Genetic research spurs thoughts of biblical life spans

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BOSTON, Massachusetts (AP) -- A young man climbs from bed, stares into a mirror and glimpses his future.

He has just turned 34. His body is trim, his hair thick and dark. But what's that around his eyes? Those crow's-feet are getting harder to ignore. And do his teeth look a bit ground down by decades of chewing, or is it his imagination?

He will probably repeat the same check tomorrow, and tomorrow, and tomorrow -- about 16,000 more times if he, like the average American, dies at around 80. "I don't think 80 years is long enough. There's a lot of things I want to do," he laments.

But what can he -- or anyone -- do about getting old? He can't stop it, any more than he can dispel rain clouds roiling on the horizon, any more than ancient alchemists could distill a real elixir of immortality.

Or can he?

Elixir Pharmaceuticals' Stevan Obradovic studies DNA from centenarian blood samples

His name is David Sinclair. He is biologist at Harvard Medical School. His job is to prevent aging.

Catapulted by advances in biotechnology, scores of researchers have begun to pinpoint genes that may prolong human life while delaying its late-stage diseases, frailties and maybe even gray hair and wrinkles. Their remarkable successes in laboratory animals -- like worms that live four times longer than normal -- have already germinated several drug companies. They hope to develop compounds to stretch healthy lifetimes beyond limits once presumed to be fixed.

Some respected researchers envision millions living as long as Jeanne Calment of France, who died at age 122 in 1997. Tom Johnson, a University of Colorado geneticist, thinks people could one day live to 350 years old, spanning the ages like Methuselah and the other biblical patriarchs.

"I am absolutely convinced we are going to be able to extend human life," Johnson says. "This is not science fiction."

Under the best circumstances, a life-prolonging drug could conceivably arise in five years, says longevity guru Cynthia Kenyon, a molecular geneticist at the University of California-San Francisco.

While enthusiastic about distant prospects, some others predict only modest advances for the near future, because aging is such a fundamental and complex process. "I think it would be sensationalist and crazy to think we'd be seeing people living to 120, 130," argues Thomas Perls, a Boston University aging specialist who studies the genetics of centenarians.

In truth, no one knows for sure what can be accomplished or how soon. However, for the first time in human history, an intense and methodical quest is under way to turn off aging with proven science, instead of snake oil.

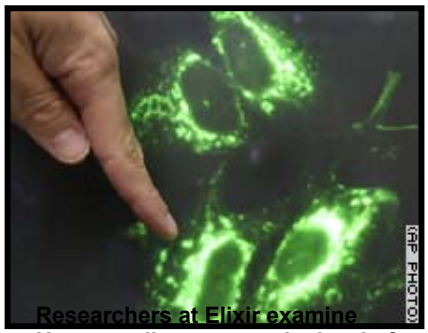
A biological trigger switch

Whatever else they accomplish, the hyperdriven, often brash scientists in this new field of aging genetics are already challenging the classic theories of aging and disease.

For centuries, aging has been understood as a scattered, chaotic, inevitable breakdown of the body and its organs. Like a car with too many miles, it eventually wears out. You can keep fixing parts, but others soon break down.

There was special reason for doubt in the genetic approach to slowing aging. Evolutionary theory dictates that we inherited genes that most helped our ancestors reach sexual maturity, not ones that helped or hurt them afterward.

If so, a genetic trigger for aging would be a long shot, except for one thing.



Researchers at Elixir examine Human cells to gauge the level of a protein made by certain genes, which may hold promise for extending life.

At first, it was more of a biological curiosity. In the 1930s, Cornell University nutritionist Clive McCay discovered that underfed rats live a lot longer than others. Just cut calories by about 30 percent, balance their diet, and they survive about 40 percent longer or more. The technique works in fish, fleas, and other species, and early data suggest it works in monkeys too, say researchers at the University of Wisconsin and the National Institute of Aging.

Underfeeding has revealed a second remarkable power: It keeps animals healthy, largely free of aging ailments like cancer and heart disease. They stay strong and energetic. They even keep more fur.

"On one side, the calorie-restricted mice are jumping, and running around, and looking young," says **Stephen Spindler**, a biochemist who does such experiments at the University of California-Riverside. "On the other side, the litter mates look old. They're gray, and they have more balding. They move less. It makes me want to go on a diet."

Even if it proved to work in people -- still an open question -- few would likely tolerate such a Spartan diet.

Maybe dieting isn't necessary, though. Researchers suspected that the effects of underfeeding point to some built-in biological switch after all: a set of master genes that can delay aging. Could they be found? And could their effect be mimicked by a drug that boosts or blocks the right proteins, the soldier molecules that do the work assigned by genes?

Kenyon, of the University of California-San Francisco, knew of a microscopic roundworm that, when starved or overcrowded, slips into suspended animation. In this hardened condition known as dauer, it can hold out for months. It would otherwise die within about three weeks.

