NEWS

The Quest to Reverse Time's Toll

Scientists and entrepreneurs are optimistic to varying degrees about prospects for extending the human life-span

Tom Johnson has a way to get rich quick, if he wants to: Go into the business of grinding up his worms for snake oil. Johnson studies aging at the University of Colorado, Boulder; his work with nematodes has revealed that changing a single gene can dramatically increase the worm's life-span. Some years ago a clinic in Guadalajara, Mexico, proposed that he supply them with extracts from long-lived nematodes to rejuvenate elderly patients. "I get two or three similar offers a year," says Johnson.

Aging research is hot these days. And so is a commercial "antiaging" movement that is being fueled by demographics as millions of baby boomers hit their 50s. "Aging is probably the process that humans have most tried to conquer for our entire history," says Johnson. The difference today is "we now know that we can alter aging."

Scientists have known for decades that a very low calorie diet extends life in some species. Recently they have begun to directly manipulate the mechanisms of aging with gene alterations that substantially extend the life-span of fruit flies, nematodes, and mice. Using markers generated by the Human Genome Project, researchers expect to come up with a flood of new candidates for genes influencing the processes of aging. These discoveries, and the promise of more to come, have spawned a host of new companies dedicated to reversing aging's toll.

George Roth, chief of molecular physiology and genetics at the National Institute on Aging (NIA), counts about 40 recent scientist-run start-ups, most of them looking for life-extending genes—and many of which have already fallen by the wayside. There's also bustling commerce in antiaging products ranging from vitamin supplements to potentially dangerous hormone preparations that purport to reverse diseases of aging. Some merchants try to give their products a veneer of plausibility by citing recent research with telomeres, antioxidants, or hormones. Scientists such as zoologist Steven Austad of the University of Idaho in Moscow are wary. When groups interested in life extension ask him for advice, "I tend to avoid them like the plague. ... I don't want to end up on their Web site."

Seeking youth. Oscar Wilde's *The Picture of Dorian Gray* represents an eternal human goal.

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Researchers as entrepreneurs

But nowadays everybody's in the game. "I would be surprised if any legitimate biogerontologist did not have some commercial affiliation," says pioneering aging researcher Leonard Hayflick, now a consultant to Genentech in South San Francisco.

One way they hope to make money is by looking at those who survive to extreme old age. Centenarians seem to be healthier than most old people: Witness Frenchwoman Jeanne Calment, the oldest person on record, who died in 1997 at 122. Last year, Thomas Perls of Beth Israel Deaconess Medical Center in Boston, director of the New England Centenarian Study, with molecular geneticists Louis M. Kunkel and Annibale A. Puca of Children's Hospital, Boston, founded a company called Centagenetix that is scanning the genomes of his subjects to find genes that set them apart.

Leonard Guarente of the Massachusetts Institute of Technology is coming at the problem from a different starting point: yeast. Several years ago he found a gene called *Sir2* that, when its expression was increased, extended yeast's life-span. Guarente believes different organisms may share some universal survival-promoting mechanisms—and *Sir2* may be one of them. He's so optimistic that he has founded a company, in partnership with Cynthia Kenyon, a nematode researcher at the University of California, San Francisco, called Elixir, to see if they can make an aging retardant from the gene product.

Roth of NIA is looking for a guaranteed blockbuster. He's involved in a company called GeroTech, the goal of which is to make a "calorie restriction mimetic"—a drug to make your body think you're starving even while you're eating normally. Roth says he already has encouraging results from restricting monkeys' calories: One of his subjects has lived to 38 instead of the usual 25.

The biggest player in the antiaging research industry is Geron Corp. in Menlo Park, California, which has numerous patents on telomerase, the enzyme that restores telomere length. Telomeres shorten as cells age and lose their ability to divide. Calvin Harley, chief scientific officer, says Geron's researchers have shown that they can transplant aging human skin cells, the telomerase in which has been activated, onto immunocompromised mice, where they behave like young cells. The company is also working on both gene and drug therapies for telomerase activation in age-related diseases.

Despite the heady possibilities, some researchers caution that longevity probably comes with a downside. "We evolved in a high-hazard environment with disease, food shortages, droughts, accidents—enormous selective pressure to get the job done fast," observes George Martin of the University of Washington, Seattle. "You have genes to make you develop rapidly, have progeny early. There was no need to develop robust quality-control mechanisms allowing you to live beyond reproduction."

Mechanisms that serve the youthful organism may precipitate aging or disease later on, notes Martin, who is also editor-in-chief of the Science of Aging Knowledge Environment (*Science*'s SAGE KE, sageke.sciencemag.org). Human growth hormone, for example, a favorite of antiaging hucksters, affects metabolism and physiological indicators such as muscle mass. But it also creates undesirable side effects, such as raised glucose levels, and may even shorten life. Other mechanisms are also two-edged. Telomerase is implicated not just in cell renewal but cancer. Even the cancer-fighting *p53* gene, when up-regulated, has been found to hasten aging in rats (*Science*, 4 January, p. 28). "It's difficult to retard aging without affecting something else," says Austad. "Genes evolve in a certain context be-

cause they do something well at that level of expression. If you soup them up, there's always a price to pay."

On the edge

S. Jay Olshansky, a biodemographer at the University of Illinois, Chicago, cautions that researchers should be careful of the company they keep. "There is so much money to be made," he says, that he and others are "really concerned" that some scientists "have either crossed the line or are about to cross the line."

