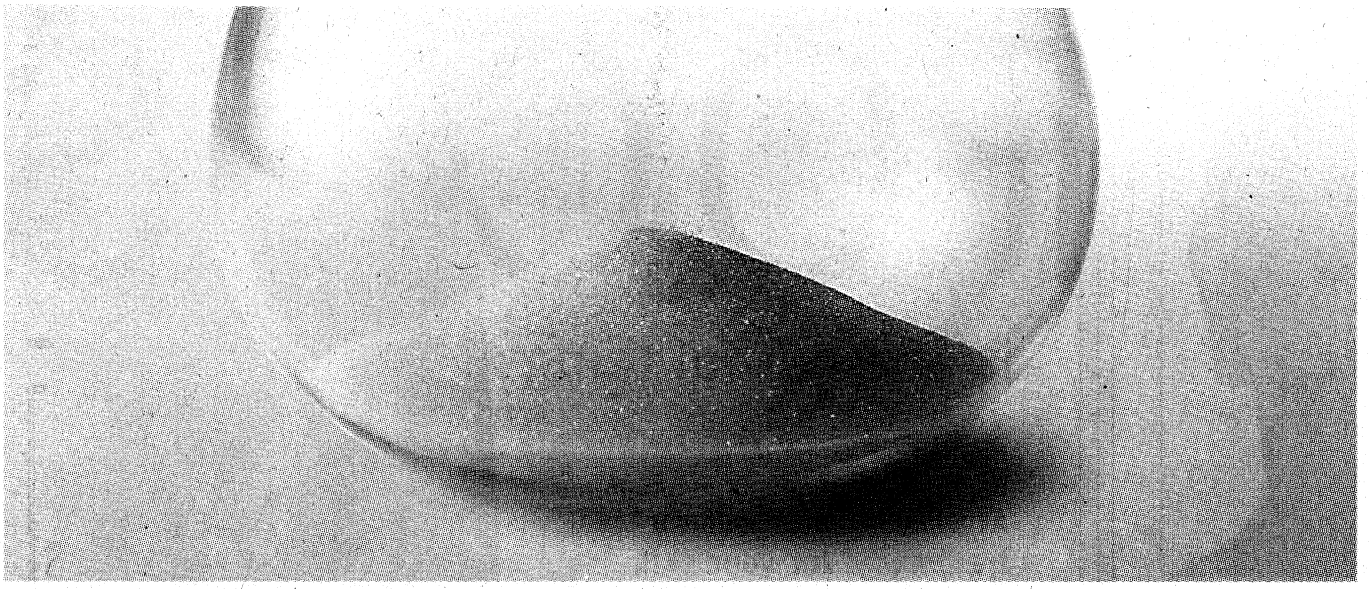
Los Angeles Times, December 25, 2006 Monday HEALTH/section F; Page 1

CAN WE LIVE LONGER?



YAMADA TARO *Getty Images*

As more people hit the century mark and beyond, scientists search for the key. Genes, diet and inflammation are just some of the clues.

By ANDREAS VON BUBNOFF
and CHRISTIE ASCHWANDEN
Special to The Times

CENTENARIANS were a rare breed when Jeanne Louise Calment was born in 1875. But by the time she died in 1997 at the record-setting age of 122 years and 164 days, her club was distinctively less elite.

Today, centenarians comprise the fastest-growing segment of the population. In developed countries, their numbers have been doubling every five to seven years, and the age that they achieve has been rising steadily — from 110 in 1930 to 120 in 1995.

Trailing along in their impressive wake, the less-remarkable folks are doing better too. The average U.S. life expectancy has been increasing for more than 100 years and hit a record high in 2004: 80.4 years for women and 75.2 years for men.

Just how long can this go on?

It is a matter of fierce debate. Scientists aren't sure if we will ever be able to expand human life span to 100 years or beyond for *most* people, not just the lucky few favored by genes and environment. They're also divided on whether science will [*See Life span, Page F7*]

Los Angeles Times, December 25, 2006 Monday HEALTH/section F; Page 7(1)

[*Life span, from Page F1*]
come up with a pill or other remedy that lets people break through what seems like a biological barrier unbreachable by even the Calments of this world.

The answers are intertwined with one of the most basic biological mysteries: why creatures, be they humans, rats or rhinos, all wither and die. That riddle is yet to be solved — but scientists are gathering tantalizing clues.