This state is directed by a gene, daf-2, that controls growth by helping manufacture an insulin-like hormone. Kenyon wondered if worms with disabled variants of this gene might turn into spry, wiggly Methuselahs. In her tests, they did. Similar manipulations worked in flies and mice. A raft of such discoveries in the 1990s helped legitimize the new field of aging genetics.

"Aging had been cast kind of into the trash heap of biology, particularly in molecular terms. There's nothing much you can do about it, so what's the point?" says Kenyon, a 40-something dynamo who talks in a teenager's rapid-fire bursts and gives her age as 150.

Over the past 15 years, researchers have discovered several dozen genes that prolong life significantly in yeast, roundworms, fruit flies and mice. As in underfed animals, they appear to put off not just death, but the hobbling conditions of old age.

Most of these genes carry deadpan scientific monikers: p66shc, ctl-1, Lamin A. Others were mercifully christened in whimsy like age-1, clock, Methuselah, and INDY -- for "I'm Not Dead Yet," a name inspired by a line from a Monty Python movie.

Many longevity genes first tracked in animals have human counterparts. Other genes were first spotted in humans.

Nerve researcher Gabrielle Boulianne, of the University of Toronto, was studying one of them in 1998. She was researching amyotrophic lateral sclerosis, the degenerative nerve condition known as Lou Gehrig's disease. It had been linked to a gene known as SOD1, which treats metabolic waste products. Since fruit flies carry a twin gene, she transplanted and supercharged the human gene in their nerve cells, hoping to develop a research model for the disease.

What happened next was unforeseen: The flies lived an average of up to 40 percent longer. "In some respects, I was shocked," Boulianne says. "That was not the original goal."

Gatekeeper genes

Already, longevity genes are beginning to answer some big questions, as they flag the likely mechanisms of aging.

In keeping with underfeeding experiments, some of these genes help resist environmental threats, like food shortages, overheating or infection. Some slow down metabolism or boost its efficiency. Others help recondition the body's protein building blocks or reduce the destruction of gene-degrading free radicals. Still others make hormones that control growth and cell division, a process that goes awry in cancer.

Many of these genes, like gatekeepers, open or close access to other genes. At the Massachusetts Institute of Technology, Lenny Guarente -- Sinclair's mentor -- is pursuing a gatekeeper gene common to mice and humans, SIRT1. It is tied to several players implicated in aging: sugar metabolism, hormone signaling, and cellular death.

In theory, such genes can block the chemical messengers that spur aging ailments like cancer, heart disease and Alzheimer's. These researchers dream of one pill that fits all.

"It's a new way in thinking about diseases," says Guarente, a lanky 51-year-old with an impish smile who looks like he may have already found an aging secret and tried it.

Elixir Pharmaceuticals, which he co-founded in Cambridge, Massachusetts, plans to test several drugs in animals. Since its early days in 2001, it has raised $36.5 million and grown to a staff of about 30, according to CEO Edward Cannon.

He acknowledges it's still unclear how to move a longevity drug to market. Given even the paltry human life span now, the thorough testing required by the U.S. Food and Drug Administration would take too long. Cannon says the first longevity drugs might be approved for specific diseases of aging, but prescribed more broadly by some doctors to prolong life.

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-- Tom Johnson, geneticist

"It's a great business opportunity," says **Xi Zhao-Wilson**, CEO of a competitor, **Biomarker Pharmaceuticals** in Campbell, California. "The market is huge, we know that."

Some executives say their longevity products might be marketed first for pets or as human dietary supplements, allowing makers to skirt full-blown human testing. It's a market where claims are sometimes made on shaky grounds, but the longevity companies say their products would be based on solid science.

Some biologists worry that likely side effects are being undersold already. They say that nearly any drug that alters the workings of a powerful master gene will probably stir up unintended effects. They warn of infertility, sluggish metabolism or weakened immunity.

Longevity researcher Steven Austad at the University of Idaho says all aging genes found so far would do harm "not necessarily apparent in the laboratory."

Yet he felt confident enough to bet a colleague $150, on a lark, that someone born by 2000 will be alive and well in the year 2150. Assuming that person wouldn't be either of them, the two scientists banked their combined $300 to pay the winner's descendants when the bet is decided.

By then, the pot is estimated at $500 million, thanks to something that only gets better with time: compound interest.

Taking Austad's bet was sociologist S. Jay Olshansky, an authority on aging demographics at the University of Illinois-Chicago. "You get many of these gene jockeys grossly exaggerating and extending the work done on invertebrates and other organisms to ... humans," he says. But even he holds great hope for the field in the long run.

Some scientists and scholars say it's already time to start considering how to handle the profound impact long-life drugs would have on society. Will they tack on extra years of sickness to the bonus years of health, overwhelming the medical system? Can society create enough jobs for older workers and support retirees longer?

Political scientist Francis Fukuyama, on The President's Council on Bioethics, says such problems beg for discussion because a proven longevity drug would be "almost impossible to stop."

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