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Prolonging Life

Should scientists try to increase the human lifespan?

The number of elderly Americans is rising sharply. More than 1 million people will be at least 100 years old by 2050 — up from just 50,000 centenarians in 2000. With more and more Americans living longer, policymakers worry that Social Security and Medicare costs will drain money from health and education programs for the young. Meanwhile, researchers are trying to prolong life even more, making old age a time of health and activity, not sickness and frailty. Some envision a future when people routinely live in good health to 100 or longer, aided, perhaps, by drugs that turn on "longevity" genes, newly discovered secrets of long-lived people and even computer chips and tiny robotic devices implanted in humans to help them remain vigorous. But many gerontologists and ethicists argue that the human body is far too complex for such drastic changes and that scientists should focus on improving health care for all Americans, not increasing longevity.

José Temprana celebrates his new citizenship with a kiss in Miami on June 29, 2007 — at age 105. Born in Cuba, he was a sponge diver and lobster fisherman before he was jailed for 30 years for opposing Fidel Castro. He fled to Florida after his release.

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MANAGING EDITOR: Thomas J. Billitteri
tjb@cqpress.com

ASSISTANT MANAGING EDITOR: Kathy Koch
kkoch@cqpress.com

CONTRIBUTING EDITOR: Thomas J. Colin
tcolin@cqpress.com

ASSOCIATE EDITOR: Kenneth Jost

STAFF WRITERS: Marcia Clemmitt, Peter Katel

CONTRIBUTING WRITERS: Sarah Glazer, Alan Greenblatt, Barbara Mantel, Tom Price, Jennifer Weeks

DESIGN/PRODUCTION EDITOR: Olu B. Davis

ASSISTANT EDITOR: Darrell Dela Rosa

FACT CHECKER: Michelle Harris

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Prolonging Life

By Beth Baker

The Issues

Edith Furstenberg lives in her own apartment in a Baltimore retirement community. She has to use a walker now, but overall she is healthy and feels positive about life at her age. She's 103.

"The good things are that you can still enjoy life, and like food, and like to meet people," she says. "I have enough money to not worry about my next meal or where I'm going to sleep."

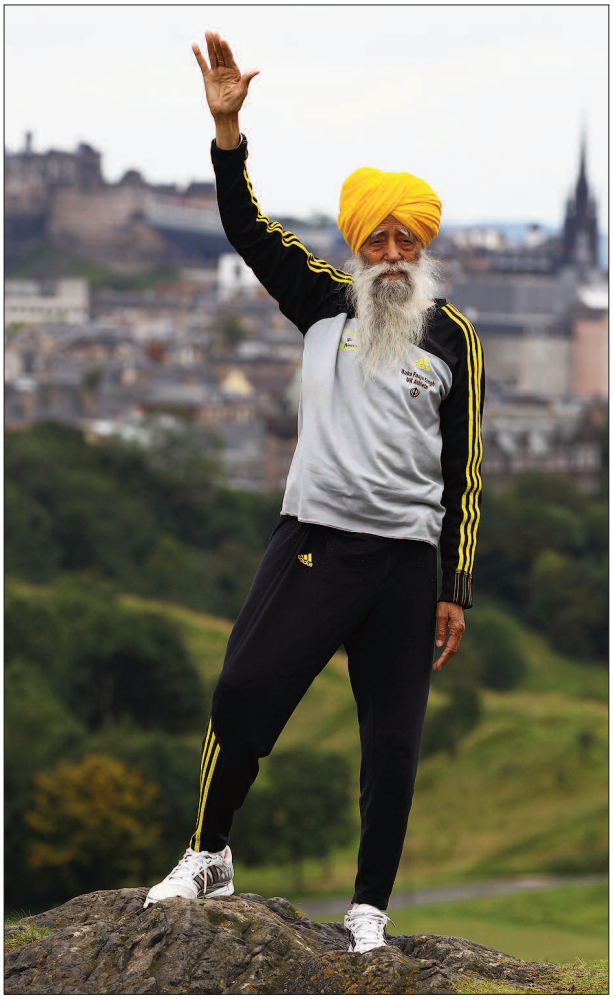
Centenarians like Furstenberg are now the fastest-growing age group in the United States. By 2050 the United States will have an estimated 1.1 million centenarians, up from just 50,000 in 2000. [1]

Not all will be doing as well as Furstenberg.

Dorothy Barnthouse, for example, celebrated her 100th birthday in June in the Kansas nursing home where she has lived for seven years. Extremely frail, her memory all but gone, she has no diagnosable disease and takes no medication, says her daughter, Anne Baber.

But her mother is nearly deaf and has no friends. "I think it's a horrible life," says Baber, who regularly visits.

