

Youthful Pursuit

Researchers Seek Key to Antiaging In Calorie Cutback

**A Controversial Hypothesis Draws Scientists, Investors;
Will It Work in Humans? Fighting Fat in Lab Mice**

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In the 1930s, researchers stumbled onto a surprisingly simple way to slow the biological forces of aging: cutting normal calorie intake by about a third. Scientists found it boosts animals' life spans by 30% to 40%, and considerable evidence suggests that calorie restriction, or CR, would slow human aging too.

But only steely ascetics could hack its hunger pangs. So the finding remained a little-known curiosity in the back halls of science.

Now a coterie of scientists and biotech ventures are rekindling interest in CR as they try to mimic its antiaging effects with medicines. It is still a highly speculative quest, and many researchers fret that it hasn't completely shaken its association with centuries of dubious nostrums to slow aging, from inhaling virgins' breath to eating gold to implanting monkey glands.

Much of the new focus is on a substance in red wine called resveratrol. The interest in it started three years ago when a group led by Harvard Medical School biologist David Sinclair reported that it boosted yeast cells' life span by 70% via a mechanism resembling CR. He later co-authored a study showing that it also boosts life span in fruit flies and roundworms. But his tendency to make bold leaps based on tentative data has also sparked intense controversy. One big question: Does he really understand the workings of CR well enough to mimic them in a drug?

Last spring, Italian scientists reported that resveratrol boosted life span more than 50% in a kind of short-lived fish. Intriguingly, fish on resveratrol had much faster swimming speeds as they aged, and spent far more time moving around, than did undosed control fish.

At least two groups of researchers are now testing whether resveratrol can extend life span in mice -- the first such studies in mammals. At a meeting of the American Aging Association in June, Dr. Sinclair and colleagues presented preliminary results from a study showing that resveratrol had "CR-like protective effects" against the buildup of fatty deposits in the livers of mice on high-calorie diets. That suggests that resveratrol could lead to new drugs for diseases of aging associated with rich diets, such as adult-onset diabetes.

A company that Dr. Sinclair co-founded in 2004, Sirtris Pharmaceuticals Inc., of Cambridge, Mass., has begun testing a resveratrol-based drug in diabetic patients. It has raised \$82 million from venture capitalists, a hefty sum for an early-stage biotech. (Sirtris's chief executive, Christoph Westphal, is married to a reporter for this newspaper.)

It faces competition from Elixir Pharmaceuticals Inc., also based in Cambridge, which Dr. Sinclair's former mentor, Massachusetts Institute of Technology biologist Leonard Guarente, co-founded in 1999 to develop drugs based on gene variants that slow aging. The niche also includes [BioMarker Pharmaceuticals](#) and LifeGen Technologies, both of which focus on mimicking CR with drugs.

The companies hope to develop therapies for diseases, not antiaging pills. One reason is that the Food and Drug Administration doesn't recognize aging as a problem warranting treatment. But if a drug could retard aging, it might delay the onset and possibly the progression of age-related diseases. "When you slow aging," says University of Illinois epidemiologist S. Jay Olshansky, "you push a host of diseases to later ages at one fell swoop -- cancer, heart disease, Alzheimer's, diabetes, as well as everything else that's negative about growing older."

Some researchers believe antiaging drugs could also improve health in late life -- rather than prolong misery -- letting people stay in relatively good shape until a swift demise. Their case rests partly on the svelte, energetic look of old animals on CR. "Often it's hard to identify the cause of death" in post-mortem studies on such animals, says Richard Weindruch, a University of Wisconsin CR researcher. "The only apparent problem is that they died."

THE BATTLE AGAINST AGING

Key antiaging medical advances:

- **1935:** Cornell scientists report calorie restriction's antiaging effect in rodents.
- **1956:** University of Nebraska researcher proposes that "free radicals" cause aging, indicating that antioxidants may slow it.
- **1989:** U.S. and British scientists propose that calorie restriction triggers an evolutionarily ancient "starvation response" to slow aging.
- **1992:** University of California at San Francisco researchers find a gene mutation that doubles life span in roundworms.
- **1996:** Southern Illinois University scientists report gene mutation that extends life span in mice.
- **2000:** MIT's Leonard Guarente and colleagues report that "SIR" genes actuate calorie restriction's antiaging effects in yeast.
- **2003:** Harvard's David Sinclair and others report that resveratrol, a substance in red wine, extends yeast life span.
- **February 2006:** Italian scientists report resveratrol extends life span of a fish species.