Just last month, a study reported that mice manipulated to have a slightly lower body temperature live longer than mice with a regular body temperature. Another reported that a substance found in red wine — resveratrol — extended the life span of overfed, obese mice.

A slew of theories on aging have been suggested over the centuries. Some people, turning to the Bible, believed it was moral transgression. Others — from ancient Greece to the 19th century — held that aging came from a progressive loss of heat, moisture or both.

Today, scientists are focusing on a few leading contenders — such as damage to cells and tissues from highly active chemicals called free radicals, chronic inflammation, a built-in limit to the number of times our cells can divide, or a slow, steady stiffening of tissues by a lifetime of exposure to sugar.

All of these are only theories at this point — albeit with some science to support each of them, says Dr. Robert Butler, president and chief executive of the International Longevity Center, a not-for-profit think tank in New York City. None has reached the point where it can fully explain aging.

Tantalizingly, scientists have discovered that they can extend life span in animals by restricting how much they eat: In rats and mice, a 30% reduction in caloric intake extends life span by a third.

And they've found that tinkering with certain genes allows rodents and other animals to also live longer.

The clues inside

One gene they're interested in is known as Sir2: Increasing the number or activity of Sir2 genes in fruit flies and worms can extend their life span by 30% to 50%, says MIT researcher Leonard P. Guarente. He says he's now testing whether the same is true in mice.

The Sir2 gene appears to play a key role in extending life span when animals restrict their calories, at least in worms, yeast and flies. Thus, understanding the human version of the gene should offer clues as to why we wither and die.

As it turns out, that gene directs formation of a key enzyme that senses how much immediate energy body cells have to sustain themselves with — and if those levels are low, it activates emergency stress responses.

Researchers are now looking for drugs that can increase the activity of that enzyme. If they're able to do so, and if the drugs act as they hope they will, "I believe we will break [the 122-year age] limit," says David Sinclair, an associate professor of pathology at Harvard Medical School.

They have made some headway. Three years ago, Sinclair's lab discovered that resveratrol, a compound found in red wine and grape skins, seems to activate that enzyme. A study in February showed that feeding resveratrol to fish extends their maximum life span by 59%.

Another study, published in the journal Nature in November, showed that obese mice — which normally have shortened life spans — can live just as long as lean mice if they're fed resveratrol. The mice had healthier livers and heart tissue, more normal blood sugar levels and the agility of lean mice.

This doesn't mean resveratrol's an anti-aging elixir. It's unclear if the chemical would have the same effects in humans. And even if it did, people would have to ingest it in huge doses — on the order of dozens of supplement pills or hundreds of bottles of red wine a day, says Joseph Baur of Harvard Medical School, lead author of the obese-mouse study.

Sinclair (who is a cofounder of Sirtris Pharmaceuticals Inc., a Cambridge, Mass., company seeking chemicals that act like resveratrol) says he takes resveratrol himself. "I am doing it as a personal experiment, but I certainly wouldn't recommend anyone else to do it," he says. "We don't know what the long-term effects are, and the products that are currently available are untested."

Adds Susan Roberts, a nutrition researcher at Tufts University, "I think you would be nuts to take it until we have more data."

Sirtris is one of a few companies seeking compounds that can do what resveratrol does with much more clout. Sirtris has started clinical trials in diabetes patients with an improved version of resveratrol that's 10 to 20 times more powerful to test its safety and see if it can normalize blood sugar, says Chief Executive Dr. Christoph Westphal. In about a year, he says, Sirtris plans a trial to test the safety of a compound 1,000 times more potent than resveratrol.

The goal is not necessarily to increase human life span, Westphal says, but to treat age-related sicknesses such as Alzheimer's and diabetes.

Studies in worms, flies and mice have unearthed other genes that can affect life span, such as ones in fruit flies called *SOD* and *methuselah* and another, in mice, called P66.

Some of the genes are involved in the repair of cell damage. This fits nicely with a theory that aging is a side effect of turning food into energy, which creates free radicals that damage tissues, proteins and DNA. The idea gets further support from a study, to be published in January, by Dr. Richard A. Miller, a researcher who studies aging at the University of Michigan. He has found that skin cells from longer-lived rodents are more resistant to free radical damage than cells from shorter-lived rodents.