The expected growth in centenarians is part of a continuing, dramatic increase in the number of elderly Americans. Yet even as politicians and policymakers worry about their impact on Social Security and Medicare costs, many researchers hope to expand the ranks of centenarians even more significantly.



Getty Images/Jeff J. Mitchell

Century-old Fauja Singh, an Indian-born Sikh, is the first runner to officially enter next year's Edinburgh Marathon. With seven 26-mile marathons under his belt since his 89th birthday, he says it will be his last. In the United States, where life expectancy has been steadily rising, more than 1 million people are expected to be at least 100 years old by 2050 — up from just 50,000 centenarians in 2000.

Meanwhile, gerontologists, bioethicists and demographers are wondering how successful scientists will be and whether having millions more very old people benefits either individuals or society.

The biology of aging — biogerontology — was once a backwater of research, but today it's hot. "This is the amazing golden age of biology," comparable to Einstein's golden age of physics, says Woodring E. Wright, a professor of cell biology at the University of Texas Southwestern Medical Center. "The molecular biology revolution that started in the 1970s is realizing its potential now. The tools that we have and the pace at which things are being discovered are exploding. It's mind-boggling."

Scientists are delving into the changes that occur at the cellular and molecular level as people age. Researchers have discovered that dozens of gene mutations may be associated with longevity, and they are testing new compounds for their effects on aging and diseases of the elderly.

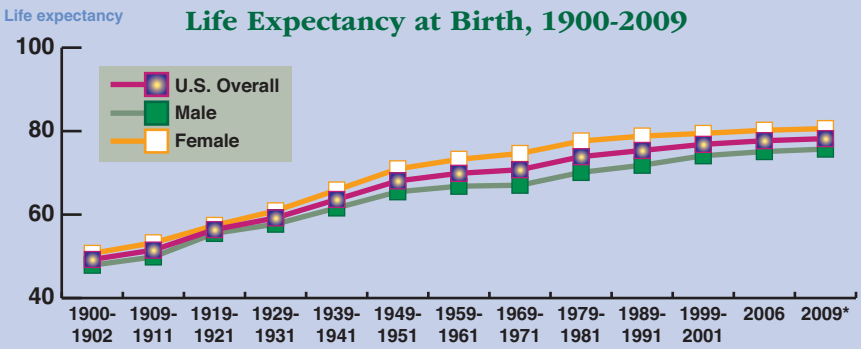
Many researchers share the goal of "compressed morbidity" — keeping people healthy until a ripe old age, when they would die painlessly and quickly. Reaching that goal, though, is extremely difficult. Researchers at the University of Southern California found that as life expectancy continues to rise, the length of time that older people are sick or disabled increases. In fact, the average number of healthy years has actually decreased since 1998, they found. [2]

The answers to basic questions about aging are not fully understood. Why do people age, and can the process be manipulated? What is the role of genes in aging? Will average life expectancy continue to grow? Can the maximum human lifespan — now about 120 — be significantly increased?

The questions are not just theoretical. Understanding the basic mechanisms of aging is fundamental to determining if older people's vulnerability to age-related diseases —

U.S. Life Expectancy Rose Steadily

Americans born today can expect to live to 78 — nearly 30 years longer than a century ago. Scientists attribute the increase largely to medical advances and improved access to public health measures. Life expectancy for females is five years longer than males'. Healthier habits and stronger social connections may help women live longer.



** Preliminary data*

Sources: Elizabeth Arias, "United States Life Tables, 2006," National Vital Statistics Reports, *Centers for Disease Control and Prevention, June 2010, www.cdc.gov/nchs/data/nvsr/nvsr58/nvsr58_21.pdf; Kenneth D. Kochanek,* et al., *"Deaths: Preliminary Data for 2009,"* National Vital Statistics Reports, *Centers for Disease Control and Prevention, March 2011, www.cdc.gov/nchs/data/nvsr/nvsr59/nvsr59_04.pdf*

including cancer, heart disease, Alzheimer's and diabetes — can be altered. At the same time, accurately projecting life expectancy influences planning for Social Security, Medicare and Medicaid, which helps shape today's discussions over tax policy and the federal deficit.

To better answer these questions, researchers look at aging in biological rather than chronological terms. "Aging is a biological process and not a disease," says S. Michal Jazwinski, director of the Center for Aging at Tulane University in New Orleans. "Aging is characterized by the decline in the ability of the organism to withstand stress, damage and diseases." That decline can occur at different ages for different individuals.

