultry, fish, nuts, legumes and eggs.

Even when the pyramid was being developed, though, nutritionists had long known that some types of fat are essential to health and can reduce the risk of cardiovascular disease. Furthermore, scientists had found little evidence that a high intake of carbohydrates is beneficial. Since 1992 more and more research has shown that the USDA pyramid is grossly flawed. By promoting the consumption of all complex carbohydrates and eschewing all fats and oils, the pyramid provides misleading guidance. In short, not all fats are bad for you, and by no means are all complex carbohydrates good for you. The USDA's Center for Nutrition Policy and Promotion is now reassessing the pyramid, but this effort is not expected to be completed until 2004. In the meantime, we have drawn up a new pyramid that better reflects the current understanding of the relation between diet and health. Studies indicate that adherence to the recommendations in the revised pyramid can significantly reduce the risk of cardiovascular disease for both men and women.

How did the original USDA pyramid go so wrong? In part, nutritionists fell victim to a desire to simplify their dietary recommendations. Researchers had known for decades that saturated fat—found in abundance in red meat and dairy products—raises cholesterol levels in the blood. High cholesterol levels, in turn, are associated with a high risk of coronary heart disease (heart attacks and other ailments caused by the blockage of the arteries to the heart). In the 1960s controlled feeding studies, in which the participants eat carefully prescribed diets for several weeks, substantiated that saturated fat increases cholesterol levels. But the studies also showed that polyunsaturated fat—found in vegetable oils and fish—reduces cholesterol. Thus, dietary advice during the 1960s and 1970s emphasized the replacement of saturated fat with polyunsaturated fat, not total fat reduction. (The subsequent doubling of polyunsaturated fat consumption among Americans probably contributed greatly to the halving of coronary heart disease rates in the U.S. during the 1970s and 1980s.)




**OLD FOOD PYRAMID**

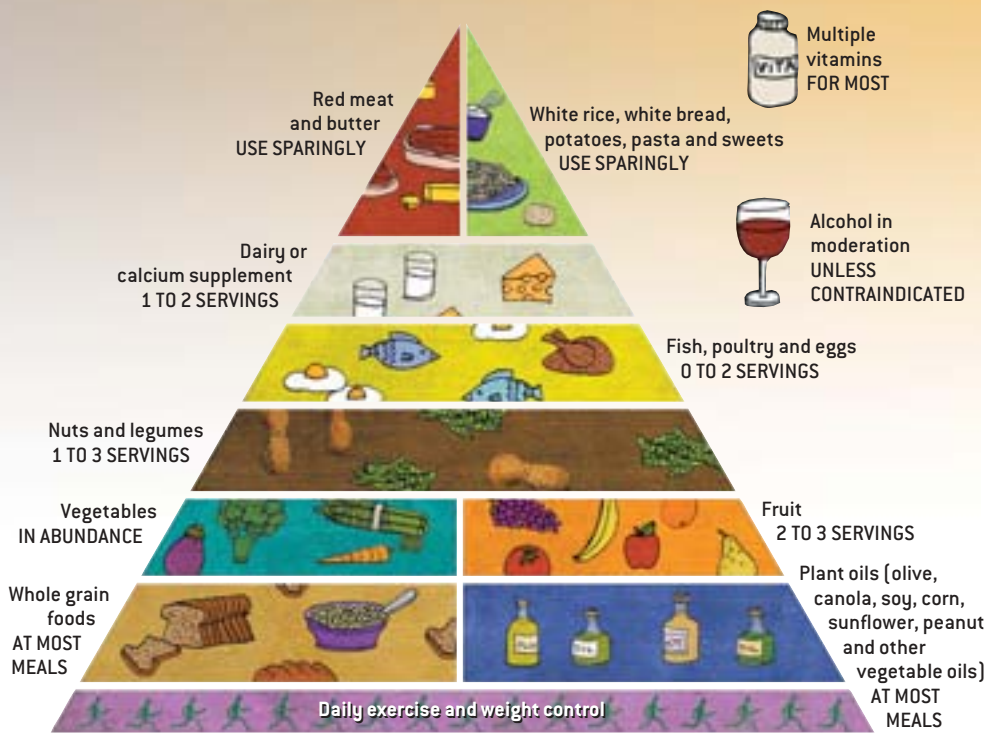
conceived by the U.S. Department of Agriculture was intended to convey the message "Fat is bad" and its corollary "Carbs are good." These sweeping statements are now being questioned.

*For information on the amount of food that counts as one serving, visit www.nal.usda.gov:8001/py/pmap.htm*

## Overview/*The Food Guide Pyramid*

- The U.S. Department of Agriculture's Food Guide Pyramid, introduced in 1992, recommended that people avoid fats but eat plenty of carbohydrate-rich foods such as bread, cereal, rice and pasta. The goal was to reduce the consumption of saturated fat, which raises cholesterol levels.
- Researchers have found that a high intake of refined carbohydrates such as white bread and white rice can wreak havoc on the body's glucose and insulin levels. Replacing these carbohydrates with healthy fats—monounsaturated or polyunsaturated—actually lowers one's risk of heart disease.
- Nutritionists are now proposing a new food pyramid that encourages the consumption of healthy fats and whole grain foods but recommends avoiding refined carbohydrates, butter and red meat.

RICHARD BORGE (*preceding pages*); USDA/DHHS (*old pyramid*)




## NEW FOOD PYRAMID

outlined by the authors distinguishes between healthy and unhealthy types of fat and carbohydrates. Fruits and vegetables are still recommended, but the consumption of dairy products should be limited.

The notion that fat in general is to be avoided stems mainly from observations that affluent Western countries have both high intakes of fat and high rates of coronary heart disease. This correlation, however, is limited to saturated fat. Societies in which people eat relatively large portions of monounsaturated and polyunsaturated fat tend to have lower rates of heart disease [*see illustration on next page*]. On the Greek island of Crete, for example, the traditional diet contained much olive oil (a rich source of monounsaturated fat) and fish (a source of polyunsaturated fat). Although fat constituted 40 percent of the calories in this diet, the rate of heart disease for those who followed it was lower than the rate for those who followed the traditional diets of Japan, in which fat made up only 8 to 10 percent of the calories. Furthermore, international comparisons can be misleading: many negative influences on health, such as smoking, physical inactivity and high amounts of body fat, are also correlated with Western affluence.

Unfortunately, many nutritionists decided it would be too difficult to educate the public about these subtleties. Instead they put out a clear, simple message: "Fat is bad." Because saturated fat represents about 40 percent of all fat consumed in the U.S., the rationale of the USDA was that advocating a low-fat diet would naturally reduce the intake of saturated fat. This recommendation was soon reinforced by the food industry, which began selling cookies, chips and other products that were low in fat but often high in sweeteners such as high-fructose corn syrup.

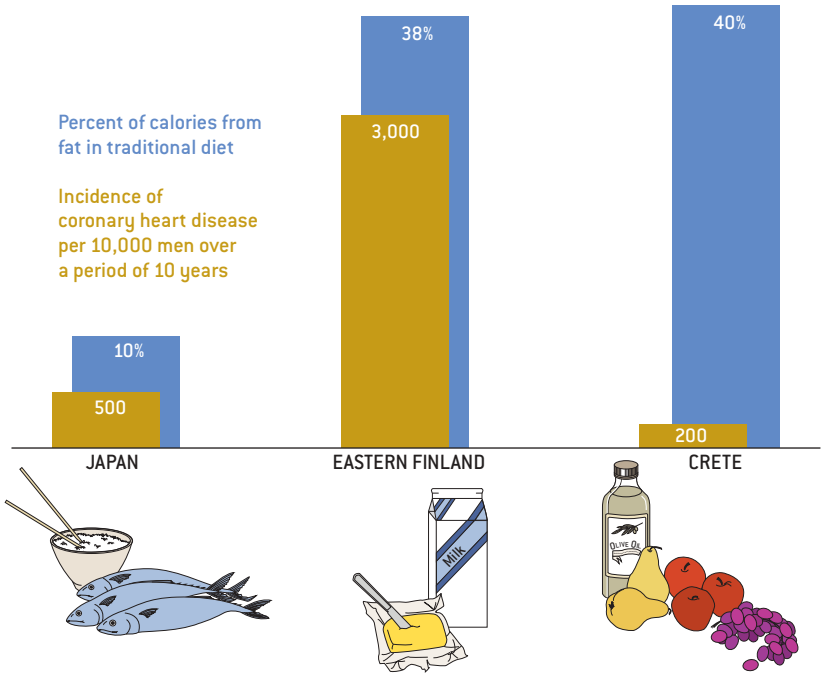
When the food pyramid was being developed, the typical American got about 40 percent of his or her calories from fat, about 15 percent from protein and about 45 percent from carbohydrates. Nutritionists did not want to suggest eating more protein, because many sources of protein (red meat, for example) are also heavy in saturated fat. So the "Fat is bad" mantra led to the corollary "Carbs are good." Dietary guidelines from the American Heart Association and other groups recommended that people get at least half their calories from carbohydrates and no more than 30 percent from fat. This 30 percent limit has become so entrenched among nutritionists that even the sophisticated observer could be forgiven for thinking that many studies must show that individuals with that level of fat intake enjoyed better health than those with higher levels. But no study has demonstrated long-term health benefits that can be directly attributed to a low-fat diet. The 30 percent limit on fat was essentially drawn from thin air.

The wisdom of this direction became even more questionable after researchers found that the two main cholesterol-carrying chemicals—low-density lipoprotein (LDL), popularly known as "bad cholesterol," and high-density lipoprotein (HDL), known as "good cholesterol"—have very different effects on the risk of coronary heart disease. Increasing the ratio of LDL to HDL in the blood raises the risk, whereas decreasing the ratio lowers it. By the early 1990s controlled feeding studies had shown that when a person replaces calories from saturated fat with an equal amount of calories from carbohydrates the levels of LDL and total cholesterol fall, but the level of HDL also falls. Because the ratio of LDL to HDL does not change, there is only a small reduction in the person's risk of heart disease. Moreover, the switch to carbohydrates boosts the blood levels of triglycerides, the component molecules of fat, probably because of effects on the body's endocrine system. High triglyceride levels are also associated with a high risk of heart disease.

The effects are more grievous when a person switches from either monounsaturated or polyunsaturated fat to carbohydrates. LDL levels rise and HDL levels drop, making the cholesterol ratio worse. In contrast, replacing saturated fat with either monounsaturated or polyunsaturated fat improves this ratio and would be expected to reduce heart disease. The only fats that are significantly more deleterious than carbohydrates are the trans-unsaturated fatty acids; these are produced by the partial hydrogenation of liquid vegetable oil, which causes it to solidify.

RICHARD BORGE

## Fat and Heart Disease




INTERNATIONAL COMPARISONS reveal that total fat intake is a poor indicator of heart disease risk. What is important is the type of fat consumed. In regions where saturated fats traditionally made up much of the diet (for example, eastern Finland), rates of heart disease were much higher than in areas where monounsaturated fats were prevalent (such as the Greek island of Crete). Crete's Mediterranean diet, based on olive oil, was even better for the heart than the low-fat traditional diet of Japan.

Found in many margarines, baked goods and fried foods, trans fats are uniquely bad for you because they raise LDL and triglycerides while reducing HDL.

### The Big Picture

TO EVALUATE FULLY the health effects of diet, though, one must look beyond cholesterol ratios and triglyceride levels. The foods we eat can cause heart disease through many other pathways, including raising blood pressure or boosting the tendency of blood to clot. And other foods can prevent heart disease in surprising ways; for instance, omega-3 fatty acids (found in fish and some plant oils) can reduce the likelihood of ventricular fibrillation, a heart rhythm disturbance that causes sudden death.

The ideal method for assessing all these adverse and beneficial effects would be to conduct large-scale trials in which individuals are randomly assigned to one diet or another and followed for many years. Because of practical constraints and cost, few such studies have been conducted, and most of these have focused on patients who already suffer from heart disease. Though limited, these studies have supported the benefits of replacing saturated fat with polyunsaturated fat, but not with carbohydrates.

The best alternative is to conduct large epidemiological studies in which the diets of many people are periodically assessed and the participants are monitored for the development of heart disease and other conditions. One of the best-known examples of this research is the Nurses' Health Study, which was begun in 1976 to evaluate the effects of oral contraceptives but was soon extended to nutrition as well. Our group at Harvard University has followed nearly 90,000 women in this study who first completed detailed questionnaires on diet in 1980, as well as more than 50,000 men who were enrolled in the Health Professionals Follow-Up Study in 1986.

After adjusting the analysis to account for smoking, physical activity and other recognized risk factors, we found that a participant's risk of heart disease was strongly influenced by the type of dietary fat consumed. Eating trans fat increased the risk substantially, and eating saturated fat increased it slightly. In contrast, eating monounsaturated and polyunsaturated fats decreased the risk—just as the controlled feeding studies predicted. Because these two effects counterbalanced each other, higher overall consumption of fat did not lead to higher rates of coronary heart disease. This finding reinforced a 1989 report by the National Academy of Sciences that concluded that total fat intake alone was not associated with heart disease risk.

But what about illnesses besides coronary heart disease? High rates of breast, colon and prostate cancers in affluent Western countries have led to the belief that the consumption of fat, particularly animal fat, may be a risk factor. But large epidemiological studies have shown little evidence that total fat consumption or intakes of specific types of fat during midlife affect the risks of breast or colon cancer. Some studies have indicated that prostate cancer and the consumption of animal fat may be associated, but reassuringly there is no suggestion that vegetable oils increase any cancer risk. Indeed, some studies have suggested that vegetable oils may slightly reduce such risks. Thus, it is reasonable to make decisions about dietary fat on the basis of its effects on cardiovascular disease, not cancer.

