Tests begin on drugs that may slow aging

In experiments with mice and other laboratory animals, certain chemicals, caloric restriction and the change of single genes have all brought noticeable increases in life span. Can the same be true for humans?

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It may be the ultimate free lunch — how to reap all the advantages of a calorically restricted diet, including freedom from disease and an extended healthy life span, without eating one fewer calorie. Just take a drug that tricks the body into thinking it's on such a diet.

It sounds too good to be true, and maybe it is. Yet such drugs are now in clinical trials. Even if they should fail, as most candidate drugs do, their development represents a new optimism among research biologists that aging is not immutable, that the body has resources that can be mobilized into resisting disease and averting the adversities of old age.

This optimism, however, is not fully shared. Evolutionary biologists, the experts on the theory of aging, have strong reasons to suppose that human life span cannot be altered in any quick and easy way. But they have been confounded by experiments with small laboratory animals, like roundworms, fruit flies and mice. In all these species, the change of single genes has brought noticeable increases in life span.

With theorists' and their gloomy predictions cast in the shade, at least for the time being, experimental biologists are pushing confidently into the tangle of linkages that evolution has woven among food intake, fertility and life span.

"My rule of thumb is to ignore the evolutionary biologists — they're constantly telling you what you can't think," Gary Ruvkun of the Massachusetts General Hospital remarked this June after making an unusual discovery about longevity.

Excitement among researchers on aging has picked up in the last few years with the apparent convergence of two lines of inquiry: single gene changes and the diet known as caloric restriction.

In caloric restriction, mice are kept on a diet that is healthy but has 30 percent fewer calories than a normal diet. The mice live 30 or 40 percent longer than usual with the only evident penalty being that they are less fertile.

People find it almost impossible to maintain such a diet, so this recipe for longevity remained a scientific curiosity for many decades. Then came the discovery of the single gene changes, many of which are involved in the body's regulation of growth, energy metabolism and reproduction. The single gene changes thus seem to be pointing to the same biochemical pathways through which caloric restriction extends life span.

If biologists could only identify these pathways, it might be possible to develop drugs that would trigger them. Such drugs could in principle have far-reaching effects. Mice on caloric restriction seem protected from degenerative disease, which may be why they live longer. A single drug that protected against some or all the degenerative diseases of aging would enable people to enjoy more healthy years, a great benefit in itself, even if it did not extend life span.

Working with David Sinclair, left, MIT researcher Leonard P. Guarente found a gene that prolongs life span in yeast. PHOTO: NY TIMES NEWS SERVICE

The leading candidates for such a role are drugs called sirtuin activators, which may well be mimicking caloric restriction, in whole or in part. The chief such drug is resveratrol, a minor ingredient of grapes and red wine. Sirtris Pharmaceuticals, of Cambridge, Massachusetts, is now conducting clinical trials of resveratrol, in a special formulation, and of small-molecule drugs that also activate sirtuin but can be given in much lower doses. The resveratrol formulation and one of the small chemicals have passed safety tests and are now being tested against diabetes and other diseases. The Food and Drug Administration does not approve drugs to delay aging, because aging in its view is not a disease.

The sirtuin activators have a strong scientific pedigree. They emerged as the surprising outcome of a quest begun in 1991 by Leonard Guarente of MIT to look for genes that might prolong life span in yeast, a single-cell organism. Working with David Sinclair, now at Harvard Medical School, he discovered such a gene, one called sir-2. People and mice turned out to have equivalent genes, called sirt genes, that produce proteins called sirtuins.

Guarente then found that the sirtuins can detect the energy reserves in a cell and are activated when reserves are low, just what would be needed for a protein that mediates the effects of caloric restriction. Sinclair and colleagues screened a number of chemicals for their ability to activate sirtuin, and resveratrol landed at the top of the list. The chemical was already known as the suspected cause of the French paradox, the fact that the French eat a high fat diet without penalty to their longevity.

The two researchers and their colleagues thus argued that caloric restriction works by activating sirtuins, and so drugs that activate sirtuins should offer the same health benefits.

In 2004 Sinclair co-founded Sirtris with Christoph Westphal, a scientific entrepreneur. Helped by growing interest in the sirtuin story, Westphal was able to sell the company last year to GlaxoSmithKline for US$720 million.

Sinclair says that "the results from the Sirtris compounds are promising and will be submitted for publication in coming months."

But despite the high promise and strong scientific foundation of the sirtuin approach, it has yet to be proved that Sirtris' drugs will work. The first of many questions is that of whether caloric restriction applies at all to people.

Two experts on aging, Jan Vijg of the Albert Einstein College of Medicine and Judith Campisi of the Lawrence Berkeley National Laboratory, argued recently in *Nature* that the whole phenomenon of caloric restriction may be a misleading result unwittingly produced in laboratory mice. The mice are selected for quick breeding and fed on rich diets. A low-calorie diet could be much closer to the diet that mice are adapted to in the wild, and therefore it could extend life simply because it is much healthier for them.

"Life extension in model organisms may be an artifact to some extent," they wrote. To the extent caloric restriction works at all, it may have a bigger impact in short-lived organisms that do not have to worry about cancer than in humans. Thus the hope of mimicking caloric restriction with drugs "may be an illusion," they write.

To decide whether life extension by caloric restriction is an artifact of mice in captivity, why not try it on wild mice? Just such an experiment has been done by Steven Austad of the University of Texas Health Science Center.

Austad reported that caloric restriction did not extend the average life span of wild mice, suggesting the diet's benefits are indeed an artifact of mice in captivity. But others interpret his results differently. Richard Miller of the University of Michigan, says the maximum life span of the wild mice was extended, and so the experiment was a success for caloric restriction.