When people are younger, the body can keep up with normal wear-and-tear that occurs from everyday processes such as metabolizing food. Over time, though, damage to the cells accumulates and the familiar signs of aging appear: gray hair, wrinkles and difficulty reading small print. Even before those outward manifestations, though, aging is well under way. At age 20 the lung tissue begins to stiffen and rib cage muscles to shrink. Contraction of the thymus gland, important in the immune system, begins in the first few years of life, and by age 30 most of the decline has occurred. After reproduction, the body's natural repair mechanisms cannot keep up with the cellular decline that comes with aging.

"Aging is wear and tear minus repair," as Walter M. Bortz, M.D., clinical associate professor of medicine at Stanford University, puts it. [3]

But what causes this decline? Why are some like Edith Furstenberg still enjoying life at 103, while most die closer to 80?

"There's not a clearly identified single mechanism that underlies or mediates aging," says Richard J. Hodes, director of the National Institute on Aging. "On one end [of the spectrum] are those who think that aging reflects a series of largely random events over a period of time. . . . On the other are those who think aging is a biologically programmed event. It's hard to imagine that the truth isn't a combination of these two."

Throughout history, most people did not live long enough to reach old age. Death was usually accidental and quick. It came, for example, from an attack by a saber-toothed tiger, an infection or childbirth. In the United States, average life expectancy in 1900 was only about 45. Old age was much rarer than today, and high childhood mortality kept the average low.

U.S. life expectancy is now about 78 — 75 for men, 80 for women. [4] But it varies considerably by region, race and economic status, with the poor and least educated dying earlier than others.

Much of the increase in life expectancy over the 20th century stemmed from advances in public health, such as cleaner air and water, as well as improved maternity care and vaccines and antibiotics for infectious disease.

More recently, advances in modern medications and procedures such as coronary bypass surgery and kidney dialysis again extended lives. Whether the rise will continue is hotly debated in gerontology circles. (*See "At Issue," p. 821.*)

Many researchers believe that because old age is a relatively recent phenomenon, there is no genetic program that instructs the body to age. Instead, they view aging as a byproduct of advances in medicine and public health — or, as geriatrics researcher Bruce Carnes of the University

of Oklahoma calls it, living past "our biological warranty."

Biogerontologist Leonard Hayflick, a professor of anatomy at the University of California, San Francisco, says the question is not, why don't humans live longer, but rather why do they live so long past reproductive maturity? In other words, once child rearing is over and children have left home, why do people keep on living for decades? The answer, Hayflick says, is that to ensure survival of the species to reproductive maturity, all animals — including humans — evolved with excess capacity, much like a wristwatch with a one-year warranty that might keep ticking well beyond 365 days.

Other scientists believe that the aging process is not so random, but instead is influenced by genetic regulation and evolution.

Whether or not there is a genetic program for human aging, most researchers agree that genetic mutations influence individual longevity. Nir Barzilai, director of the Institute for Aging Research at Albert Einstein College of Medicine in New York City, has been following nearly 500 Ashkenazi Jews — those of Eastern European descent — ranging in age from 95 to 109. In a recent study, he and his colleagues found that these very old people did not have healthier behaviors than others of their age in a national survey group. [5] Only 43 percent of men in the study group reported regular moderate physical activity, for example, compared to 57 percent in the comparison group.

Barzilai was not surprised by the results. "I have a woman who is 107 years old now," he says. "She's been smoking for 95 years. People say, then it must be the diet. What diet? Chicken fat?"

He believes the answer lies in mutations of genes associated with longevity that are two or three times more common in centenarians than in people who don't live so long. Scientists estimate that up to a third of longevity is determined by genetic variations and two-thirds by environment and lifestyle.

The message, says Barzilai, is not that healthy behaviors don't matter. Not smoking, eating right and exercising help protect most people from illness. But those who hit the genetic jackpot might live healthily past 100 no matter their lifestyle.

Whether living longer means more years of health or sickness is the question gerontologists hope to answer. "The big challenge of our time will be, is aging a resource or a liability?" says Bortz, who is 80. "Are [elderly people] going to suck energy from our communities and governments, or are we going to add to it?"

Here are other key questions being debated by citizens, policy-

U.S. Ranks 50th in Life Expectancy

The average American can expect to live to age 78, placing the United States 50th worldwide in life expectancy at birth. Japan ranks first among industrialized nations, or about 15 years more than the global average. Scientists say genetics, healthy living and quality of life play central roles in longevity.