Finally, one must consider the impact of fat consumption on obesity, the most serious nutritional problem in the U.S. Obesity is a major risk factor for several diseases, including type 2 diabetes (also called adult-onset diabetes), coronary heart disease, and cancers of the breast, colon, kidney and esophagus. Many nutritionists believe that eating fat can contribute to weight gain because fat contains more calories per gram than protein or carbohydrates. Also, the process of storing dietary fat in the body may be more efficient than the conversion of carbohydrates to body fat. But recent controlled feeding studies have shown that these considerations are not practically important. The best way to avoid obesity is to limit your total calories, not just the fat calories. So the critical issue is whether the fat composition of a diet can influence one's ability to control caloric intake. In other words, does eating fat leave you

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more or less hungry than eating protein or carbohydrates? There are various theories about why one diet should be better than another, but few long-term studies have been done. In randomized trials, individuals assigned to low-fat diets tend to lose a few pounds during the first months but then regain the weight. In studies lasting a year or longer, low-fat diets have consistently not led to greater weight loss.

## Carbo-Loading

NOW LET'S LOOK at the health effects of carbohydrates. Complex carbohydrates consist of long chains of sugar units such as glucose and fructose; sugars contain only one or two units. Because of concerns that sugars offer nothing but "empty calories"—that is, no vitamins, minerals or other nutrients—complex carbohydrates form the base of the USDA food pyramid. But refined carbohydrates, such as white bread and white rice, can be very quickly broken down to glucose, the primary fuel for the body. The refining process produces an easily absorbed form of starch—which is defined as glucose molecules bound together—and also removes many vitamins and minerals and fiber. Thus, these carbohydrates increase glucose levels in the blood more than whole grains do. (Whole grains have not been milled into fine flour.)

Or consider potatoes. Eating a boiled potato raises blood sugar levels higher than eating the same amount of calories from table sugar. Because potatoes are mostly starch, they can be rapidly metabolized to glucose. In contrast, table sugar (sucrose) is a disaccharide consisting of one molecule of glucose and one molecule of fructose. Fructose takes longer to convert to glucose, hence the slower rise in blood glucose levels.

A rapid increase in blood sugar stimulates a large release of insulin, the hormone that directs glucose to the muscles and liver. As a result, blood sugar plummets, sometimes even going below the baseline. High levels of glucose and insulin can have negative effects on cardiovascular health, raising triglycerides and lowering HDL (the good cholesterol). The precipitous decline in glucose can also lead to more hunger after a carbohydrate-rich meal and thus contribute to overeating and obesity.

In our epidemiological studies, we have found that a high intake of starch from refined grains and potatoes is associated with a high risk of type 2 diabetes and coronary heart disease. Conversely, a greater intake of fiber is related to a lower risk of these illnesses. Interestingly, though, the consumption of fiber did not lower the risk of colon cancer, as had been hypothesized earlier.

Overweight, inactive people can become resistant to insulin's effects and therefore require more of the hormone to regulate their blood sugar. Recent evidence indicates that the adverse metabolic response to carbohydrates is substantially worse among people who already have insulin resistance. This finding may account for the ability of peasant farmers in Asia and elsewhere, who are extremely lean and active, to consume large amounts of refined carbohydrates without experiencing diabetes or heart disease, whereas the same diet in a more sedentary population can have devastating effects.

The best way to avoid obesity is to LIMIT YOUR TOTAL CALORIES, not just the fat calories.

## Eat Your Veggies

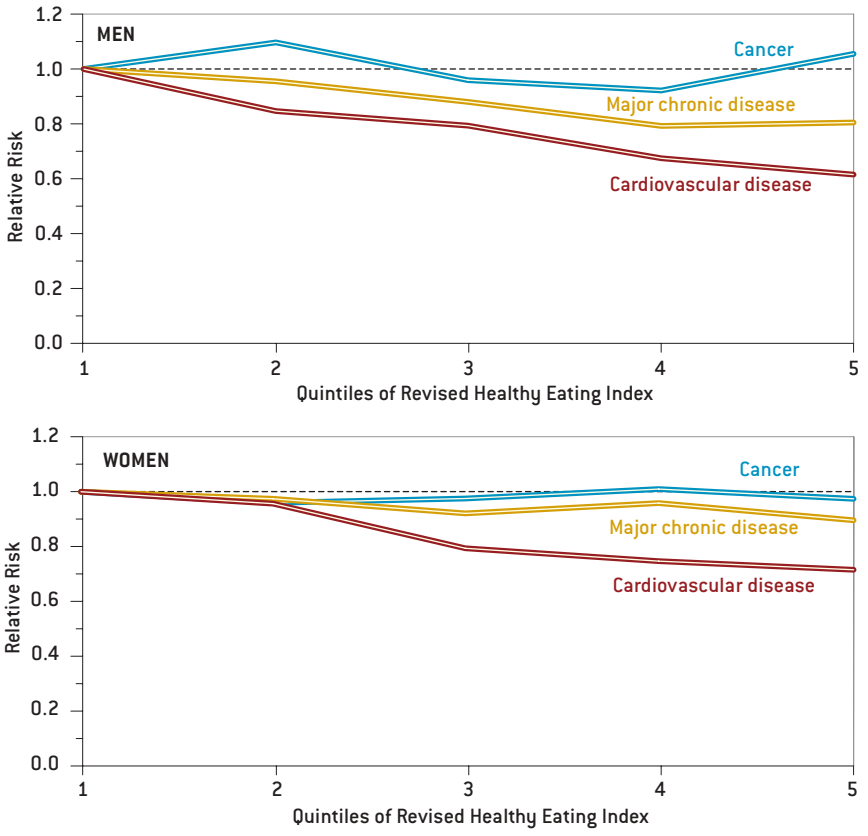
HIGH INTAKE OF FRUITS and vegetables is perhaps the least controversial aspect of the food pyramid. A reduction in cancer risk has been a widely promoted benefit. But most of the evidence for this benefit has come from case-control studies, in which patients with cancer and selected control subjects are asked about their earlier diets. These retrospective studies are susceptible to numerous biases, and recent findings from large prospective studies (including our own) have tended to show little relation between overall fruit and vegetable consumption and cancer incidence. (Specific nutrients in fruits and vegetables may offer benefits, though; for instance, the folic acid in green leafy vegetables may reduce the risk of colon cancer, and the lycopene found in tomatoes may lower the risk of prostate cancer.)

The real value of eating fruits and vegetable may be in reducing the risk of cardiovascular disease. Folic acid and potassium appear to contribute to this effect, which has been seen in several epidemiological studies. Inadequate consumption of folic acid is responsible for higher risks of serious birth defects as well, and low intake of lutein, a pigment in green leafy vegetables, has been associated with greater risks of cataracts and degeneration of the retina. Fruits and vegetables are also the primary source of many vitamins needed for good health. Thus, there are good reasons to consume the recommended five servings a day, even if doing so has little impact on cancer risk. The inclusion of potatoes as a vegetable in the USDA pyra-

THE AUTHORS

*WALTER C. WILLETT* and *MEIR J. STAMPFER* are professors of epidemiology and nutrition at the Harvard School of Public Health. Willett chairs the school's department of nutrition, and Stampfer heads the department of epidemiology. Willett and Stampfer are also professors of medicine at Harvard Medical School. Both of them practice what they preach by eating well and exercising regularly.

# Benefits of the New Pyramid




HEALTH EFFECTS OF THE RECOMMENDATIONS in the revised food pyramid were gauged by studying disease rates among 67,271 women in the Nurses' Health Study and 38,615 men in the Health Professionals Follow-Up Study. Women and men in the fifth quintile (the 20 percent whose diets were closest to the pyramid's recommendations) had significantly lower rates of cardiovascular disease than those in the first quintile (the 20 percent who strayed the most from the pyramid). The dietary recommendations had no significant effect on cancer risk, however.

mid has little justification, however; being mainly starch, potatoes do not confer the benefits seen for other vegetables.

Another flaw in the USDA pyramid is its failure to recognize the important health differences between red meat (beef, pork and lamb) and the other foods in the meat and beans group (poultry, fish, legumes, nuts and eggs). High consumption of red meat has been associated with an increased risk of coronary heart disease, probably because of its high content of saturated fat and cholesterol. Red meat also raises the risk of type 2 diabetes and colon cancer. The elevated risk of colon cancer may be related in part to the carcinogens produced during cooking and the chemicals found in processed meats such as salami and bologna.

Poultry and fish, in contrast, contain less saturated fat and more unsaturated fat than red meat does. Fish is a rich source of the essential omega-3 fatty acids as well. Not surprisingly, studies have shown that people who replace red meat with chicken and fish have a lower risk of coronary heart disease and colon cancer. Eggs are high in cholesterol, but consumption of up to one a day does not appear to have adverse effects on heart disease risk (except among diabetics), probably because the effects of a slightly higher cholesterol level are counterbalanced by other nutritional benefits. Many people have avoided nuts because of their high fat content, but the fat in nuts, including peanuts, is mainly unsaturated, and walnuts in particular are a good source of omega-3 fatty acids. Controlled feeding studies show that nuts improve blood cholesterol ratios, and epidemiological studies indicate that they lower the risk of heart disease and diabetes. Also, people who eat nuts are actually less likely to be obese; perhaps because nuts are more satisfying to the appetite, eating them seems to have the effect of significantly reducing the intake of other foods.

Yet another concern regarding the USDA pyramid is that it promotes overconsumption of dairy products, recommending the equivalent of two or three glasses of milk a day. This advice is usually justified by dairy's calcium content, which is believed to prevent osteoporosis and bone fractures. But the highest rates of fractures are found in countries with high dairy consumption, and large prospective studies have not shown a lower risk of fractures among those who eat plenty of dairy products. Calcium is an essential nutrient, but the requirements for bone health have probably been overstated. What is more, we cannot assume that high dairy consumption is safe: in several studies, men who consumed large amounts of dairy products experienced an increased risk of prostate cancer, and in some studies, women with high intakes had elevated rates of ovarian cancer. Although fat was initially assumed to be the responsible factor, this has not been supported in more detailed analyses. High calcium intake itself seemed most clearly related to the risk of prostate cancer.

More research is needed to determine the health effects of dairy products, but at the moment it seems imprudent to recommend high consumption. Most adults who are following a good overall diet can get the necessary amount of calcium by consuming the equivalent of one glass of milk a day. Under certain circumstances, such as after menopause, people may need more calcium than usual, but it can be obtained at lower cost and without saturated fat or calories by taking a supplement.

## A Healthier Pyramid

ALTHOUGH THE USDA'S food pyramid has become an icon of nutrition over the past decade, until recently no studies had evaluated the health of individuals who followed its guidelines. It very likely has some benefits, especially from a high intake of fruits and vegetables. And a de-

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crease in total fat intake would tend to reduce the consumption of harmful saturated and trans fats. But the pyramid could also lead people to eat fewer of the healthy unsaturated fats and more refined starches, so the benefits might be negated by the harm.

To evaluate the overall impact, we used the Healthy Eating Index (HEI), a score developed by the USDA to measure adherence to the pyramid and its accompanying dietary guidelines in federal nutrition programs. From the data collected in our large epidemiological studies, we calculated each participant's HEI score and then examined the relation of these scores to subsequent risk of major chronic disease (defined as heart attack, stroke, cancer or nontraumatic death from any cause). When we compared people in the same age groups, women and men with the highest HEI scores did have a lower risk of major chronic disease. But these individuals also smoked less, exercised more and had generally healthier lifestyles than the other participants. After adjusting for these variables, we found that participants with the highest HEI scores did not experience significantly better overall health outcomes. As predicted, the pyramid's harms counterbalanced its benefits.

Because the goal of the pyramid was a worthy one—to encourage healthy dietary choices—we have tried to develop an alternative derived from the best available knowledge. Our revised pyramid [*see illustration on page 20*] emphasizes weight control through exercising daily and avoiding an excessive total intake of calories. This pyramid recommends that the bulk of one's diet should consist of healthy fats (liquid vegetable oils such as olive, canola, soy, corn, sunflower and peanut) and healthy carbohydrates (whole grain foods such as whole wheat bread, oatmeal and brown rice). If both the fats and carbohydrates in your diet are healthy, you probably do not have to worry too much about the percentages of total calories coming from each. Vegetables and fruits should also be eaten in abundance. Moderate amounts of healthy sources of protein (nuts, legumes, fish, poultry and eggs) are encouraged, but dairy consumption should be limited to one to two servings a day. The revised pyramid recommends minimizing the consumption of red meat, butter, refined grains (including white bread, white rice and white pasta), potatoes and sugar.

Trans fat does not appear at all in the pyramid, because it has no place in a healthy diet. A multiple vitamin is suggested for most people, and moderate alcohol consumption can be a worthwhile option (if not contraindicated by specific health conditions or medications). This last recommendation comes with a caveat: drinking no alcohol is clearly better than drinking too much. But more and more studies are showing the benefits of moderate alcohol consumption (in any form: wine, beer or spirits) to the cardiovascular system.

## Men and women eating in accordance with THE NEW PYRAMID had a lower risk of major chronic disease.

Can we show that our pyramid is healthier than the USDA's? We created a new Healthy Eating Index that measured how closely a person's diet followed our recommendations. Applying this revised index to our epidemiological studies, we found that men and women who were eating in accordance with the new pyramid had a lower risk of major chronic disease [*see illustration on previous page*]. This benefit resulted almost entirely from significant reductions in the risk of cardiovascular disease—up to 30 percent for women and 40 percent for men. Following the new pyramid's guidelines did not, however, lower the risk of cancer. Weight control and physical activity, rather than specific food choices, are associated with a reduced risk of many cancers.