Still, some experts on aging doubt that enough is known about CR to guide the development of drugs that mimic its effects. "We know a lot about CR's effects," says Edward Masoro, a leading gerontologist. "But what bothers me is that I don't think we've figured out CR's basic mechanism yet."

Dr. Sinclair's idea that resveratrol mimics CR has come under heavy fire. His main adversaries are two researchers who used to rub elbows with him when they all studied together with MIT's Dr. Guarente. The skeptics maintain that resveratrol's mode of action is still murky; instead, they are looking at other mechanisms that may account for how CR works.

The resveratrol doses used in the life-span-extension studies in animals were far higher than the amount people can get by drinking wine -- they were roughly equivalent to hundreds of glasses a day. Resveratrol is available as a dietary supplement, but to replicate the doses used in the studies, a person would need to take scores of pills a day. (Sirtris says it is developing prescription drugs that work like resveratrol but are hundreds of times more potent.) The dietary supplements haven't been tested in clinical trials, so their efficacy isn't proven, nor is it clear what

dose might make people live healthier or longer. And although they seem safe at modest doses, megadoses may not be.

Nevertheless Dr. Sinclair, a 37-year-old Australia native, thinks taking small doses over time may yield health benefits and has been taking the supplements for three years.

The story of resveratrol has its roots in scientists' increased understanding of CR. In 1989 researchers theorized that it activates a "starvation response" whose genetic machinery evolved eons ago to enable survival through periods of food shortage -- such as droughts -- by retarding the rate of aging. The response blocks growth and reproduction in order to free up energy to slow aging. The energy is siphoned to cellular systems that limit damage from harmful "free radical" molecules and other toxins produced as metabolic byproducts in cells.

The theory explained longstanding mysteries about CR, such as the fact that animals on CR become resistant to toxic chemicals and temporarily lose the ability to reproduce. It also had a dismaying implication: Our obesity-fostering, high-calorie diets are putting us in fast-aging-and-reproducing mode. That may be why childhood obesity is closely linked to early puberty, which now begins before age eight in many girls, and why adult obesity is linked to such a wide swath of aging diseases -- cancer, heart disease, diabetes, arthritis, even Alzheimer's.

But an important piece of CR's machinery remained hidden: the activator that senses calorie intake and, when it is low, triggers cellular changes that retard aging. This CR off-on switch is the holy grail of gerontology, the study of aging. In principle, drugs that turn it on could ward off or ameliorate degenerative diseases of aging, just as CR does in animals.

Many scientists are looking for the switch. And to the consternation of some of them, Dr. Guarente, 54, and Dr. Sinclair assert that they know what it is. Further, Dr. Sinclair's research indicates that resveratrol toggles it in order to slow aging. Their shared view on CR's basic mechanism has sparked a furious debate.

Its roots go back to 1991, when Dr. Guarente's lab at MIT began hunting for life-span-boosting mutations in baker's yeast.

The grandson of Italian immigrants, Dr. Guarente grew up in Revere, Mass., a blue-collar town near Boston. In his memoir "Ageless Quest," he recalls that as a child, "I was precocious by local standards -- I quit smoking in third grade."

By the mid-1990s, Dr. Guarente's lab had zeroed in on so-called SIR, or silent information regulator, genes. SIR mutations enabled yeast cells to divide an abnormally large number of times before dying, a form of extended life span. But how they worked wasn't clear until the group made further discoveries, one of which was Dr. Sinclair's first claim to fame.