Life Expectancy at Birth for Select Countries
(2011 estimates and world ranking)

Japan (5)	82.25 years
Australia (9)	81.81
Italy (10)	81.77
Canada (12)	81.38
France (13)	81.19
Spain (14)	81.17
Germany (27)	80.07
United Kingdom (28)	80.05
Greece (30)	79.92
Belgium (37)	79.51
South Korea (41)	79.05
United States (50)	78.37
Cuba (57)	77.70
Libya (58)	77.65
Argentina (68)	76.95
China (95)	74.68
Iraq (145)	70.55
Iran (146)	70.06
North Korea (149)	68.89
Russia (161)	66.29
Global average	67.07

Source: "Life Expectancy at Birth," The World Factbook, *Central Intelligence Agency, 2011, https://www.cia.gov/library/publications/the-world-factbook/fields/2102.html#us*

makers and health-care and medical professionals:

Can the human lifespan be extended?

The longest documented human lifespan is 122 years, a record held by Frenchwoman Jeanne Calment, who died in 1997. This limit is not set in stone, but neither is it likely to change significantly, say many researchers.

"A maximum lifespan is like the Olympics," says Carnes, the University of Oklahoma geriatrics researcher. "A world record gets set, and at some point it will be broken, but probably not by very much."

Geriatrician and aging pioneer William H. Thomas of Ithaca, N.Y., founder of the Eden Alternative and Green House projects, agrees. "The human being has an encoded arc, a lifespan that's written into the genetic code," he says. "The same is true for dogs and cats and whales and lions and mice. If you look around you, what you find is that every creature of a certain species has an arc of lifespan." He does not believe the lifespan is very malleable.

University of Texas cell biologist Wright is among those who disagree. "I'd be surprised if we were not able to make a significant extension of the human lifespan in the next 20 or 30 years," he says, pointing to studies that have successfully extended the lives of laboratory animals, including fruit flies, roundworms and mice.

Cynthia Kenyon, a renowned biochemist and biophysicist at the University of California, San Francisco, played a key role in discovering that genetic regulation affects the aging process. Kenyon has conducted groundbreaking work on the small roundworm, *C. elegans*, extending its lifespan sixfold through genetic manipulation. In addition, the animals appear younger and healthier. Some of these gene mutations influence the roundworms' "insulin signaling pathway," which also plays a role in age-associated diseases in humans, such as diabetes and cancer.

"We don't know yet, but to me it seems possible that a fountain of youth, made of molecules and not simply dreams, will someday be a reality," writes Kenyon. [6]

But it's not clear if genetic manipulation could extend the lifespan of humans. "A genetic intervention that increases a worm's lifespan by fourfold might have a significantly less impressive effect in a mouse's lifespan," according to the National Institute on Aging. "For similar reasons, a finding in mice might be promising, but does not mean that it will work the same way or at all in humans." [7]

Similarly, Tulane's Jazwinski, who has spent much of his career studying aging in yeast, cautions that while animals provide clues for researchers, each species has significant differences. In humans, for example, variants of a protein called apolipoprotein (APoE) are associated with both longevity and Alzheimer's disease. "It seems likely this lipoprotein and the processes it supports, which involve fat transport, are very important," he says. "This is something that you would not have found even in [higher-level animals such as] mice."

Researchers focus on extending the lifespan of animals, he adds, because it is measurable. But that doesn't mean an ever-longer lifespan is the goal of science. "What we're trying to do is probe the aging process," he says. "Once we start studying this in humans, we no longer try to extend the lifespan. We're trying to figure out why people live as long as they do. Underlying that, we're really also interested in healthy aging — not just long life, but healthy life."

Some researchers, though, are interested in extending the human lifespan. Caloric restriction, for example, is known to extend the lifespan of animals and perhaps humans. The late Ray Walford, a pioneering researcher at the University of California at Los Angeles, believed humans could live to 140 by reducing their caloric intake by 30-40 percent.

Brian M. Delaney, president of the Calorie Restriction Society, in Newport, N.C., acknowledges that Walford's theory cannot be scientifically proved without following a group of people for 140 years and comparing them to those on a regular diet. "That said, there's a lot of reason to believe that people who start this diet in their mid-to-late 20s and follow it relatively strictly probably would be able to live much longer," he says. (*See p. 820 for more on caloric restriction.*)

On the outer fringe of lifespan-extension advocacy are futurists such as Ray Kurzweil and Aubrey de Grey (*See sidebar, p. 816.*) De Grey, a British biogerontologist trained in computer science, believes that scientists will soon figure out how to repair age-associated damage to the body's cells, allowing some people who are alive today to survive for thousands of years. Indeed, he maintains, therapies will soon be invented to not only stop but actually reverse aging and associated diseases.

"People 60, 70 or even older would be quite suitable for these therapies," he wrote in an email. "These therapies will [do] repair and maintenance at the molecular and cellular level, so people will be restored to the condition of a young adult, irrespective of how old they were when they received the therapies."