Of course, uncertainties still cloud our understanding of the relation between diet and health. More research is needed to examine the role of dairy products, the health effects of specific fruits and vegetables, the risks and benefits of vitamin supplements, and the long-term effects of diet during childhood and early adult life. The interaction of dietary factors with genetic predisposition should also be investigated, although its importance remains to be determined.

Another challenge will be to ensure that the information about nutrition given to the public is based strictly on scientific evidence. The USDA may not be the best government agency to develop objective nutritional guidelines, because it may be too closely linked to the agricultural industry. The food pyramid should be rebuilt in a setting that is well insulated from political and economic interests. SA

### MORE TO EXPLORE


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# Drink to Your Health?

By Arthur L. Klatsky

**Three decades of research shows that drinking small to moderate amounts of alcohol has cardiovascular benefits. A thorny issue for physicians is whether to recommend drinking to some patients**

## Addressing an Illinois temperance society in 1842, Abraham Lincoln

said something about "intoxicating liquor" that probably got a frosty reception. "It is true that … many were greatly injured by it," the future president noted. "But none seemed to think the injury arose from the use of a bad thing but from the abuse of a very good thing."

America has always had trouble deciding whether alcohol is a bad thing or a good thing. Millions who remember Prohibition, when all alcoholic beverages were illegal, now witness a constant stream of advertisements from producers of alcoholic beverages encouraging people to drink. Despite alcohol's popularity today, however, many still consider abstinence a virtue. Certainly, heavy drinking and alcoholism deserve deep concern for the terrible toll they take on alcohol abusers and society in general. But worry about the dangers of abuse often leads to emotional denials that alcohol could have any medical benefits. Such denials ignore a growing body of evidence indicating that moderate alcohol intake wards off certain cardiovascular (circulatory system) conditions, most notably heart attacks and ischemic strokes (those caused by blocked blood vessels). A few studies even show protection against dementia, which can be related to cardiovascular problems.

### The Alcohol Effect

A DISCUSSION OF moderate drinking requires a working definition of "moderate." Simple definitions of light, moderate or heavy are somewhat arbitrary, but a consensus in the medical literature puts the upper limit for moderate drinking at two standard-size drinks a day. Studies show that drinking above that level can be harmful to overall health, although sex, age and other factors lower and raise the boundary for individuals.

The main medical benefit of reasonable alcohol use seems to be a lowering of the risk for coronary heart disease (CHD), which results from the buildup of atherosclerosis (fatty plaque) in the arteries that feed blood to the heart. (The word "atherosclerosis" is in fact a descriptive union of two Greek words: *athera,* for "gruel" or "porridge," referring to the fatty deposits, and *sclera,* for "hard," pertaining to the loss of vessel flexibility.)

Atherosclerosis restricts blood flow to the heart and can promote the formation of vessel-blocking clots. It can thereby cause angina (chest discomfort resulting from low oxygen levels in the heart muscles), heart attack (the death of heart tissue that occurs when a blood clot or narrowing of the arteries prevents blood from reaching the heart) and death, often without warning. The condition usually starts at a young age but takes decades to blossom into overt CHD. The most common form of heart disease in developed countries, CHD causes about 60 percent of deaths from cardiovascular ills and about 25 percent of *all* deaths in those nations.

Pathologists uncovered the first clues to the value of alcohol in the early 1900s, noting that the large arteries of people who died of alcoholic liver cirrhosis seemed remarkably "clean"—that is, free of atherosclerosis. One explanatory hypothesis assumed that alcohol was a nebulous solvent, essen-

tially dissolving the buildup in the arteries; another explanation held that heavier drinkers died before their atherosclerosis had a chance to develop. Neither idea truly explained drinkers' unblocked arteries, however.

A more telling hint emerged in the late 1960s, when Gary D. Friedman of the Kaiser Permanente Medical Center in Oakland, Calif., came up with a novel idea: use computers to unearth unknown predictors of heart attacks. The power of computing could first identify healthy people who had risk factors similar to heart attack victims. Such factors include cigarette smoking, high blood pressure, diabetes, elevated levels of low-density-lipoprotein (LDL, or "bad") cholesterol, low levels of high-density-lipoprotein (HDL, or "good") cholesterol, male gender, and a family history of CHD. Friedman then searched for predictors of heart attacks by comparing the patients and the newly found controls in hundreds of ways—for example, their exercise and dietary habits and their respective levels of various blood compounds. The computers spit out a surprising discovery: abstinence from alcohol was associated with a higher risk of heart attack.

Various studies had missed the connection because they neglected to examine alcohol use as a behavior separate from smoking. We now know that because drinkers often also use cigarettes, the negative impact of smoking was masking the beneficial effect of alcohol. In 1974 my Kaiser Permanente colleagues Friedman and Abraham B. Siegelaub and I were the first, to our knowledge, to publish an examination of moderate drinking in the absence of smoking. We saw a clear connection between alcohol consumption and a decreased risk of heart attack.

Since then, dozens of investigations in men and women of several racial groups in various countries have correlated previous alcohol use with current health. These studies have firmly established that nondrinkers develop both fatal and nonfatal CHD more often than do light to moderate drinkers. In addition, in 2000 Giovanni Corrao of the University of Milan-Bicocca in Italy, Kari Poikolainen of the Järvenpää Addiction Hospital in Finland and their colleagues combined the results of 28 previously published investigations on the relation between alcohol intake and CHD. In this meta-analysis, they found that the risk of developing CHD went down as the amount of alcohol consumed daily went up from zero to 25 grams. At 25 grams—the amount of alcohol in about two standard drinks—an individual's risk of a major CHD event, either heart attack or death—was 20 percent lower than it was for someone who did not drink at all.

New data about alcohol protecting against death from CHD are even more impressive. At a meeting of the American Heart Association last November, my Kaiser Permanente colleagues Friedman, Mary Anne Armstrong and Harald Kipp and I discussed an updated analysis of 128,934 patients who had checkups between 1978 and 1985, with 16,539 of them dying between 1978 and 1998. CHD was responsible for 3,001 of those deaths. We discovered that those who had one or two alcoholic drinks a day had a 32 percent lower risk of dying from CHD than abstainers did.

The possible mechanisms by which alcohol has such an apparently profound effect on cardiovascular health primarily involve cholesterol levels and blood clotting. Blood lipids, or fats, play a central role in CHD. Numerous studies show that moderate drinkers have 10 to 20 percent higher levels of heart-protecting HDL cholesterol. And people with higher HDL levels, also known to be increased by exercise and some medications, have a lower risk of CHD.

That lower risk stems from HDL's ability to usher LDL cholesterol back to the liver for recycling or elimination, among other effects. Less cholesterol then builds up in the walls of blood vessels, and so less atherosclerotic plaque forms. Alcohol seems to have a greater influence on a different HDL subspecies ($HDL_3$) than on the type increased by exercise ($HDL_2$), although both types are protective. (The biochemical pathways in the liver that could account for alcohol's ability to raise HDL levels remain incompletely known; it is thought that alcohol probably affects liver enzymes involved in the production of HDL.) Three separate analyses aimed at determining specific contributions of alcohol all suggest that the higher HDL levels of drinkers are responsible for about half of the lowered CHD risk.

Alcohol may also disrupt the complex biochemical cascade behind blood clotting, which can cause heart attacks when it occurs inappropriately, such as over atherosclerotic regions in coronary arteries. Blood platelets, cellular components of clots, may become less "sticky" in the presence of alcohol and therefore less prone to clumping, although data on this question remain ambiguous. A 1984 study by Raffaele Landolfi and Manfred Steiner of Brown University's Memorial Hospital revealed that alcohol intake increases the level of prostacyclin, which interferes with clotting, relative to the level of thromboxane, which promotes clotting. Walter E. Laug of the University of Southern California Keck School of Medicine showed that alcohol raises levels of plasminogen activator, a clot-dissolving enzyme. Finally, several studies suggest that alcohol lowers levels of another promoter of blood clots, fibrinogen.

Overall, alcohol's anticlotting capac-

## Overview/*Alcohol and Heart Health*

- An assortment of studies from around the world indicates that drinking in small to moderate amounts decreases the risk of dying from coronary heart disease by almost one third.
- Some research points to red wine as being particularly protective against coronary heart disease. Other healthful habits of red wine drinkers, however, may be partly responsible for the apparent effect.
- A select group of people—those with CHD or at risk for CHD and without risks associated with alcohol itself—may wish to consult their physicians about moderate drinking as part of a heart-healthy diet.

## "STANDARD" SERVINGS OF ALCOHOLIC BEVERAGES

ALTHOUGH THERE IS NO formal definition of a standard-size drink, something of a consensus does exist. Beer is often sold in a 12-ounce bottle or can, which is a useful reference point as one standard drink. The amount of alcohol, about 0.6 ounce, in 12 ounces of beer is virtually the same as is found in a 5-ounce glass of wine or a 1.5-ounce glass of distilled spirits, such as vodka, gin, bourbon or scotch. Wine and distilled spirits in these amounts are thus also considered standard drinks.

ity is not as well established as its HDL effect, and some effects, such as platelet clumping, may be reversed by heavy or binge drinking. Nevertheless, anticlotting appears to have a role in the lower risk for heart attacks enjoyed by moderate drinkers. In addition, studies have shown a beneficial effect on CHD risk in people who have far fewer than two drinks a day—say, three or four drinks a week. Anticlotting could be a major factor in the protection accorded by alcohol in these small amounts, which seem insufficient to affect HDL levels greatly.

Although alcohol reduces heart disease risk mainly by raising HDL levels and reducing clotting, it acts in other ways that could lower the risk more subtly. Moderate drinking may lessen CHD risk indirectly by decreasing the risk of type 2 (adult-onset) diabetes, which is a powerful predictor of CHD. This benefit appears to be related to enhanced insulin sensitivity, which promotes proper glucose usage. (Heavy drinking, however, has been connected to higher blood glucose levels, a marker for future diabetes.) Evidence is also growing that inflammation contributes to CHD, and alcohol's anti-CHD power may be related to an anti-inflammatory action on the endothelial tissue that lines blood vessels.

Before accepting alcohol's benefits, an epidemiologist attempts to locate hidden factors possibly at work. For instance, could lifelong abstainers differ from drinkers in psychological traits, dietary habits, physical exercise habits or other ways that might account for their higher CHD risk without the need to invoke the absence of alcohol? Were such traits to explain away alcohol's apparent protection, they would need to be present in both sexes, various countries and several racial groups. Considering that no such traits have been identified, the simpler and more plausible explanation is that light to moderate alcohol drinking does indeed enhance cardiovascular health.

In fact, the available evidence satisfies most standard epidemiological criteria for establishing a causal relation. The numerous studies examining light and moderate alcohol intake and health reach consistent conclusions. The prospective studies that exist have the correct temporal sequence—that is, individuals' habits of interest are identified, after which their health is monitored over the long term, and alcohol users have different health profiles than nondrinkers do. The positives associated with alcohol can be attributed to biologically plausible mechanisms. Alcohol offers specific enhancement of cardiovascular health, not general protection against all illness. And alcohol's effect can be identified independent of known "confounders," other alcohol-related factors that could be responsible for a subject's cardiovascular condition.

The 30 percent reduction in risk is, perhaps surprisingly to some, less convincing evidence than the arguments above, because a strong *unknown* con-

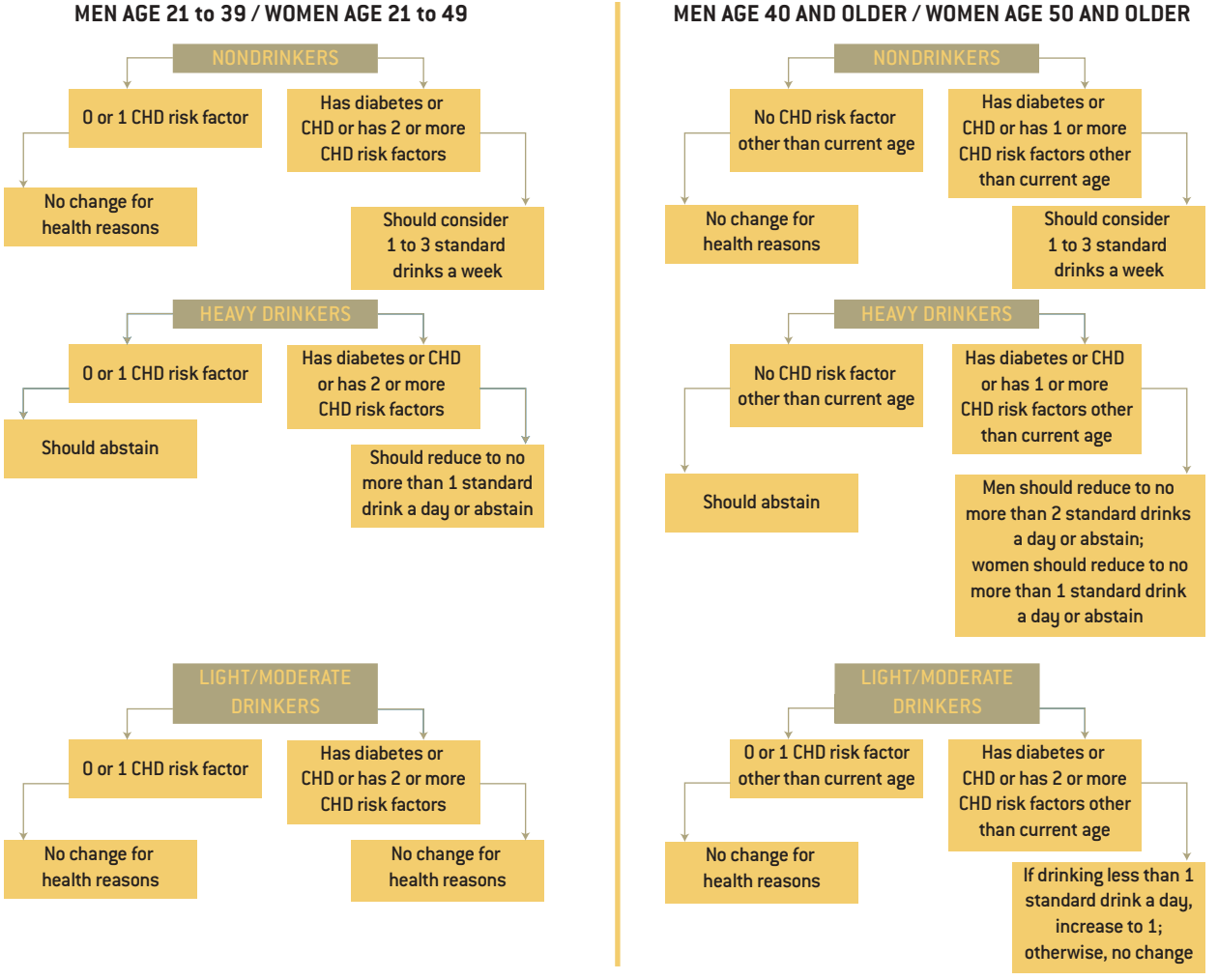
## HOW ALCOHOL MIGHT PROTECT AGAINST CHD