There are other genes too. In mice, several genetic mutations are known to result in lower levels of a protein called insulin-like growth factor 1 (IGF1), and some of these mutant mice live 50% longer than normal mice. Scientists also see longer life spans when tinkering with similar genes in roundworms and flies.

One reason could be stress-resistance: Cells from mice with less IGF1 can better resist damage from free radicals or heavy metal poisoning, Miller says. (Worms with such mutations are more stress-resistant also, he adds.)

These findings could one day result in life-expanding drugs, says aging researcher Andrzej Bartke, director of geriatric medicine at the Southern Illinois University School of Medicine in Springfield, Ill.

Bartke, who studies mice with lower-than-normal IGF1 levels, says companies are currently trying to develop drugs that inhibit the hormone as a possible cancer treatment — but "from what we see in these mice with low IGF1, I wouldn't be surprised if they get drugs that turn out to be an anti-aging substance."

Studying the source

Centenarians — for obvious reasons — are being intensively studied for the clues they may offer about aging.

If they're doing something right, Dr. Nir Barzilai, who studies centenarians at the Albert Einstein College of Medicine in New York, says he hasn't found their secret yet. So far, he's asked 400 of them all kinds of questions about the way they live their lives, and "I don't have anything to tell you," he says. They don't seem to live more healthful lives. Among the 400, he hasn't found a single vegetarian. This bugs his research coordinator, who is a vegetarian herself, he says. "She has almost made it her ambition now to find one."

It is mostly genes that protect the oldest of the old, Barzilai says. Scientists know that having a close centenarian relative increases the chance of getting that old ten- to twentyfold — up from 1/10,000 for the general population.

Researchers are only beginning to pinpoint the genes that may be at play.

Barzilai, for example, has found that centenarians are more likely to have a version of a gene that protects them from inflammation, and make lesser amounts of an inflammatory protein called CRP. Their children have less hypertension, heart attacks, strokes, lower insulin levels and less diabetes than children of non-centenarians — implying that their resistance to aging is genetic, at least in part.

Barzilai also found evidence that structures on the end of their chromosomes — the structures that harbor the DNA in our cells — may differ from those of people who don't live as long. These so-called telomeres tend to become shorter every time a cell divides and are thought to set a limit to the number of times cells in the human body *can* divide. Centenarians' white blood cells have longer telomeres than those of most 85-year-olds, Barzilai found — and their children have longer telomeres than age-matched controls.

Barzilai isn't sure how to interpret these findings. "I don't know how it works, but [telomeres] are at least a marker of *something*," he says.

It may be kind of depressing to hear that the key to extreme old age — until, that is, someone comes up with a magical pill — has largely to do with luck and genes. But there is one key way in which scientists think people may be able to extend their lives: by eating dramatically less.

Rats, fed about 40% less rodent chow than what they would normally eat, live about 40% longer than is usual — 47 months instead of 33. The same has been found for mice, hamsters, fruit flies, worms, fish and spiders.

If the same could be achieved in humans, the results would be impressive, the University of Michigan's Miller says. "A 40% increase would have the average woman living to about 112, and many past 126, and a few past 140," he says.

So far, there is no proof that a similar extension of maximum lifespan *is* possible in our species. But rhesus monkeys and humans whose calories are restricted — in experiments in the case of the monkeys and by choice in the case of human beings — do seem healthier and show fewer signs of aging.

For example, rhesus monkeys fed 30% fewer calories get fewer cancers and are less prone to develop diabetes.

Richard Weindruch, a professor of medicine at the University of Wisconsin who directs the monkey study, says he expects the monkeys, who were started on the diet when they were young adults, to become 10% to 20% older than normal monkeys.

Caloric restriction also seems to be healthful for humans, as exemplified by faddists who have been inspired by the data on worms and rodents and decided to try it for themselves.

A January 2006 study of 25 caloric restriction enthusiasts published in the Journal of the American College of Cardiology found that people who eat about 30% fewer calories have more flexible hearts that look 10 to 15 years younger and also had lower blood levels of inflammation-linked proteins. This suggests that caloric restriction reduces inflammation, which usually increases with age and makes tissues stiffer, says principal author Dr. Luigi Fontana at the Washington University School of Medicine in St. Louis.

Chronic inflammation is linked to many age-related diseases such as cardiovascular diseases, diabetes, neurodegenerative diseases and osteoarthritis, says inflammation researcher Dr. Claudio Franceschi of the University of Bologna, Italy.