Believing that science can so dramatically manipulate the complex systems that make up the human body is hubris, others say. In a lengthy critique of de Grey in 2005, 28 prominent researchers, while noting their wide range of views on aging, wrote, "None of us, however, believes that plans to 'engineer' the body to prevent ageing indefinitely or to turn old people young again have the remotest chance of success." [8]

Researchers must be wary of unintended consequences of their work, cautions Thomas Kirkwood, director for aging and health at England's Newcastle University. "The complexity of the aging process is so great that we should not be so arrogant as to assume we will solve it all quickly or that we will be able to solve it all without great difficulty," he says. "We are learning a great deal, but there is still so much more that we don't know than that which we know. No one would thank us for screwing it up. There's nothing worse than medical treatment that turns out after a while to have horrible side effects."

Says the University of California's Hayflick, skeptically: "The probability that we'll all live to be 200 has always been 25 years in the future."

A Glossary on Aging

Antioxidants — compounds that may protect cells from damage by "free radicals" by slowing oxidation.

Cellular senescence — point at which a cell stops dividing and producing new cells; may contribute to aging.

Free radicals — unstable molecules in the body that break apart when they encounter oxygen. Free radicals damage cells and may contribute to aging.

Life expectancy — average number of years a person is expected to live. U.S. life expectancy at birth in 2009 was 78.2 years. At age 70 it was 15.1 years, meaning that 70-year-olds, on average, could expect to live to 85. Those reaching 100 years could expect to live another 2.2 years.

Maximum or potential lifespan — the greatest age reached by any member of a given population or species. The oldest human, Frenchwoman Jeanne Calment, lived to 122.

Telomeres — substances at the end of chromosomes of cellular DNA that act as caps; the caps prevent the ends from fraying, which can damage an organism's genes and lead to disease. Over time, telomeres become shorter, hastening aging.

Should the lifespan be extended?

Would it be desirable, or ethical, if scientists extended human life by decades?

"I don't believe in radical life extension," says bioethicist Daniel Callahan of the Hastings Center, a bioethics research institute in Garrison, N.Y. "I think it's silly and irresponsible — silly because I don't think biology will let us get away with it and irresponsible in that it could raise all sorts of social problems and justice issues between the age groups."

Callahan, an octogenarian, has written extensively on the societal problems associated with an aging population, which he sees as using more and more resources and leaving less for young people's education and health care.

Physician and author Sherwin Nuland agrees. "There are so many far more important things that scientific funding should be applied to that we don't have enough money for," says Nuland, whose best-selling books include *How We Die*. "Obviously, there are diseases that will require gigantic amounts of funding — to think that the resources of our scientists and economic establishment would be directed toward the narcissistic notion of extending human life is just a bizarre way of looking at what our real needs are on this Earth."

Investing in research to radically extend human life is a distraction from the primary goal of keeping people healthy, says Thomas Perls, an associate professor of medicine and geriatrics at Boston University and director of its New England Centenarian Study, one of the oldest and largest of its kind. "What we need to worry about is that we're going to have 7 billion people on this planet," he says. "We have to figure out how to feed them, how to keep them healthy and safe, and worry about their quality of life — and not worry about some stupid pill" to increase lifespan.

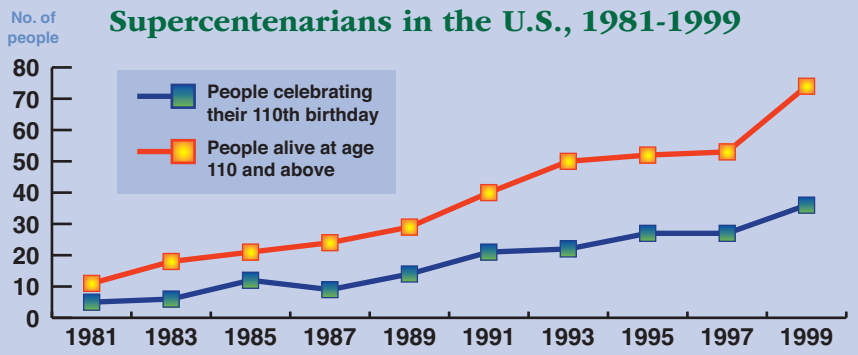
But advocates of lifespan extension stress that their goal is not just for people to live decades longer, but to live longer in good health, rather than in a nursing home or with dementia. In the future they foresee age no longer being accompanied by a vulnerability to diseases such as diabetes and Alzheimer's.