That line is not always clear, and reputable scientists may differ on where it should be drawn. For example, the Life Extension Foundation (LEF), based in Fort Lauderdale, Florida, sells a vast assortment of products from vitamins to a product called pregnenolone that is said to contain "brain-boosting nutrients that function via a variety of mechanisms to correct the molecular devastation that aging inflicts on the brain." It had a long-running battle with the Food and Drug Administration over its claims. (A court eventually ruled in LEF's favor.)

LEF also funds research, including tests of possible longevity compounds on mice by Richard Weindruch of the University of Wisconsin, Madison, and Stephen Spindler of the University of California (UC), Riverside. Spindler, who is still at UC, is now chief technical officer of a LEF-founded company called LifeSpan Genetics, which uses gene chips to study the ability of compounds to mimic genomic effects of calorie restriction.

Former NIA researcher Richard Cutler has an association with a company that Olshansky and Austad, at least, find distinctly problematic. Cutler, who studies antioxidants, compounds that prevent damage to cells from byproducts called free radicals, now works at Kronos, a reputable nonprofit in Phoenix, Arizona, devoted to uncovering some of the secrets of aging. He also advises a company called Youngevity in Carrollton, Texas, which touts products containing a mix of "miracle minerals" captured from the waters of Vilcabamba, Ecuador, whose denizens "live their lives in a state of youthfulness." The Youngevity Web site cites his research as evidence that antioxidants can "significantly extend our health span," although Cutler readily acknowledges that antioxidant supplements would benefit only a minority of people with oxidative stress from circumstances such as infectious diseases. "Youngevity makes a strong sell, that's true," he says. "I've been asked [by Kronos] to quit. I probably will." He told *Science* he will ask Youngevity to use more accurate wording. Cutler's boss at Kronos, Mitch Harman, was distressed when he learned that Cutler's name was still on the Youngevity Web site: "I'm trying to do legitimate research and get tarred with the same brush."

CREDIT: STR/AP

Special genes? Oldest documented human, Madame Calment, at 122.

Cutler stands firmly with his scientific colleagues, however, in distancing himself from the 7-year-old American Academy of Anti-Aging Medicine, founded by physician Ron Klatz. "Practical immortality"—that is, living maybe a few hundred years if we want—is the group's ultimate goal, according to Klatz, who told *Science* that "antiaging medicine has been smeared by the gerontology establishment, [which is] perfectly comfortable with the concept that aging is immutable." The group, which claims to have 10,000 physician and scientist members, refers the public to antiaging clinics and products and offers physicians certification in "antiaging medicine." Olshansky says he goes to the annual convention in Las Vegas "to collect information on the latest antiaging quackery."

If it's "antiaging," he notes, it's quackery by definition. Some potions and elixirs may indeed have some effect on aging's manifestations, but they don't touch the still-mysterious processes at the core. Figuring out those processes will drive research—and many commercial endeavors—for years to come.

–CONSTANCE HOLDEN

Cracking the Secrets of Aging

It's hard to fight senescence, scientists admit, because "we still don't know how to define aging per se," says former National Institute on Aging head Robert Butler, now director of the U.S. branch of the International Longevity Center in New York City. Theories abound, however, including the accumulation of cell damage (from oxygen free radicals and environmental toxins) and glycation (stiffening of tissue with formation of sugar-protein bonds). Another is the progressive shortening of telomeres, the tips of chromosomes, as cells divide. Scientists are still not sure whether aging is a unitary phenomenon—the result, perhaps, of a predictable pattern of altered gene expression—or "a set of processes that happen to occur in rough synchrony," says Richard Miller of the University of Michigan Institute of Gerontology in Ann Arbor.

Meanwhile, the life-extending effect of calorie restriction offers researchers tantalizing clues. It's been replicated in a number of species, including spiders: Those fed about two-thirds of their regular diet lived longer, and dogs and rodents experienced later onset of diseases of aging, including arthritis and cancer. Scientists speculate that calorie restriction triggers a mechanism that probably evolved at times of food shortage, changing a variety of gene functions that affect parameters such as glucose levels and body temperature so the body goes into a conservation mode. Some believe it works by slowing down energy utilization and its "wear and tear" on cells.

Even if researchers can figure out ways to slow the aging process, opinion varies on the ultimate limits to human life-span. S. Jay Olshansky, a biodemographer at the University of Illinois, Chicago, says that "anything past 130 is ridiculous." But William Haseltine of Human Genome Sciences in Rockville, Maryland, thinks stem cells will ultimately prove the route to virtual immortality. In an interview last year with Fool.com, Haseltine predicted that it will one day be possible to "reseed the body with our own cells that are made more potent and younger, so we can repopulate the body."

Nematode man Tom Johnson of the University of Colorado, Boulder, is also optimistic. There are no "aging" genes, he notes, because natural selection washes its hands of an organism once it has passed the age of procreation. "The very absence of an evolutionary reason to die makes it relatively easy to manipulate life-span," he says. "If humans are as malleable as worms, we could see life-spans of 350."

But the picture is obscured because there are no "biomarkers" for aging—such as a biochemical that predictably changes in level with age—as there are for, say, cancer or diabetes. Gray hair, which correlates about 0.7 with age, is still "as good as you could do" for a marker, says gerontologist Leonard Hayflick. At this point, the most reliable biomarker for aging is death.

–C.H.