And there are other tantalizing data. Recently, a six-month clinical trial in Baton Rouge, La., randomly assigned a dozen people to eat 25% fewer calories and another dozen to eat normally. The study reported a number of health gains in those eating less: lower body temperatures (which could result in production of fewer free radicals) and lower insulin levels, thus better sugar control. Both of these factors have been linked to longer life span in epidemiological studies.

The insulin difference may be especially important, because poor sugar control can lead to accelerated stiffening of tissues.

Participants in the trial also had higher levels of "good" (HDL) cholesterol in the blood and decreased DNA damage from exposure to free radicals, says Eric Ravussin, a researcher at the Pennington Biomedical Research Center in Baton Rouge, who led the trial.

The study found no adverse effects such as bone loss or, for women, abnormal menstrual cycles. The researchers next plan a larger, two-year trial.

This may all sound wonderful, but not everyone is convinced that caloric restriction can induce the same life-span extension in humans as it does in animals.

For one thing, most people — unlike the enthusiasts — probably wouldn't start doing it before midlife and wouldn't do it as intensely, says John Speakman of the University of Aberdeen in Scotland. Animal studies show that the later you start and the less you restrict, the less of a benefit you get, he says.

"By the time people start thinking, 'Oh my god, I am going to die soon,' they are probably going to be in their 40s," Speakman says.

In fact, in a paper to be published soon, he has calculated that a 15% caloric restriction for four decades after the age of 39 would only add an extra 2.4 years. This is not exactly fountain-of-youth material.

Others say the effects in humans would not be as strong as in mice even if people did it all their lives and did it properly. Jay Phelan, an evolutionary biologist at UCLA, says that men in Okinawa eat almost 20% less their entire life than other Japanese men but live less than a year longer. He's extrapolated these data to what would be expected if people ate 35% less for their entire life. He found it would only extend the average lifespan by about 2 years.

"What it tells me," he says, "is that humans aren't just mice blown up to 200 pounds."

Phelan says he doesn't think there will ever be a way to significantly extend human life span. "Millions of years and billions of people living a variety of lifestyles that result in life spans that never exceed 122 demonstrate that it is unlikely that some new method will dramatically extend this," he says.

Of course, all could change if scientists find a drug that can work on the very process of aging and somehow force a pharmaceutical wrench into its works. But even if we do find a drug that lets all of us live to be Jeanne Louise Calment, or perhaps even to an age that makes Calment seem youthful, would we — should we — take it?

"I wouldn't take it," says aging researcher Leonard Hayflick of UC San Francisco. "We all relate to each other with respect to the other person's age," he says. "If my aging stopped and my wife's continued, the discontinuities in our lives would be intolerable."

Los Angeles Times, December 25, 2006 Monday; Page F7(3)

Small advantage?

As scientists sift through factors linked to aging, they've encountered a curiosity: that size and height may be somehow linked to life span.

They've found, for instance, that mice whose bodies have low levels of a protein called IGF1 not only live longer — they're also smaller than regular mice.

This makes some sense, because IGF1 is known to regulate bone and muscle growth, stimulate cells to divide and protect them from dying. Less of it *should* result in smaller mice.

But it's not the only hint that a smaller body size could be related to longer life span. Small dogs live longer than large dogs, as a rule, perhaps because of differences in IGF1. In fact, body size might even play a role in the human life span.

Back in 1992, Thomas Samaras, a former aerospace engineer living in San Diego, published a study arguing that short people have a life-span edge — reporting that shorter baseball players tend to live longer than taller ones.

"He took a lot of beating for this," says Andrzej Bartke, director of geriatric medicine at the Southern Illinois University School of Medicine in Springfield, Ill. "And now the field is slowly coming around to see that he was probably onto something."

Dr. Nir Barzilai, who studies centenarians at the Albert Einstein College of Medicine in New York, has found that female offspring of centenarians are 1 inch shorter, on average, than age-matched controls. What's more, 3 of 100 centenarians he has looked at have mutations that affect IGF1 function.

— ANDREAS VON BUBNOFF

BRANDI SIMONS *Associated Press*

HIGH MARKS: *Otis Clark, 103, and Phyllis Whitchurch, 102, celebrated Oklahoma's centennial recently. Average U.S. life span has risen steadily for more than a century and hit a record high in 2004.*