"People's first reaction to extending the lifespan is based on the current medical model, where you're not affecting aging, all you're doing is preventing dying — the Dorian Gray model," says University of Texas cell biologist Wright. "If the average lifespan were 20 years longer, there would be changes that have to occur, and those are going to produce some disruptions. But the fact that there are disruptions does not mean it's not a good thing to do, since everyone would like" a long, healthy life. (*See "At Issue," p. 821.*)

The main question, says S. Jay Olshansky, a professor of public health at the University of Illinois at Chicago, is whether longer life is lived in good health or sickness and frailty. Although he doesn't think it's a realistic

More People in U.S. Living Past 110

Thirty-six people in the United States reached 110 years of age in 1999, bringing the number of supercentenarians alive then to 74. Scientists largely credit advances in medicine and preventive treatments for the rising figures.



Source: "The Emergence and Explosion of Supercentenarians," Max Planck Institute for Demographic Research

goal, he says, "I don't have any issue with extending healthy life. Actually, we'd benefit tremendously by the extension of healthy life."

But what about the economic impact? With millions of workers unemployed, manufacturing dwindling and the economy stubbornly sluggish, what effect would legions more older people have? Would they work longer, making it even more difficult for young workers to find jobs? Or would they be retired for many more decades and still expect their monthly Social Security checks?

Robert H. Binstock, a professor of aging, health and society at Case Western Reserve University in Cleveland, is an optimist. "That's a lot of consumption, to live to be 100," he says. "There could be enough jobs right there, in and of itself, generated by demand."

He is among those concerned, however, about the thorny ethical issues that might emerge if a life-extension therapy went on the market. "Suppose this capacity, whether delivered through a pharmaceutical or however, costs money," he says. "Would it have differential impact in terms of developed and developing nations? Who is it really accessible to?"

Oklahoma's Carnes foresees equity problems in the United States, as well. "I believe the wealthy people will have interventions to extend their healthy lives, and the poor and middle class will die at regular ages because they will not have the money to benefit from these interventions, and they will not be mass produced and equitably distributed."

But de Grey envisions such interventions would be universally available. "Paying for them is not going to be a problem at all, because people who receive these therapies will thereby avoid being a drain on the economy — they will remain contributors to the nation's wealth," he says. "Thus, whether it's paid for by taxation or by insurance or whatever, the money will be a no-brainer investment."

The University of California's Hayflick raises other questions. What if one spouse wants to take the potion to stop aging or extend life, and the other does not? Could individuals choose when to stop aging? His greatest fear, though, is adding to what he sees as today's global overpopulation. Those seeking to manipulate the aging process, he writes, "have an obligation to deal with the consequences before they begin to tinker." [9]

Robert Engelman, executive director of Worldwatch Institute, an environmental research organization based in Washington, says that generally, living longer translates into later childbearing, which has a good effect. "When you raise the average age of childbearing, you slow down population growth even if women have as many children," he explains, "because you're slowing down successions of generations."

At the same time, Engelman says, there's no question that if people live longer they will leave a larger environmental footprint, from consuming more food that removes critical nutrients from the soil to adding to greenhouse gases or destroying woods and farmland to build retirement communities. If older people continue to work, the environment might suffer, he says, because economic growth is "at the root of environmental degradation. If everybody is going to live decades longer, it will be a greater challenge to find ways to make longer life and economic growth environmentally sustainable," he says. "But I don't know if it will be impossible."

Nuland also has environmental objections to extending the human lifespan. "We live in a very delicate balance," he says. "Our climate, our atmosphere, our cells have evolved over billions of years to this balance. I'm scared silly to play with it, which we certainly would be doing by prolonging the lives of this generation."

Should the government invest in extending longevity?

The federal government supports research on aging, much of it using animals, through the National Institute

Continued on p. 814

'Best and Brightest' Kids Reveal Longevity Secrets

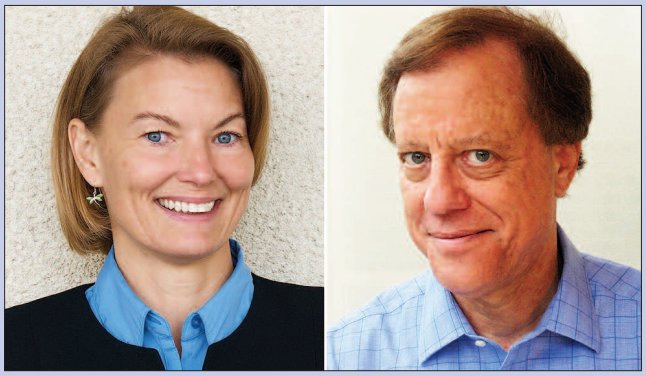
Those with good habits lived the longest.

In 1921 Stanford University psychologist Lewis Terman began an unusual quest. At elementary schools throughout California he asked teachers to select one or two of the brightest children — 1,528 youngsters in all. He planned to track each child into adulthood.