| *Alcohol Effect* | *Probable Action* | *Evidence* |
|---|---|---|
| Raises blood HDL cholesterol | Removes and transports LDL cholesterol from vessel wall | Solid supporting evidence; effect explains at least half of alcohol's benefit |
| Lowers blood LDL cholesterol | Reduces level of one major CHD risk factor | Evidence weak; effect probably not independent of diet |
| Lowers the oxidation of LDL | Prevents the plaque formation associated with LDL oxidation | Largely hypothetical, although antioxidants are plentiful in red wine |
| Lowers levels of fibrinogen in blood | Lessens the risk of clot formation on atherosclerotic plaques | Moderate supporting data |
| Exerts other anticlotting actions: lessens platelet stickiness; raises levels of prostacylin; lowers levels of thromboxane | Lessens the risk of clot formation on atherosclerotic plaques | Inconsistent data; possible reversal of effect with heavy or binge drinking |
| Lessens insulin resistance | Lessens key risk factor for adult-onset diabetes and atherosclerosis | Evidence comes from a small number of studies |
| Lessens psychosocial stress | Unclear | No supporting data or likely mechanism |
| Improves conditioning of heart muscle | Imparts better resistance to damage from oxygen deprivation | Preliminary supporting evidence |

## MAKING THE DRINKING DECISION

Roger R. Ecker, a cardiovascular surgeon at Summit Medical Center in Oakland, Calif., and I developed these charts to help individuals determine whether to include alcoholic beverages, and in what amounts, in their diets. The charts are designed to be used by physicians in consultation with patients. Coronary heart disease (CHD) risk factors are listed at the bottom. "Light/Moderate" is defined as up to one standard drink a day for women and up to two standard drinks a day for men. "Heavy" is three or more drinks a day for men and two or more drinks a day for women.

These charts do *not* apply to the following people, who should abstain from alcoholic beverages: anyone under the age of 21; pregnant women; nondrinkers with a family history of alcoholism, with moral or religious beliefs that preclude alcohol, with a personal history of alcohol abuse, with known organ damage from alcohol, with any chronic liver disease, or with a genetic risk of breast or ovarian cancer. —*A.L.K.*




**Coronary heart disease (CHD) risk factors, according to National Cholesterol Education Program guidelines:**

1. Family history of CHD (father or brother younger than 55 with CHD, mother or sister younger than 65 with CHD)
2. Smoking
3. High blood pressure
4. Total cholesterol higher than 200
5. HDL cholesterol lower than 35 (if HDL is higher than 60, subtract one risk factor)
6. Age 40 and older for men, 50 and older for women

founder could still account for the connection. To take an extreme example, consider a hypothetical set of genes that confers on the possessor 60 percent less CHD risk *and* causes a strong predisposition toward liking moderate amounts of alcohol. The independent consequences of the genes could appear causally linked. (In fact, however, no such confounder is known or likely, and the 30 percent risk reduction appears to be a probable measure of alcohol's beneficial effect.)

Because heavy drinking is not more protective than lighter drinking, this absence of a clear dose-response relation is also a weakness. Nevertheless, the collected data make a strong case for the cardiac benefits of controlled drinking. I

## DRINKING: RISKS AND BENEFITS

| Light/Moderate Drinking | | Heavy Drinking | |
|---|---|---|---|
| RISKS | BENEFITS | RISKS | BENEFITS |
| ***Established*** | ***Probable*** | ***Noncardiovascular*** | None |
| Heavy drinking | Decreased risk of CHD | Liver cirrhosis | |
| | Decreased risk of ischemic stroke | Pancreatitis | |
| ***Unresolved*** | Decreased risk of gallstones | Certain cancers | |
| Breast cancer | | Accidents | |
| Fetal damage | ***Possible*** | Homicides | |
| | Decreased risk of diabetes | Suicides | |
| ***Unlikely*** | Decreased risk of peripheral vascular disease (narrowing or clogging of the arteries carrying blood to the arms and legs) | Fetal damage | |
| Bowel cancer | | Degenerative disorders of the central nervous system | |
| Hemorrhagic stroke | | | |
| High blood pressure | | ***Cardiovascular*** | |
| | | High blood pressure | |
| | | Arrhythmia | |
| | | Hemorrhagic stroke | |
| | | Cardiomyopathy (damaged heart muscle) | |

should note, however, that the kind of study considered to be the gold standard in human research—a prospective randomized blinded clinical trial—has not yet been done. Such a study might, for example, engage a large pool of nondrinkers, half of whom, chosen at random and without the knowledge of the researchers, would commence a moderate drinking regimen, while the other half remained abstainers. The two groups would be followed for years in a search for eventual differences in cardiovascular disease and heart-related deaths.

### To Drink or Not to Drink

MOST PEOPLE DRINK for reasons other than alcohol's health benefits, and many of them are already using alcohol in amounts that appear to promote cardiovascular health. But the accumulated research on alcohol's positive effects presents a challenge to physicians. On one hand, mild to moderate drinking seems better for heart health than abstinence for select people. On the other hand, heavy drinking is clearly dangerous. It can contribute to noncardiovascular conditions such as liver cirrhosis, pancreatitis, certain cancers and degenerative neurological disorders, and it plays a part in great numbers of accidents, homicides and suicides, as well as in fetal alcohol syndrome. (No conclusive evidence links light to moderate drinking to any of these problems.)

Heavy drinking also contributes to cardiovascular disorders. Too much alcohol raises the risk of alcoholic cardiomyopathy, in which the heart muscle becomes too weak to pump efficiently; high blood pressure (itself a risk factor for CHD, stroke, heart failure and kidney failure); and hemorrhagic stroke, in which blood vessels rupture in or on the surface of the brain. Alcohol overindulgence is also related to "holiday heart syndrome," an electrical signal disturbance that disrupts the heart rhythm. The name refers to its increased frequency around particular holidays during which people engage in binge drinking.

Given the potential dangers of alcohol, how can individuals and their physicians make the decision as to whether to include alcoholic beverages in their lives and, if so, in what amounts? The ability to predict accurately an individual's risk of a drinking problem would be a great boon; the least disputed possible consequence of moderate drinking is problem drinking. Individual risk can be approximated using family and personal histories of alcohol-related problems or conditions, such as liver disease or, of course, alcoholism. Even when known factors are taken into account, however, unpredictable events late in life may result in deleterious drinking changes.

Exactly because of these dangers, public health concerns about alcohol until recently have been appropriately focused solely on the reduction of the terrible social and medical consequences of heavy drinking. And the correlation between total alcohol consumption in society and alcohol-related problems has been used to justify pushes for abstinence. Ultimately, however, a more complex message is necessary. Merely recommending abstinence is inappropriate health advice to people such as established light drinkers at high risk of CHD and at low risk of alcohol-related problems—which describes a large proportion of the population. Of course, the most important steps for this group are proper diet and exercise; effective treatment of obesity, diabetes, high blood pressure and high cholesterol; and avoidance of tobacco. But there is a place on that list of beneficial activities for light drinking. Most light to moderate drinkers are already imbibing the optimal amount of alcohol for cardiovascular benefit, and they should continue doing what they are doing.


THE AUTHOR

*ARTHUR L. KLATSKY* is a senior consultant in cardiology and an adjunct investigator at the division of research at the Kaiser Permanente Medical Center in Oakland, Calif. A graduate of Harvard Medical School, he headed the medical center's division of cardiology from 1978 to 1994 and directed its coronary care unit from 1968 to 1990. Since 1977 he has been principal investigator of a series of studies of the link between drinking alcoholic beverages and health. His 1974 *Annals of Internal Medicine* article [see More to Explore, on next page] was the first published epidemiological report of an inverse relation between alcohol drinking and coronary disease; it was cited in 1995 by the National Institute on Alcohol Abuse and Alcoholism as one of 16 seminal articles in alcohol research. His most recent honor was a Health Forum Cardiovascular Health Fellowship for 2000–2001. Klatsky has completed six marathons and in 1990 climbed Mount Kilimanjaro.

## WINE, BEER OR SPIRITS?

Beer, wine and liquor all seem to be related to a lower risk of coronary heart disease (CHD). A tantalizing question, however, is whether one kind of drink—wine, for example—is better than the others. The short answer: the jury is still out.

The death rate from CHD in France, where red wine consumption is common, is only about half that in the U.S., despite similar fat intake and sedentary lifestyles. That observation led to the catchphrase "the French paradox" and the idea that red wine is *the* beneficial alcoholic beverage. This belief has a hypothetical basis—red wine especially contains a number of ingredients with potential antioxidant and other atherosclerosis-fighting benefits.

An excellent 1995 Danish study, in which almost 13,000 people were followed during a 12-year period, suggested that wine drinkers have lower death rates from CHD than do other alcohol imbibers. My Kaiser Permanente colleagues Mary Anne Armstrong and Gary D. Friedman and I published on the risk of CHD death (in 1990) and the risk of CHD hospitalization (in 1997); in these investigations, which included almost 130,000 Californians, wine and beer drinkers had a lower CHD risk than did hard-liquor drinkers. At a meeting of the American Heart Association in November 2002, I presented new data that updated the 1990 study. We were surprised to find that those drinking wine daily had about a 25 percent lower risk of CHD death than did those who drank beer and wound up taking in the same amount of alcohol. And the wine drinkers had about a 35 percent lessened CHD death risk compared with the light to moderate hard-liquor drinkers. Significantly, there was no difference in apparent benefit between red wine and white wine.

A vexing complication of all these studies, however, is that the overall habits of wine drinkers, beer drinkers and hard-liquor drinkers tend to differ greatly. In Denmark, for example, wine drinking goes hand in hand with a healthful diet (high in fruits, vegetables, fish, salads and olive oil) and two other markers for better health in general: higher socioeconomic status and higher IQ. In our California studies, those who preferred wine also smoked less, had more education and had more temperate drinking habits than those who preferred beer or hard liquor.

Lifestyle differences among those who prefer one type of alcoholic beverage over another thus make it exceedingly difficult to determine whether the differences in apparent health effects are actually related to the beverage type itself (and therefore to wine constituents besides alcohol), to drinking pattern (imbibed slowly and with food, for wine) or to other factors. —*A.L.K.*

Abstainers should never be indiscriminately advised to drink for health; most have excellent reasons for not drinking. Yet there are exceptions. One case is the person with CHD who "goes clean"—quits smoking, switches to a spartan diet, starts exercising and, with good intentions, gives up the habit of a nightly bottle of beer or glass of wine. This self-imposed prohibition should be repealed. In addition, a number of infrequent drinkers might think about increasing their alcohol intake to one standard drink daily, especially men older than 40 and women older than 50 at high risk of CHD and low risk of alcohol-related problems. But women also have to consider one possible drawback of alcohol: several studies link heavy drinking—and a few even link light drinking—to an increased risk of breast cancer, a less common condition than heart disease in postmenopausal women but certainly quite a serious one. For young women, who are generally at low short-term risk of CHD and therefore may not benefit greatly from alcohol's positive cardiovascular effects, this possible breast cancer link looms larger in estimating the overall risks and benefits of alcohol. And for all women, the upper limit on moderate drinking should be considered one drink a day.

The only clear-cut message regarding alcohol and health, then, is that all heavy drinkers should reduce or abstain, as should anyone with a special risk related to alcohol, such as a family or personal history of alcoholism or preexisting liver disease. Beyond that, however, the potential risks and benefits of alcohol are best evaluated on a case-by-case basis. Cardiovascular surgeon Roger R. Ecker and I constructed an algorithm that can help health practitioners and their patients decide how much—if any—alcohol is right for a given individual [*see box on page 28*].

In short, health professionals should provide balanced, objective guidelines regarding their patients' use of alcohol, and such advice needs to be tailored to each person. I believe that it is possible to define a clear, safe limit for alcohol consumption that would offer a probable benefit to a select segment of the population. The ancient Greeks urged "moderation in all things." Three decades of research shows that this adage is particularly appropriate when it comes to alcohol. SA

### MORE TO EXPLORE

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# Gaining on Fat

by W. Wayt Gibbs, *staff writer*

Throughout most of human history, a wide girth has been viewed as a sign of health and prosperity. It seems both ironic and fitting, then, that corpulence now poses a growing threat to the health of many inhabitants of the richest nations. The measure of the hazard in the U.S. is well known: 59 percent of the adult population meets the current definition of clinical obesity, according to a 1995 report by the Institute of Medicine, easily qualifying the disease for epidemic status. Epidemiologists at Harvard University conservatively estimate that treating obesity and the diabetes, heart disease, high blood pressure and gallstones caused by it rang up $45.8 billion in health care costs in 1990, the latest year studied. Indirect costs because of missed work pitched another $23 billion onto the pile. That year, a congressional committee calculated, Americans spent about $33 billion on weight-loss products and services. Yet roughly 300,000 men and women were sent early to their graves by the damaging effects of eating too much and moving too little.