Dr. Guarente recalls that Dr. Sinclair, who came to MIT in 1995 to do post-doctoral studies, breezed into his lab as if out of a Crocodile Dundee movie, greeting everyone with a cheery, "Hello, mate." The eldest son of parents who both worked in medical diagnostics, he was known in high school as a talented class clown and risk-taker, a kid who aced science classes but got in trouble for setting off minor explosions in chemistry lab. The idea of taking part in unorthodox, high-risk studies on aging suited him.

In a key experiment, Dr. Sinclair showed that yeast cells' machinery for copying chromosomes runs amok as the cells age, eventually killing them. Hailed as a major advance, the discovery got Dr. Guarente on Good Morning America. It also helped him formulate a theory positing that proteins made by SIR genes activate CR's antiaging action. A SIR gene found in mammals, dubbed SIRT1, seems especially important: It makes a protein that Drs. Guarente and Sinclair

believe triggers the slowed-aging mode in mammals when calorie intake is low. In their view, it's either the gerontological grail or a crucial part of it -- hence, stimulating it might slow aging.

Drugs that juice up proteins' activity are very rare. But in 2003, Dr. Sinclair, then at Harvard, heard that scientists at Biomol International LP, a Plymouth Meeting, Pa., biotech firm, had observed signs of SIRT1 activation in test-tube experiments with certain plant compounds. The most promising one was resveratrol. That was doubly exciting, for dozens of studies on the red-wine ingredient had previously suggested that it lowered the risks of heart disease, cancer and various other disorders of aging -- just what a substance that slows aging should do.

Dr. Sinclair soon began the study about resveratrol's effects on yeast aging. But a year after it appeared, studies by other researchers cast doubt on the idea that SIR genes are key actuators of CR.

The sharpest questions were raised by two researchers who also studied under Dr. Guarente: University of Washington biologists Brian Kennedy and Matt Kaeberlein. Their data suggest that CR can exert antiaging effects independently of SIR genes, and that other genes are more central to CR -- at least in yeast. "My view is that CR probably has nothing to do" with SIR genes in lower animals, says Dr. Kaeberlein. In short, according to him, Drs. Guarente and Sinclair haven't necessarily found the grail.

Undaunted, Dr. Sinclair joined forces with a researcher at the National Institute on Aging, Rafael de Cabo, to plan one of the ongoing studies of resveratrol in mice. But he had a problem: He lacked the \$20,000 needed to buy mice. Then he got a call out of the blue from Tom LoGiudice, foreman at the U4EA ("euphoria") Ranch near Thousand Oaks, Calif. Mr. LoGiudice had phoned on behalf of the ranch's owner, Harman Rasnow, who was considering taking resveratrol pills and wanted to know more about them. When Mr. LoGiudice heard about Dr. Sinclair's problem, he arranged for his boss to talk directly to the researcher. "I have an 85-year-old passion for longevity," says Mr. Rasnow, pinpointing his age. "David sounded like he was really onto something. So I told him, 'I'll send you a check for \$20,000.' "

Dr. Sinclair later got another call from Mr. LoGiudice, this time inviting him to make a pitch for funding to one of Mr. Rasnow's wealthy acquaintances, Paul Glenn, a venture capitalist and a longtime supporter of research on aging. After Dr. Sinclair did so, the Glenn Foundation for Medical Research in Santa Barbara, Calif., awarded \$5 million to Harvard Medical School to launch a center on the basic mechanisms of aging with Dr. Sinclair as its founding director. Now plans are afoot to expand the center into a leading institute on aging, says Mr. Glenn, with start-up funding of \$75 million to \$100 million.

Sirtris, the company Dr. Sinclair co-founded, says it has made progress. Test-tube and animal studies suggest that its early-stage drugs may help treat various neurological killers as well as diabetes, says Dr. Westphal. The company plans soon to begin testing a drug in people with MELAS syndrome, a rare metabolic disorder that afflicts youngsters with potentially fatal brain and muscle deterioration. At a recent meeting on aging research, a Sirtris scientist reported that SIRT1-activating compounds, including resveratrol, dramatically lowered blood levels of glucose and insulin in mice that get diabetes on high-fat diets, as well as helped to keep their weight down -- just as CR does.

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