He wanted to find out two things, explains Leslie R. Martin, a professor of psychology at the University of California (UC), Riverside: "Were they normal people? It was thought if you were too smart you'd be an egghead and be maladjusted. He also wanted to find predictors of greatness — to groom future leaders."

Each year, Terman collected data on the children, first from their parents and later from the subjects themselves — everything from their personality traits to how many books were in their home when they were growing up to their favorite games and their parents' marital happiness.

Terman died in 1956, but his study of the remaining members of the group continues. The "best and brightest" in childhood ended up pursuing a variety of career paths, including janitors, truck drivers, movie directors, business owners and professionals of all kinds.



www.howardsfriedman.com/longevityproject/

Leslie R. Martin and Howard S. Friedman are taking a fresh look at Lewis Terman's landmark study.

In 1990, Martin teamed up with Howard S. Friedman, a distinguished professor of psychology at UC, to take a fresh look at the "Termanators," as they call the study group. They decided the vast trove of information about such a large group offered a unique opportunity to identify traits that might predict who lives to old age.

Martin and Friedman found, to their amazement, a disconnect between the subjects' long lives and the common medical advice typically doled out today.

"Surprisingly, the long-lived among them did not find the secret to health in broccoli, medical tests, vitamins or jogging. Rather, they were individuals with certain constellations of habits and patterns of living," they write in their new book, *The Longevity Project.* [1]

Above all, they found, those who lived longest tended to be the most conscientious. "These were individuals who are responsible, who are organized, persistent, honest — that constellation of characteristics was the strongest predictor of long life," says Martin. They also were less likely to smoke or drink heavily, had more stable marriages and moved steadily in their careers, rather than jumping from job to job. "That gave them a great deal of satisfaction," she says. "It makes sense, but we hadn't anticipated that."

Another surprise was the limited benefits of cheerful optimism, which is often touted as a boon to better health and a boost for people facing a medical crisis. Martin and Friedman found that lifelong optimists were often risk-taking devil-may-care types. "What we're able to see in a longitudinal study like ours is that if every decision is overlaid with extra optimism, it influences the way you make decisions and the way you evaluate risks," says Martin. "These cheerful, optimistic kids were doing more negative health behaviors — they were heavier drinkers, more likely to be smokers and tended to have riskier hobbies."

Indeed, it was no surprise that smoking was far and away the biggest predictor of early death, she says. The study did not gather information on diet, but it did look at exercise and other activities. "It didn't matter how active you were as a kid. If you became sedentary, it wasn't like you'd put good health in the bank," she says. "It essentially erased itself. But if you were sedentary as a kid and became active in adulthood, it gave you benefits over time."

The type of activity did not matter, she adds. What seemed to count most was pursuing something the study participants genuinely enjoyed and sustained, whether it was swimming, woodworking or gardening.

The study also confirmed the strong importance of social connections and helping others, a finding Martin finds especially encouraging. "It takes a long time and a lot of effort to change your personality," she says, "whereas helping others is relatively easy to adjust. You can volunteer an hour or two a week. That brings you into contact with other people, and you're also doing for others and getting a sense of meaning."

Friedman and Martin think there is more to be learned from the two-dozen Termanators in their 90s who are still alive. Meanwhile, from a public-policy perspective, Martin believes that more attention should be given to simple, inexpensive strategies that improve not only longevity but also quality of life for older people.

"How do we set in place a healthy path, a healthy trajectory?" she asks. That "doesn't mean that you'll never have a health problem but that you'll have fewer, so that fewer interventions will be needed."

— Beth Baker

[1] Howard S. Friedman and Leslie R. Martin, *The Longevity Project* (2011), pp. ix-x.

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on Aging (NIA). The ultimate goal is helping people live longer and healthier rather than simply pushing the lifespan boundary.

"It's about extending the health span," says Albert Einstein College's Barzilai, who receives NIA funding. "Our goal is to prevent age-related, chronic debilitating disease." If in doing so scientists also succeed in prolonging the lifespan, "We'll have to apologize for that," he jokes.

Other researchers say NIA and the National Institutes of Health (NIH) would get further toward the goal of a long and healthy lifespan by shifting priorities. NIA's annual budget of roughly $1 billion is considerably smaller than that of institutes focused on diseases such as cancer ($5 billion), heart, lung and blood ($3 billion) and allergy and infectious diseases ($4.5 billion). [10] Only a small portion — $174 million — of NIA's budget goes to the Biology of Aging Program while nearly half — about $500 million — goes to Alzheimer's disease. [11]

But aging is the common risk factor for the major causes of death in modern society — heart disease, cancer, diabetes, Alzheimer's — and much more funding should be put into figuring out why, say many biologists. Get to the root, they say, and perhaps a common cause — and solution — would be discovered.