The problem is as frustrating as it is serious. Quick and easy solutions—liquid diets, support groups, acupressure, appetite-suppressing "aroma sticks" and even the best-intentioned attempts to eat less and exercise more—have all failed in well-controlled trials to reduce the weight of more than a small fraction of their obese adherents by at least 10 percent for five years—an achievement shown to increase life expectancy sharply.

The discovery last summer of leptin, a natural hormone that cures gross obesity when injected into mutant mice that lack it, raised hopes of a better quick fix. Those hopes have faded as subsequent studies have found no fat people who share the leptin-related mutations seen in mice. But the identification of leptin is only one of many important advances over the past several years that have opened a new chapter in the understanding of obesity.

Armed with powerful new tools in molecular biology and genetic engineering, scientists are seeking physiological explanations for some of the most puzzling aspects of the fattening of industrial society. Why is obesity on the rise, not just in the U.S. but in nearly all affluent countries? How is it that some individuals remain fat despite constant diets, whereas others eat what they want without gaining a pound? Why is it so hard to lose a significant amount of weight and nearly impossible to keep it off? Perhaps most important, what can be done to slow and eventually reverse this snowballing trend? The traditional notion that obesity is simply the well-deserved consequence of sloth and gluttony has led to unhelpful and sometimes incorrect answers to these questions. Science may at last offer better.

### What Makes the World Go Round

Contrary to conventional wisdom, the U.S. is not the fattest nation on earth. Obesity is far more common on Western Samoa and several other Pacific islands. On Nauru, a mere dot of eight square miles once covered to overflowing with seabird guano, the 7,500 islanders have traded that valuable source of phosphate to fertilizer companies in exchange for one of the highest per capita incomes in the world. Many also traded their plows for lounge chairs and their traditional diet of fish and vegetables for Western staples such as canned meats, potato chips and beer. Within the course of a generation, the change has taken its toll on their bodies. By 1987 well over 65 percent of men and 70 percent of women on Nauru were obese, and one third suffered from diabetes.

Many countries, developed and developing, are heading in the same direction at an alarming pace. Changes in diet alone do not explain the trend. Surveys—some of which admittedly are of dubious accuracy—show that the proportion of calories Americans get from fat has dropped about eight points since the 1980s, to 34 percent. Yet the prevalence of obesity has risen by a similar amount in nearly the same period. Britons ate 10 percent fewer calories overall in 1991 than in 1980, according to government estimates, while the number of heavyweights doubled. Polls that show gasoline consumption and hours spent watching television rising about as quickly as the rate of obesity in some countries seem to explain part of the disparity.

Evolutionary biology may provide a deeper explanation, however. In 1962

James V. Neel of the University of Michigan proposed that natural selection pressured our distant ancestors to acquire "thrifty genes," which boosted the ability to store fat from each feast in order to sustain people through the next famine. In today's relative surfeit, Neel reasoned, this adaptation has become a liability. The theory is supported by the Nauruans' plight and also by studies of the Pima Indians, a tribe whose progenitors split into two groups sometime during the Middle Ages. One group settled in southern Arizona; the other moved into the Sierra Madre Mountains in Mexico. By the 1970s most of the Indians in Arizona had been forced out of farming and had switched to an American diet with 40 percent of its calories from fat. They now endure the highest incidence of obesity reported anywhere in the world—far higher than among their white neighbors. About half develop diabetes by age 35.

Eric Ravussin, a researcher with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), has compared Pimas in Arizona with their distant relatives in Maycoba, Mexico, who still live on subsistence farming and ranching. Although the groups share most of the same genes, Pimas in Maycoba are on average 57 pounds (26 kilograms) lighter and about one inch (2.5 centimeters) shorter. Few have diabetes. Maycobans also eat about half as much fat as their counterparts to the north, and they spend more than 40 hours a week engaged in physical work. The fact that Mexican Pimas remain lean provides strong evidence that the high rate of obesity among American Pimas is the result not of a genetic defect alone but of a genetic susceptibility—exceptionally thrifty genes—turned loose in an environment that offers easy access to high-energy food while requiring little hard labor.

Because all human populations seem to share this genetic susceptibility to varying degrees, "we are going to see a continuing increase in obesity over the next 25 years" as standards of living continue to rise, predicts F. Xavier Pi-Sunyer, director of the obesity research center at St. Luke's-Roosevelt Hospital in New York City. He warns that "some less developed countries are particularly at risk. It is projected that by 2025, more than 20 percent of the population of Mexico will have diabetes."

Studies of Pimas, islanders and migrants "all seem to indicate that among different populations, the prevalence of obesity is largely determined by environmental conditions," Ravussin concludes. A few doctors have proposed changing those conditions by levying a "fat tax" on high-calorie foods or raising insurance rates for those who fail to show up at a gym regularly.

But economic and legal punishments are unlikely to garner much popular support, and no one knows whether they would effectively combat obesity. So most researchers are turning back to factors they think they can control: the genetic and biological variables that make one person gain weight while others in the same circumstances stay lean.

### Finding Genes That Fit

Doctors have long known that the tendency to gain weight runs in families—how strongly is still under debate. Numerous analyses of identical twins reared apart have shown that genetic factors alone control a large part of one's body mass index, an estimate of body fat commonly used to define obesity [*see box on next page*]. A few have found weight to be as dependent on genes as height: about 80 percent. But the majority have concluded that genetic influences are only about half that potent.

Investigators at the National Institutes of Health who examined more than 400 twins over a period of 43 years concluded that "cumulative genetic effects explain most of the tracking in obesity over time," including potbellies sprouting in middle age. Interestingly, the researchers also determined that "shared environmental effects were not significant" in influencing the twins' weight gain. That result is bolstered by five studies that compared the body mass indexes of adopted children with their biological and adoptive parents. All found that the family environment—the food in the refrigerator, the frequency of meals, the type of activities the family shares—plays little or no role in determining which children will grow fat. Apparently, only dramatic environmental differences, such as those between the mountains of Mexico and the plains of Arizona, have much effect on the mass of a people.

Just which genes influence our eating, metabolism and physical activity, and how they exert their power, remains a mystery. But geneticists do have some encouraging leads. Five genes that can cause rodents to balloon have now been pinpointed.

*Obese,* cloned by Jeffrey M. Friedman and others at the Rockefeller University, encodes a blueprint for leptin, a hormone produced by fat cells. Mice with a mutation in this gene produce either no leptin or a malformed version and quickly grow to three times normal weight. *Diabetes,* cloned last December by a team at Millennium Pharmaceuticals in Cambridge, Mass., codes for a receptor protein that responds to leptin by reducing appetite and turning up metabolism. Mice with a bad copy of this gene do not receive the leptin signal, and they, too, get very fat from infancy.

Within the past year scientists at Jackson Laboratory in Bar Harbor, Me., have cloned two other fat genes, named *fat* and *tubby.* Mice with a mutation in either of these genes put on weight gradually—more like humans do. The *fat* gene gets translated into an enzyme that processes insulin, the hormone that signals the body that it has been fed. But the protein produced by the *tubby* gene is unlike any ever seen. Researchers do

*As a costly epidemic of obesity spreads through the industrial world, scientists are uncovering the biological roots of this complex disease. The work offers tantalizing hope of new ways to treat, and prevent, the health risks of excess weight*

## A Shifting Scale

Obesity appears to be rising in most industrial nations, although comparisons are tricky because epidemiologists have never settled on consistent categories for measuring the disorder. Nearly all rely on the body mass index (BMI) [*see formula below*], because this figure is highly correlated with body fat. Still, studies have used a wide range of BMI levels, from below 27 to over 30, to categorize the obese.

The World Health Organization classifies obesity in three levels, with those having BMIs of 30 or higher considered at major risk. Doctors in the U.S. have conventionally used "ideal weight" tables assembled by the Metropolitan Life Insurance Company from actuarial data. Yet recent mortality studies, such as one published last year by Harvard University researchers who examined 115,195 nurses over 16 years, have found that the standard tables underestimate the risks of excess weight—primarily because they fail to account for smokers, who tend to be thin but unhealthy. These newer studies show risks increasing significantly at BMIs of 25 and higher. In 1995 the National Institutes of Health and the American Health Foundation issued new guidelines that define healthy weight as a BMI below 25. According to a recent report by the Institute of Medicine, 59 percent of American adults exceed that threshold.

**Calculating Body Mass Index**

$$\text{BMI} = \frac{w}{h^2}$$

*w* is weight in kilograms (pounds divided by 2.2)
*h* is height in meters (inches divided by 39.4)

not yet know why mice with errors in *fat*, *tubby* or *agouti yellow,* a fifth obesity gene discovered several years ago, put on extra ounces.

Although geneticists have located versions of all five genes within human DNA, "so far, when we have looked for human mutations on these genes, we haven't found them," reports L. Arthur Campfield, a research leader at Hoffmann–La Roche, the drug company that has bought the rights to Millennium's work on the leptin receptor. In fact, clinical studies by Friedman and others have shown that unlike *obese* and *diabetes* mice, heavy humans generally produce a normal amount of leptin given the amount of fat they are carrying. At least at first glance, there seems to be nothing wrong with their leptin systems.

All of which is no surprise to most obesity researchers, who have long maintained that there must be multiple genes that interact with one another and with economic and psychological pressures to set an individual's susceptibility to weight gain. Although identifying clusters of interrelated genes is considerably trickier than finding single mutations, some labs have made headway in mice. David West of the Pennington Biomedical Research Center in Baton Rouge, La., has been crossing one strain that fattens dramatically on a high-fat diet with a closely related strain that remains relatively lean on the same menu. By tracking the way the trait is passed from one generation to the next, West has proved that the fat sensitivity is carried by one to four dominant genes, and he has narrowed down the chromosome segments on which they could lie. Interestingly, the *tubby* gene happens to rest within one of these segments.

Eventually the genes involved in human weight regulation should be found. But that is the simple part. To make a dent in obesity, physiologists will then have to figure out how all these genes work in real bodies outside the lab. The first step will be to resolve once and for all an old dieters' debate: Do we or do we not have set points—predetermined weights at which our bodies are happiest—and can they be changed?

### Set up for Failure

A typical American adult gains about 20 pounds between the ages of 25 and 55. "If you figure that an adult ingests 900,000 to one million calories a year and you calculate the energy cost of those additional 20 pounds," observes Rudolph L. Leibel, co-director of the human metabolism laboratory at Rockefeller, you find that "just a few tenths of 1 percent of the calories ingested are in fact being stored. That degree of control or balance is extraordinary."

Multiple feedback loops maintain the body at a stable weight by shunting messages through the bloodstream and the autonomic nervous system between the brain, the digestive tract, muscle—and, it turns out, fat. Until recently, fat was generally considered just a passive storage tissue. In fact, says Ronald M. Evans of the Salk Institute in La Jolla, Calif., "it is a type of endocrine tissue. Fat secretes signals—hormones such as leptin—and also monitors and responds to signals from other cells."

Last December, Evans reported his discovery of a new hormone, with the catchy name of 15d-$PGJ_2$, that is produced inside fat cells and seems to trigger the formation of new ones, at least in children. Any drug that tried to interfere with the hormone to prevent new fat from forming would probably work only in children, Evans says, because fat cells in adults usually inflate in size rather than increase in number. But a synthetic molecule that mimics 15d-$PGJ_2$, called troglitazone, does appear to be an effective drug for the type II diabetes associated with obesity, because it also signals muscle cells to respond normally to insulin.

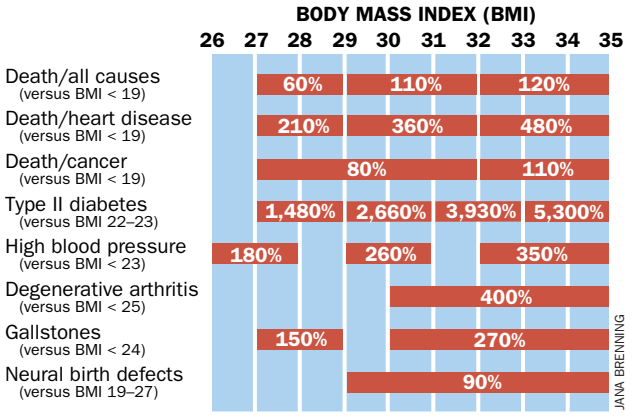
In mapping the maze of intertwined pathways that control short-term appetite as well as factors (such as fat and carbohydrate levels) that change over days or weeks, researchers are slowly working out how all these signals combine to hold weight steady. Two major theories vie for acceptance: set point and settling point.

The set-point hypothesis is the older and more deterministic. It asserts that the brain continuously adjusts our metabolism and subconsciously manipulates our behavior to maintain a target weight. Although the set point may change with age, it does so according to a fixed genetic program; diet or exercise can move you away from your set point, at least for a time, but the target itself cannot change—or so the theory goes. Last year Leibel and his colleagues Michael Rosenbaum and Jules Hirsch, who are three of the strongest proponents of the set-point theory, completed a study that seems to support their hypothesis.