Laboratory mice are inbred, and researchers can get different results depending on the breed they use. To put the mouse data on a firmer footing, the National Institute on Aging has set up a program to test substances in three laboratories simultaneously. Its first round of candidate agents for reversing aging include green tea extract and two doses of resveratrol.

The resveratrol tests are still under way, but last month the results with another substance, the antifungal drug rapamycin, were published. Rapamycin was found to extend mice's lives significantly even though by accident the mice were already the equivalent of 60 years old when the experiment started.

Rapamycin has nothing to do with caloric restriction, so far as is known, but the study provided striking proof that a chemical can extend life span.

Another result, directly related to the caloric restriction approach, emerged last month from a long-awaited study of rhesus monkeys kept on such a diet. The research was led by Richard Weindruch of the University of Wisconsin. As fellow primates, the monkeys are the best possible guide to whether the mouse results will apply in people. And the answer they gave was ambiguous.

The monkeys who had spent 20 years on caloric restriction were in better health than their normally fed counterparts, and suffered less diabetes, cancer and heart disease, apparently confirming that caloric restriction holds off the degenerative diseases of aging in primates as well as rodents.

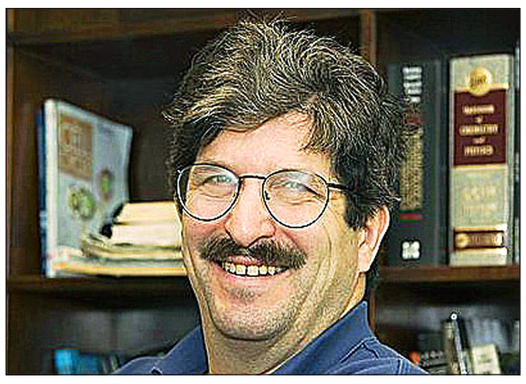
But as for life span, the diet extended life significantly only if the researchers excluded deaths that were apparently unrelated to aging, such as under the anesthesia necessary to take blood samples. When all deaths were counted, life span was not significantly extended.

Some researchers think it is perfectly valid to ignore such deaths. Others note that in mouse studies one just counts the numbers of dead mice without asking what they died of, and the same procedure should be followed with monkeys, since one cannot be sure if a death under anesthesia might have been age related.

With the rapamycin and rhesus monkey results, Sinclair said, "We have more weight on the side of people who think it's going to be possible." He emphasized the ability of both caloric restriction and sirtuin-activating drugs to postpone the many diseases of aging, at least in mice. To have one drug that postponed many degenerative diseases in people would be a significant advance, he said, even without any increase in longevity.

People may live so long already that no drug could make much of a difference. Probably because of reductions in infant mortality and other types of disease, human life expectancy in developed countries has been on a remarkable, unbroken upward trend for the last 160 years. Female life expectancy at birth rose from 45 years in 1840 to 85 years in 2000.

An important difference among experts on aging is whether there is an intrinsic rate of aging. Supposing there were cures for all diseases, what would one die of, if one died at all? Vijg and Campisi believe there is a steady buildup of damage to DNA and to proteins like the collagen and elastin fibers that knit the body together. Damage to DNA means that the regulation of genes gets less precise, and this regulatory drift disrupts the stem cells that repair each tissue. Even if all disease could be treated, it is not clear that anything could overcome intrinsic aging.



Above: Gary Ruvkun of the Massachusetts General Hospital says experimental biologists looking for ways to extend human longevity should ignore the gloomy predictions of evolutionary biologists.
Top: Studies suggest that resveratrol, a substance found in red wine, can prolong life span. PHOTOS: NY TIMES NEWS SERVICE

Miller, on the other hand, said he believes that no clear distinction can be made between disease and other frailties of aging. "Anything a doctor can charge for we call disease, but wrinkled skin, white hair or not feeling good in the morning, these we don't call disease," he said.

He said he thinks that the idea of intrinsic aging is not well defined and that contrary to the theories of the evolutionary biologists, there may be simple ways to intervene in the aging process.

In the view of evolutionary biologists, the life span of each species is adapted to the nature of its environment. Mice live at most a year in the wild because owls, cats and freezing to death are such frequent hazards. Mice with genes that allow longer life can rarely be favored by natural selection. Rather, the mice that leave the most progeny are those that devote resources to breeding at as early an age as possible.

According to this theory, if mice had wings and could escape their usual predators, natural selection ought to favor longer life. And indeed the maximum life span of bats is 3.5 times greater than flightless mammals of the same size, according to research by Gerald Wilkinson of the University of Maryland.

In this view, cells are so robust that they do not limit life span. Instead the problem, especially for longer-lived species, is to keep them under control lest they cause cancer. Cells have not blocked the evolution of extremely long life spans, like that of the bristlecone pine, which lives 5,000 years, or certain deep sea corals, whose age has been found to exceed 4,000 years.

Some species seem to be imperishable. A tiny freshwater animal known as a hydra can regenerate itself from almost any part of its body, apparently because it makes no distinction between its germ cells and its ordinary body cells. In people the germ cells, the egg and sperm, do not age; babies are born equally young, whatever the age of their parents. The genesis of aging was the division of labor in the first multicellular animals between the germ cells and the body cells.

That division put the role of maintaining the species on the germ cells and left the body cells free to become specialized, like neurons or skin cells. But in doing so the body cells made themselves disposable. The reason we die, in the view of Thomas Kirkwood, an expert on the theory of aging, is that constant effort is required to keep the body cells going. "This, in the long run, is unwarranted — in terms of natural selection, there are more important things to do," he writes.