The physicians admitted 66 people to the Rockefeller hospital. Some of the patients were obese, and some had never been overweight, but all had been at the same weight for at least six months. Over the next three months the subjects ate only precisely measured liquid meals. The doctors ran an extensive battery of tests on the volunteers and then increased the calories that some were fed and put

## Weighing the Risks

Percent increase in risk by level of obesity




*SOURCES: New England Journal of Medicine; Annals of Internal Medicine; American Journal of Clinical Nutrition; Journal of the American Medical Association; Circulation*

the others on restricted diets. When the subjects had gained 10 percent or lost either 10 or 20 percent of their original weight, the tests were run again to see what had changed.

The investigation disproved some tidbits of weight-gain folklore, such as that thin people do not digest as much of their food as heavyweights. The study also found that "the idea that you will be fatter—or will require fewer calories to maintain your starting body weight—as a result of having yo-yoed down and back up again is wrong," Rosenbaum adds. Moreover, the research showed that obese people, when their weight is stable, do not eat significantly more than lean people with the same amount of muscle but less fat.

But the trial's real purpose was to determine how much of a fight the body puts up when people attempt to change the weight they have maintained for a long time—why, in other words, dieters tend to bounce back to where they started. When both lean and obese subjects dropped weight, "it seemed to set off a bunch of metabolic alarms," Leibel recalls. The subjects' bodies quickly started burning fewer calories—15 percent fewer, on average, than one would expect given their new weight. Surprisingly, the converse also seems to be true for weight gain. Even rotund people have to eat about 15 percent more than one would expect to stay very far above their set point.

That fact raises a major problem for set-point theory: How does it explain the rapid increase in the prevalence of obesity? "Clearly, set points have to be rising, just as we are getting taller in every generation," Rosenbaum says. "But set points are not changeable in adulthood, as far as we can tell. So there must be a window of opportunity sometime in childhood where the environment influences the set point," he speculates. "If you could figure out when and how that occurs, maybe you could modify the environment then, and you wouldn't have to worry about your kids getting fat 20 years down the line."

That will remain wishful thinking until set-point advocates demonstrate how weight is centrally controlled. Their best guess now, explains Louis A. Tartaglia, a scientist at Millennium, is that "the body's set point is something like a thermostat"—a lipostat, some have called it—and leptin acts like the thermometer.

As you gain weight, Friedman elaborates, "you make more leptin. That shuts off appetite, increases energy expenditure and undoubtedly does other things to restore body weight to the set point. Conversely, if you get too thin, levels of leptin fall, and now you eat more, burn less, and again your weight returns to where it started. Now that we know what the gene and its product are, we can test that simpleminded theory."

Amgen, a biotechnology firm in Thousand Oaks, Calif., that has reportedly promised Rockefeller up to $100 million for the right to produce leptin, has begun injecting the hormone into obese people in clinical trials. "The goal," Rosenbaum says, "is to co-opt your body into working with you rather than against you to maintain an altered body weight" by tricking it into believing it is fatter than it is.

But the body may not be easily fooled. In May, scientists at the University of Washington reported that they had engineered mice that lack the gene for neuropeptide Y (NPY), the most powerful appetite stimulant known. Leptin curtails NPY production; this, it was thought, is how it quells hunger. But mice lacking NPY do not lose weight—something else compensates.

Critics of the set-point hypothesis also protest that it fails to explain the high rates of obesity seen in Nauruans and American Pimas. Moreover, if body fat is centrally controlled, they argue, the amount of fat in your diet should have little impact on your weight. Numerous studies have found the contrary. One recent survey of some 11,600 Scotsmen observed that obesity was up to three times more common among groups that ate the most fat than among those who relied on sugars for most of their energy.

### Fat in the Balance

At a conference last year, researchers reviewed the evidence and judged that although the set-point hypothesis has not been disproved, there is more "biological merit" to the idea of a "settling point." This newer theory posits that we maintain weight when our various metabolic feedback loops, tuned by whatever susceptibility genes we carry, settle into a happy equilibrium with our environment. Economic and cultural changes are upsetting this equilibrium and propelling more people—those with more genetic risk factors—into obesity.

The prime culprit suspected in this trend is hardly surprising: it is the fat dripping off hamburgers, smoothing out ice cream and frying every meat imaginable. But biochemists are at last working out precisely why fat is bad. For years, they have known that people fed a high-fat meal will consume about the same amount as those given a high-carbohydrate meal. Because fat has more calories per bite, however, the subjects with greasy grins tend to ingest more energy than they can burn, a phenomenon known as passive overconsumption.

One reason for this, according to biopsychologist John E. Blundell of the University of Leeds, seems to be that the systems controlling hunger and satiety respond quickly to protein and carbohydrates but slowly to fat—too slowly to stop a high-fat meal before the body has had too much. Metabolic systems seem to favor carbohydrates (which include sugars and starches) as well. Knock down a soda or a plate of pasta, and your body will soon speed up its carbohydrate combustion. Polish off a bag of pork rinds, however, and your fat oxidation rate hardly budges, points out Jean-Pierre Flatt, a biochemist at the University of Massachusetts Medical School. Most incoming fat is shipped directly to storage, then burned later only if carbohydrate reserves dip below some threshold, which varies from person to person.

There is another way to increase the

## A Spoonful of Medicine: Obesity Drugs under Development

| TISSUES | DRUG | ACTION | DEVELOPER | STATUS |
|---|---|---|---|---|
| Brain | Dexfenfluramine | Increases the circulation of serotonin, a neurotransmitter that quells appetite | Interneuron with Wyeth-Ayerst Laboratories | Approved by the FDA in April |
| | Sibutramine | Boosts levels of both serotonin and noradrenaline in the brain, staving off hunger | Knoll Pharmaceutical | Submitted to the FDA for approval in August 1995 |
| | Neuropeptide Y inhibitors | Inactivate NPY, an appetite stimulant that also signals the body to burn more sugars and less fat | Neurogen, Pfizer, Synaptic Pharmaceutical | Phase I trials* began in March |
| | Bromocriptine | Mimics the neurotransmitter dopamine. Given at certain times of day, may reduce blood sugar and fat production by the liver | Ergo Science | Phase III trials under way for diabetes, planned for obesity |
| | Leptin | Hormone produced by fat cells and received by receptors in the hypothalamus. Some obese people may be insensitive to leptin; supplemental injections may help | Amgen | Phase I trials began in May |
| Brain, digestive tract | $CCK_A$ promoters | Increase availability of certain cellular receptors that reduce appetite when stimulated by cholecystokinin (CCK), a family of hormones and neurotransmitters | Astra Arcus USA; Glaxo Wellcome | Preclinical research |
| | Butabindide | Blocks an enzyme that restores appetite by breaking down CCK. In hungry mice, reduces food intake by 45 percent | INSERM (France) | Preclinical research |
| Digestive tract | Orlistat | Interferes with pancreatic lipase, one of the enzymes that breaks down fat, so that about one third of the fat eaten passes undigested through the body | Hoffmann–La Roche | Phase III trials complete; FDA application expected by late 1996 |
| | Insulinotropin | Synthetic version of the hormone glucagonlike peptide-1, which may improve obesity-related diabetes by slowing stomach emptying and boosting insulin levels | Novo Nordisk (Denmark) | Phase II trials under way |
| Fat | Bta-243 | Binds to $beta_3$-adrenergic receptor on fat cells, increasing the amount of fat in the blood and burned for energy | Wyeth-Ayerst Laboratories | Preclinical research |
| Fat, muscle | Troglitazone | Synthetic version of the hormone 15d-$PGJ_2$, which is produced by fat cells and somehow signals muscle cells to burn fat rather than sugars. May help reverse insulin resistance in obese diabetics | Parke-Davis; Sankyo | Approved in Japan. Phase III trials concluding in U.S.; FDA application expected by late 1996 |
| Entire body | Cytokine regulators | Change the activity of cytokines, hormonelike proteins that act as messengers among cells | Houghten Pharmaceuticals | Phase II trial under way for obesity-related diabetes |

*Drugs generally must clear three types of clinical trials before the Food and Drug Administration will approve them for sale. Phase I trials test a drug's safety, and Phase II trials study its effectiveness, both on a small number of patients. Phase III trials must prove that the drug has acceptable side effects and benefits when given to a large group of subjects.

rate at which fat is burned for energy: pack on the pounds. More fat on the body yields more fatty acids circulating in the bloodstream. That in turn boosts fat oxidation, so that eventually a "fat balance" is reached where all the fat that is eaten is combusted, and weight stabilizes. Many genetic and biological factors can influence the fat oxidation rate and thus affect your settling point in a particular environment.

Olestra, an artificial fat approved earlier this year by the Food and Drug Administration, may change that rate as well. Olestra tastes more or less like an ordinary fat, but it flows undigested through the body. A preliminary study by George A. Bray, Pennington's executive director, suggests that the ingredient may short-circuit passive overconsumption. For two weeks, Bray replaced the natural fat in his subjects' meals with olestra. "They did not compensate at all by eating more food," he reports, adding that "it remains to be seen whether that holds up in longer-term studies."

The fat balance explains in part why settling points vary among people who overeat fat: some oxidize fat efficiently at normal weights; others burn too little until excess pounds force the oxidation rate up. But the model does not by itself explain why some do not overeat at all. To answer that, Flatt has proposed a "glycogen hypothesis."

The human body can store about a day's supply of carbohydrates in the form of glycogen, a simple starch. Glycogen reserves function somewhat like fuel tanks; we partially refill the stores with each meal but rarely top them off. In fact, the range between "empty" and "full" appears to be a matter of individual preference, influenced by such factors as the diversity and palatability of food at hand, social pressures and meal habits. People who are content with lower glycogen levels or who frequently deplete them through exercise burn fat more readily than those who like to keep their tanks full, Flatt suggests. But he concedes that the "crucial link from glycogen stores to appetite remains to be proven."

Researchers need more evidence before they can pronounce either set point

or settling point—or neither—correct. James O. Hill of the University of Colorado Health Sciences Center has begun collecting some of those critical data. He is assembling a registry of the most precious resource in obesity research: the people who have lost a large amount of weight and kept it off for several years without relapse. Hill has already identified about 1,000 such individuals and has begun examining a handful for biochemical clues to their success.

Unfortunately, no current explanation of weight regulation leaves much room for voluntary control; all the metabolic cycles involved are governed subconsciously. Settling-point theory does at least suggest that sufficiently drastic changes in lifestyle might prod the body to resettle at a new weight. But without assistance, changes radical enough to make a difference are evidently uncomfortable enough to be infeasible—for millions of dieters have tried this strategy and failed.

### Getting over the Hump

Increasingly, obesity researchers argue that the most effective assistance they can provide their patients will probably be pharmacological. "The treatment philosophy of the past 40 years, which has been to train patients to eat differently, is simply not going to cure the epidemic of obesity that we see worldwide," asserts Barbara C. Hansen, director of the obesity research center at the University of Maryland School of Medicine.

Untangling the biology beneath body fat has created a plethora of new drug targets that has drawn dozens of pharmaceutical firms off the sidelines [*see table on page 35*]. The potential market is enormous, not only because obesity is common and growing but also because even an ideal drug will have to be taken indefinitely, according to Hansen and others. "Obesity isn't curable," Bray says. "It's like high blood pressure. If you don't take the medication, your blood pressure won't stay down. And if you don't take drugs—or do something—to treat obesity, your weight won't stay down."

Part of the reason for the resurgence of commercial interest is a shift in policy at the FDA, which decided in May to allow the appetite suppressant dexfenfluramine to be prescribed for obesity in the U.S., as it already is in 65 other countries. It is the first weight-loss drug approved in the U.S. in 23 years, and nearly all obesity researchers agree it has been too long coming. The FDA also recently relaxed its guidelines for obesity-drug applications. "As our compromise right now, we're suggesting that a company can present us with two years of data—in some cases, one year if the data look good enough and the company gives us a firm commitment to do follow-up studies under tight controls," says Leo Lutwak, a medical officer with the FDA's Center for Drug Evaluation & Research.

Lutwak admits that with only two years of information, the FDA may approve drugs that turn out to have serious long-term side effects. "The best we can hope for is something like insulin for the treatment of diabetes," Leibel says. Insulin rescues a type I diabetic by replacing a hormone that is missing. "But after 15 years, you begin to have complications of our inability to perfectly mimic the biology," Leibel continues. "If we're lucky, that's the kind of problem we'll face in the treatment of obesity." Lutwak responds that "when that happens, the public will be informed, and they will have to make a decision about whether it is worth it."

If the long-term cost of treatment is unknown, the benefits are becoming clearer, thanks to studies on people who have an operation, called gastroplasty, that reduces the size of the stomach. Although infrequently used in the U.S., the procedure has proved remarkably effective in Sweden. A long-term study there of 1,150 obese patients who underwent gastric surgery found that they typically dropped 66 pounds over two years—88 pounds if a more severe procedure was used—whereas control subjects given standard dietary treatment lost nothing. The surgery cured more than two thirds of those with diabetes, compared with 16 percent cured in the control group. Likewise, twice as many (43 percent) of the hypertension cases were cured by the operation.

Gastroplasty has drawbacks in addition to the risks that always accompany major surgery—principally a high rate of digestive complications. Drug treatments might be better, but Hansen's work with rhesus monkeys suggests that prevention would be best. A decade ago her team began a trial on young adult monkeys, equivalent in maturity to 20-year-old men. The researchers adjusted the animals' food supply so that they neither gained nor lost weight. "In the past 10 years we have had 100 percent success preventing both obesity and type II diabetes," Hansen asserts. "In the control group, which was simply allowed to feed freely on the same diet, half are diabetic. Because everything we know about human obesity is also true of nonhuman primate obesity, that shows you the power of weight control."

It does not, unfortunately, demonstrate a feasible way to achieve it. The NIDDK has launched a program to educate Americans about ways to avoid weight gain, but Susan Z. Yanovski, the program's director, admits that so far it has had little perceptible impact. There is no major lobbying organization for the disease, notes Pi-Sunyer, and the NIH directs less than 1 percent of its research funding at obesity. "Many people seem to be unaware of how big a health problem this is now and how big it is going to grow, particularly when you look at the increasing obesity of children," Yanovski says. Because obese adolescents usually become fat adults, "we're really heading for trouble in another 20 to 30 years," she adds.

At least one grade school intervention has had modest success, knocking a few percentage points off the number of children who turn into overweight adolescents by taking fat out of the children's lunches, giving them more strenuous recreation and educating their parents about weight control. "We have to be very careful about putting children on restrictive diets," Yanovski warns. "That is inappropriate. But we can be more proactive in getting our kids away from the television set, more physically active, riding their bikes instead of being driven everywhere. If people recognize that this is a serious public health problem affecting their children, then maybe they will start taking some action." If not, economists should start adjusting their models now to account for the tremendous health care cost increases that lie ahead. SA

### *Further Reading*


WEIGHING THE OPTIONS: CRITERIA FOR EVALUATING WEIGHT-MANAGEMENT PROGRAMS. Edited by Paul R. Thomas. National Academy Press, 1995.

REGULATION OF BODY WEIGHT: BIOLOGICAL AND BEHAVIORAL MECHANISMS. Edited by C. Bouchard and G. A. Bray. John Wiley & Sons, 1996.

originally published in
August 2002

# The Serious Search for an Anti-Aging Pill

## In government laboratories and elsewhere, scientists are seeking a drug able to prolong life and youthful vigor. Studies of caloric restriction are showing the way

By Mark A. Lane, Donald K. Ingram and George S. Roth

As researchers on aging noted in a position statement this past May, no treatment on the market today has been proved to slow human aging—the buildup of molecular and cellular damage that increases vulnerability to infirmity as we grow older. But one intervention, consumption of a low-calorie yet nutritionally balanced diet, works incredibly well in a broad range of animals, increasing longevity and prolonging good health. Those findings suggest that caloric restriction could delay aging in humans, too.

Unfortunately, for maximum benefit, people would probably have to reduce their caloric intake by roughly 30 percent, equivalent to dropping from 2,500 calories a day to 1,750. Few mortals could stick to that harsh a regimen, especially for years on end. But what if someone could create a pill that mimicked the physiological effects of eating less without actually forcing people to go hungry? Could such a caloric-restriction mimetic, as we call it, enable people to stay healthy longer, postponing age-related disorders (such as diabetes, atherosclerosis, heart disease and cancer) until very late in life?

We first posed this question in the mid-1990s, after we came upon a chemical agent that, in rodents, seemed to reproduce many of caloric restriction's benefits. Since then, we and others have been searching for a compound that would safely achieve the same feat in people. We have not succeeded yet, but our failures have been informative and have fanned hope that caloric-restriction, or CR, mimetics can indeed be developed eventually.

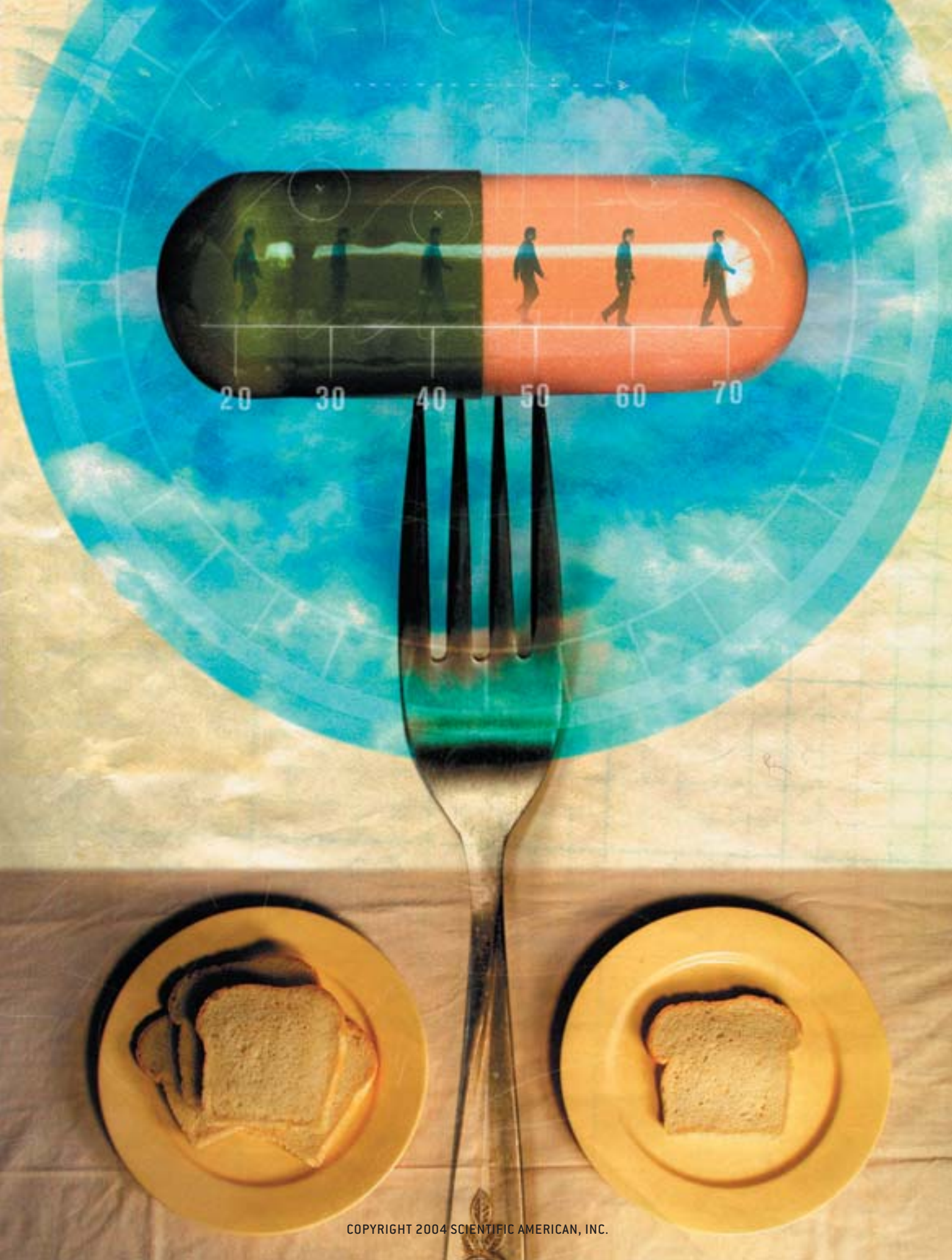
### The Benefits of Caloric Restriction

OUR HUNT FOR CR MIMETICS grew out of our desire to better understand caloric restriction's many effects on the body. Scientists first recognized the value of the practice more than 60 years ago, when they found that rats fed a low-calorie diet lived longer on average than free-feeding rats and had a reduced incidence of conditions that become increasingly common in old age. What is more, some of the treated animals survived longer than the oldest-living animals in the control group, which means that the maximum life span (the oldest attainable age), not merely the average life span, increased. Various interventions, such as infection-fighting drugs, can increase a population's average survival time, but only approaches that slow the body's rate of aging will increase the maximum life span.

The rat findings have been replicated many times and extended to creatures ranging from yeast to fruit flies, worms, fish,

CALORIC-RESTRICTION MIMETIC would, if successful, enable humans to derive many of the health and life-extending benefits seen in animals on restricted diets—without requiring people to go hungry.

STUART BRADFORD



# HOW A PROTOTYPE CALORIC-RESTRICTION MIMETIC WORKS

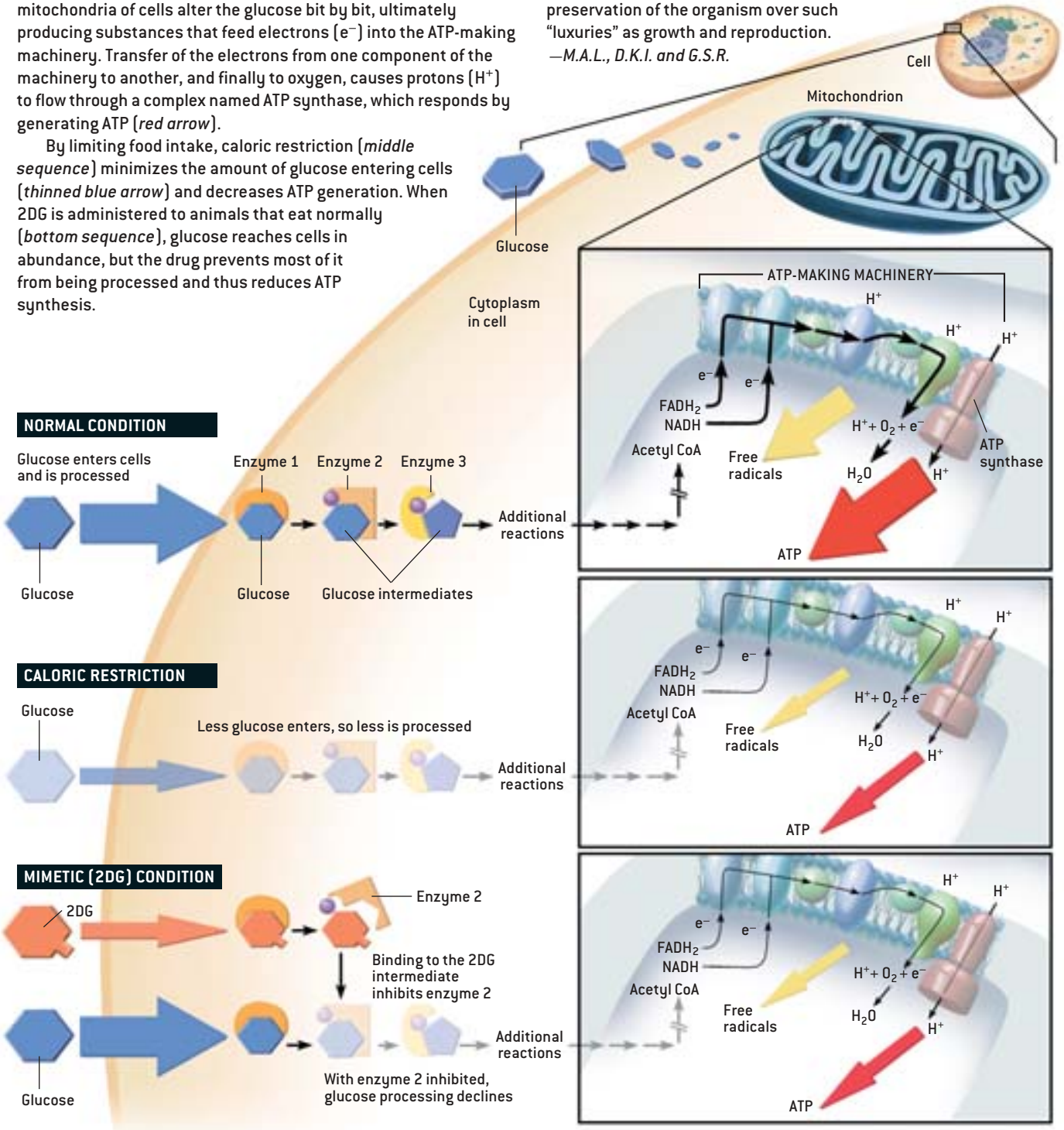
THE BEST-STUDIED CANDIDATE for a caloric-restriction mimetic, 2DG (2-deoxy-D-glucose), works by interfering with the way cells process the sugar glucose. It has proved toxic at some doses in animals and so cannot be used in humans. But it has demonstrated that chemicals can replicate the effects of caloric restriction; the trick is finding the right one.

Cells use the glucose from food to generate ATP (adenosine triphosphate), the molecule that powers many activities in the body (*top sequence*). More specifically, after glucose enters cells (*blue arrow*), a series of enzymatic reactions in the cytoplasm and mitochondria of cells alter the glucose bit by bit, ultimately producing substances that feed electrons ($e^-$) into the ATP-making machinery. Transfer of the electrons from one component of the machinery to another, and finally to oxygen, causes protons ($H^+$) to flow through a complex named ATP synthase, which responds by generating ATP (*red arrow*).

By limiting food intake, caloric restriction (*middle sequence*) minimizes the amount of glucose entering cells (*thinned blue arrow*) and decreases ATP generation. When 2DG is administered to animals that eat normally (*bottom sequence*), glucose reaches cells in abundance, but the drug prevents most of it from being processed and thus reduces ATP synthesis.

Researchers have proposed several explanations for why interruption of glucose processing and ATP production might retard aging. One possibility relates to the ATP-making machinery's emission of free radicals (*yellow arrows*), which are thought to contribute to aging and to such age-related diseases as cancer by damaging cells. Reduced operation of the machinery should limit their production and thereby constrain the damage. Another hypothesis suggests that decreased processing of glucose could indicate to cells that food is scarce (even if it isn't) and induce them to shift into an anti-aging mode that emphasizes preservation of the organism over such "luxuries" as growth and reproduction.

*—M.A.L., D.K.I. and G.S.R.*




TERESE WINSLOW

spiders, mice and hamsters. Until fairly recently, the studies were limited to short-lived creatures genetically distant from humans. But long-term projects under way in two species more closely related to humans—rhesus and squirrel monkeys—suggest that primates respond to caloric restriction almost identically to rodents, which makes us more optimistic than ever that CR mimetics could help people.

The monkey projects—initiated by our group at the National Institute on Aging in the late 1980s and by a separate team at the University of Wisconsin–Madison in the early 1990s—demonstrate that, compared with control animals that eat normally, caloric-restricted monkeys have lower body temperatures and levels of the pancreatic hormone insulin, and they retain more youthful levels of certain hormones (such as DHEAS, or dehydroepiandrosterone sulfate) that tend to fall with age.

The animals also look better on indicators of risk for age-related diseases. For example, they have lower blood pressure and triglyceride levels (signifying a decreased likelihood of heart disease), and they have more normal blood glucose levels (pointing to a reduced risk for diabetes, which is marked by unusually high blood glucose levels). Further, we have recently shown that rhesus monkeys kept on caloric restriction for an extended time (nearly 15 years) have less chronic disease, just as the risk data suggested. They and the other monkeys must be followed still longer, however, before we will know whether low food intake can increase both average and maximum life spans in monkeys: rhesus monkeys typically live about 24 years and sometimes up to 40; squirrel monkeys typically live about 19 years but may live for 28.

## The Journey Starts

BY 1995 WE WANTED to know how the many physiological and biochemical changes induced by caloric restriction led to delaying aging in mammals. For a number of reasons, we suspected that changes in cellular metabolism would be key. By "metabolism" we mean the uptake of nutrients from the blood and their conversion to energy usable for cellular activities. We focused on metabolism in part because the benefits of caloric restriction clearly depend on reducing the overall amount of fuel coming into the body for processing. Also, caloric restriction affects the aging of a wide variety of tissues, which implies that it alters biological processes carried out by all cells. Few processes are more fundamental than metabolism.

We specifically wondered whether changes related to metabolism of the sugar glucose would account for the benefits of caloric restriction. Glucose, which forms when the body digests carbohydrates, is the primary source of energy in the body—that is, it is the main material used by cells for making ATP, or adenosine triphosphate, the molecule that directly powers most cellular activities. We also wanted to know whether alterations in the secretion and activity of insulin, which influences glucose use by cells, would be important. Insulin is secreted as glucose levels in the blood rise after a meal, and it serves as the key that opens cell "doors" to the sugar. We concentrated on glucose and insulin because reductions in their levels and increases in cellular sensitivity to insulin are among the most consistent hallmarks of caloric restriction in both rodents and primates, occurring very soon after restriction is begun.

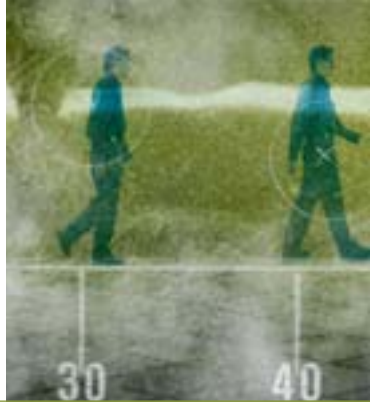
Shortly after we decided to test the hypothesis that caloric restriction retards aging by altering metabolism, others began publishing data showing that metabolic processes involving glucose and insulin influence life span. Such findings encouraged our belief that we were on the right track. For instance, a number of investigations achieved remarkable extensions of life span in nematode worms by mutating genes similar to those involved in molecular responses to insulin in mammals. More recently researchers have found that lowered intake of glucose or disruption of glucose processing can extend life span in yeast. And in fruit flies, genes involved in metabolism, such as INDY (I'm Not Dead Yet), have been implicated in life-span control.

## An "Aha!" Moment

AROUND THE TIME the nematode work came out, we began to scour the scientific literature for ways to manipulate insulin secretion and sensitivity without causing diabetes or its opposite, hypoglycemia. Our search turned up studies from the 1940s and 1950s mentioning a compound called 2-deoxy-D-glucose (2DG) that was being tested in rodents for treating cancer but that also reportedly lowered insulin levels in the blood. As we perused the literature further, we had a true "aha!" moment.

The compound apparently reproduced many classic responses to caloric restriction—among them reduced tumor growth (a response only slightly less robust than the well-known extension of life span), lowered temperature, elevated levels of glucocorticoid hormones and reduced numbers of reproductive cycles. If 2DG really could mimic many aspects of caloric restriction in animals, we

**If 2DG could mimic caloric restriction in animals, perhaps it would do the same for people.**




THE AUTHORS

*MARK A. LANE, DONALD K. INGRAM* and *GEORGE S. ROTH* researched caloric restriction together for many years at the National Institute on Aging of the National Institutes of Health. Lane, who in March became a project manager at Merck and Co., in Rahway, N.J., continues to collaborate with Ingram and Roth as a guest investigator at the NIA. Ingram is chief of the Behavioral Neuroscience Section at the institute's Laboratory of Neurosciences. Roth, who spent nearly 30 years as a full-time researcher at the NIA, is now a senior guest scientist there. He is also chief executive officer of GeroTech, a new biotechnology venture devoted to anti-aging strategies.

# CALORIC RESTRICTION'S VARIED EFFECTS

**Rodents and monkeys on caloric restriction differ from their more abundantly fed counterparts in many ways, some of which are listed below (*a*–*c*). Although the influence of these shared changes on aging remains to be clarified, the close similarities in the responses of rodents and monkeys encourage hope that the health-promoting and anti-aging effects long seen in rodents (*a*–*d*) are universal among mammals, including humans. If so, caloric-restriction mimetics should help people live well longer. The effects marked by capsules (*below*) have been reproduced in rats by the compound 2DG.**

*—M.A.L., D.K.I. and G.S.R.*

**a EFFECTS INDICATIVE OF ALTERED GROWTH, DEVELOPMENT OR METABOLISM**

- Lower body temperatures
- Later sexual maturation
- Later skeletal maturation

**b EFFECTS INDICATIVE OF IMPROVED HEALTH**

- Lower weight
- Less abdominal fat

**c EFFECTS INDICATIVE OF REDUCED RISK FOR AGE-RELATED DISEASES (SUCH AS DIABETES AND HEART DISEASE)**

- Greater sensitivity to insulin
- Lower fasting insulin levels
- Lower fasting glucose levels
- Lower cholesterol and triglyceride levels
- Lower insulin-like growth factor 1 levels
- Higher levels of "good" (HDL) cholesterol
- Slower decline in levels of the hormone DHEAS

**d EFFECTS FOUND IN RODENTS BUT STILL UNDER INVESTIGATION IN MONKEYS**

- Later onset of age-related diseases (including cancer)
- More cell suicide (which may help limit tumor growth)
- Longer average life span
- Longer maximum life span (a strong sign of slowed aging)

thought, perhaps it would do the same for people.

While we were planning our first studies of 2DG, we scanned the literature for details of how it works at the molecular level, learning that it disrupts the functioning of a key enzyme involved in processing glucose in cells. The compound structurally resembles glucose, so it enters cells readily. It is also altered by an enzyme that usually acts on glucose itself. But the enzyme that completes the next of several steps involved in glucose processing essentially chokes on the intermediate produced from 2DG. When it tries to act on this intermediate, it fails; in addition, its ability to act on the normal glucose intermediate becomes impaired [*see illustration on page 39*].

The net result is that cells make smaller amounts of glucose's by-products, just as occurs when caloric restriction limits the amount of glucose going into cells. Certain of these products serve as the raw material for the ATP-making machinery, which is composed of a series of protein complexes located in intracellular compartments called mitochondria. Deprived of this raw material, the machinery makes less ATP. In essence, 2DG tricks the cell into a metabolic state similar to that seen during caloric restriction, even though the body is taking in normal amounts of food. As long as the amount of ATP made meets the minimum requirements of cells, this diminished operation of the ATP-making machinery is apparently beneficial.

Why might reduced functioning of the ATP-producing machinery help combat aging? We can't say with certainty, but we have some ideas. A long-standing theory of aging blames the production of molecules called free radicals. The lion's share of free radicals in the body are emitted as the ATP-making machinery operates. Over time these highly reactive molecules are thought to cause permanent damage to various parts of cells, including the protein complexes responsible for generating ATP. Perhaps by reducing the rate of ATP production, 2DG and caloric restriction slow the rate at which free radicals form and disrupt cells.

The lack of glucose's by-products might retard aging in another way as well. Certain of those substances help to induce cells in the pancreas to secrete insulin after an organism eats. Reductions in the amount of those by-products would presumably limit insulin secretion and thereby minimize insulin's unwanted actions in the body. Aside from indirectly promoting excessive operation of the ATP-making machinery and thus boosting free-radical production, insulin can contribute to heart disease and to undesirable cell proliferation.

We also suspect that cells interpret reduced levels of raw materials for the ATP-making machinery as a signal that food supplies are scarce. Cells may well respond to that message by switching to a self-protective mode, inhibiting activities not needed for cell maintenance and repair—such as reproduction—and pouring most of their energy into preserving the integrity of their parts. If that idea is correct, it could explain why caloric restriction has been shown to increase production of substances that protect

cells from excess heat and other stresses.

This adoption of a self-preservation mode would mirror changes that have been proposed to occur on an organismic level in times of food scarcity. In the generally accepted "disposable soma" theory of aging, Thomas Kirkwood of the University of Newcastle in England has proposed that organisms balance the need to procreate against the need to maintain the body, or soma. When resources are plentiful, organisms can afford both to maintain themselves and to grow and reproduce. But when food is limited, the body invokes processes that inhibit growth and reproduction and takes extra care to preserve the soma.

## Testing Begins

IN OUR FIRST experiments devoted to examining 2DG's effectiveness, we delivered low doses to rats by adding it to their feed for six months. The treatment moderately reduced fasting blood glucose levels (levels measured after food was removed for 12 hours), body weight and temperature, and robustly reduced fasting insulin levels—findings consistent with the actions of caloric restriction itself. Interestingly, after an initial adjustment to the novel diet, the 2DG group did not eat significantly less food than the controls. Thus, these exciting preliminary analyses revealed that it was possible to mimic at least some sequelae of caloric restriction without reducing food intake.

Shortly after we published these results, in 1998, other groups began identifying more ways that 2DG imitates caloric restriction. For example, Mark P. Mattson, then at the University of Kentucky, and his colleagues had reported earlier that caloric restriction could attenuate damage to nerve cells and limit behavioral deficits in rodents treated with compounds toxic to brain cells. When they then treated rodents with 2DG instead of caloric restriction, they observed the same neuronal protection.

At this writing, we are in the midst of conducting long-term rodent trials of 2DG. Results from the first year of this endeavor confirm our previous findings that 2DG slightly reduces blood glucose and body temperature. We are also examining whether 2DG reduces the incidence of cancer and increases life span when fed to animals at low doses from the time they are weaned until they die.

The task becomes finding other substances that yield 2DG's benefits but are safer.

The work so far clearly provides a "proof of concept" that inhibiting glucose metabolism can re-create many effects of caloric restriction. Regrettably, however, 2DG has a fatal flaw preventing it from being the "magic pill" we were hoping for. Though safe at certain low levels, it apparently becomes toxic for some animals when the amount delivered is raised just a bit or given over long periods. The narrowness of the safety zone separating helpful and toxic doses would bar it from human use. We hope this is not a general feature of CR mimetics.

## Moving On

ASSUMING OUR long-term studies confirm that inhibiting metabolism can retard aging, the task becomes finding other substances that yield 2DG's benefits but are safer over a broader range of doses and delivery schedules. Several candidates seem promising in early studies, including iodoacetate, being investigated by Mattson's group, now at the NIA's Laboratory of Neurosciences. In animals this agent appears to protect brain cells from assaults by toxic substances, just as 2DG and caloric restriction do. Treatment with antidiabetic medications that enhance cellular sensitivity to insulin might be helpful as well, as long as the amounts given do not cause blood glucose levels to fall too low.

A great deal of research implicates glucose metabolism in regulating life span, yet other aspects of metabolism can also change in reaction to caloric restriction. When the body cannot extract enough energy from glucose in food, it can switch to obtaining energy in alternative ways. For example, it may shift to breaking down protein and fat. Pharmaceuticals that targeted these processes might serve as CR mimetics, either alone or in combination with drugs that intervene in glucose metabolism. Some compounds that act in those pathways have already been identified, although researchers have not yet assessed their potential as CR mimetics. Drugs that replicate only selected effects of caloric restriction could have a role to play as well. In theory, antioxidant vitamins might fit that bill. Research conducted to date, however, indicates that this particular intervention probably will not extend longevity.

Unlike the multitude of elixirs being touted as the latest anti-aging cure, CR mimetics would alter fundamental processes that underlie aging. We aim to develop compounds that fool cells into activating maintenance and repair activities that lead to greater health and longevity of the organism. That job is difficult but no longer seems impossible. If scientists can develop agents that offer the benefits of 2DG without its drawbacks, they will finally enable people to have their cake—a longer, healthier life—and eat it, too. SA

### MORE TO EXPLORE

**Caloric Restriction and Aging.** Richard Weindruch in *Scientific American,* Vol. 274, No. 1, pages 46–52; January 1996.

**2-Deoxy-D-Glucose Feeding in Rats Mimics Physiological Effects of Caloric Restriction.** Mark A. Lane, George S. Roth and Donald K. Ingram in *Journal of Anti-Aging Medicine,* Vol. 1, No. 4, pages 327–337; Winter 1998.

**Caloric Restriction in Primates and Relevance to Humans.** George S. Roth, Donald K. Ingram and Mark A. Lane in *Annals of the New York Academy of Sciences,* Vol. 928, pages 305–315; 2001.

The position statement on human aging mentioned at the start of this article is available at **http://www.sciam.com/article.cfm?chanID=sa004&articleID=0004F171-FE1E-1CDF-B4A8809EC588EEDF**