"The most important question is, why are old cells more likely to incur pathology than young cells? That's not investigated at all," says the University of California's Hayflick. "The problem is a very serious one because of the failure of most of the scientific community and many of the policy and decision makers to understand the difference between age-associated diseases and the fundamental biology of aging."

NIA director Hodes agrees that it's important to learn what underlying mechanisms make older people more vulnerable to disease. But the institute has to balance competing goals and interests, he says, explaining that both the biology of aging and finding treatments for age-related diseases must be supported.

Jazwinski at Tulane's Center for Aging agrees. Even as biologists search to understand the mysteries of aging and find ways to keep us healthy, he says, "You still need to take care of the disorders and diseases that appear during aging while we're waiting for that. You can't leave people dangling out there, with the idea that someday you'll be able to cure everything. There should be a balance."

Others challenge the disease focus of NIH on different grounds. Stanford University's Bortz advocates a paradigm shift away from diseases and toward wellness and prevention. "We have warehouses full of gene information, but almost nothing about health promotion and the community," he writes. [12] The most important thing for healthy aging, he says in a phone interview, is "meaningfulness. Why get out of bed in the morning? If you don't have meaning, then life is nothing more than billiard balls knocking around."

What if researchers were to succeed in their goal? What would the impact be on federal spending if older people actually lived significantly longer?

Binstock of Case Western Reserve coined the term "apocalyptic demography" to describe fears that an aging population is ruinous for the federal budget. He dismisses the doomsayers and argues that minor adjustments in Social Security could ensure the program's solvency for the next 75 years — well after baby boomers have spent their entitlement.

As for Medicare, it, too, is not the problem, Binstock argues. "People who study this say that the increase in the elderly population accounts for 10 percent of the increase in health costs," he says. "What accounts for the increases are new procedures and products, their overutilization and their prices. Medicare is not the problem."

Current projections, based on only a modest increase in life expectancy, are that Medicare as a share of gross domestic product will rise from 3.5 percent in 2009 to 5.5 percent by 2035. [13] But the impact of a significant spike in life expectancy on Medicare would depend on whether older people became healthier than they are now.

A recent study sheds light on the question. If Americans reduced their obesity and smoking, they would catch up to Western Europeans' life expectancy, which is 18 months longer. Although pension and Social Security costs would go up, they would be offset by health-care costs going down nearly $18,000 per person because of improved health, the researchers estimated. They projected that by 2050 savings from gradual health improvements in middle age could total more than $1.1 trillion, of which more than half — $632 billion — would come to the U.S. Treasury in the form of Medicare and Medicaid savings. [14]

Moreover, scientific evidence suggests that the same genes that likely allow centenarians to live so long also may protect their health. If researchers can mimic those genetic mutations in others, better health might result. "If you look at real data from CDC [the Centers for Disease Control and Prevention], the medical costs in the last two years of life for people who die when they're 100 are about one-third of those who die in their 70s," says Albert Einstein College's Barzilai. "Not only do they live longer, their medical costs were less."

If the nation is concerned about the costs of an aging population, then much more attention should be paid to health disparities among

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Chronology

1800-1930s

Modern demography and biological studies of aging emerge.

1825
British actuary Benjamin Gompertz observes that after puberty the chance of death doubles every 10 years until age 80.

1891
German biologist August Weismann proposes one of the earliest evolutionary theories of aging, that the longevity of species is shaped by their environment.

1900
Life expectancy in the United States is about 45 years; the top causes of death are pneumonia and influenza, tuberculosis and intestinal problems.

Early 1930s
Researchers Barbara McClintock of the University of Missouri and Hermann J. Muller of the University of Edinburgh in Scotland independently discover that chromosomes have end caps to protect their stability. Muller calls them telomeres from the Greek words for "end" (telos) and "part" (meros).

1931
Biologist Raymond Pearl of Johns Hopkins University finds that people who live to be 90 or older tend to have long-lived ancestors.

1934
Nutrition researcher Clive McCay of Cornell University discovers that restricting calories extends the lifespan of laboratory mice.

1950s

Mortality is linked to aging, not infection.

1950
Life expectancy in the United States is about 68; the top three causes of death are heart disease, cancer and stroke.

1952
British biologist Peter Medawar theorizes that natural selection cannot eliminate genes that become harmful later in life.

1956
Denham Harman of the University of Nebraska theorizes that unstable molecules known as "free radicals" produced through oxidation are a prime cause of aging.

1960s-1980s

Researchers advance their understanding of aging at the cellular level and in healthy, older populations.

1961
Biogerontologist Leonard Hayflick discovers that normal cells can divide only about 50 times before they die.

1975
Okinawa Centenarian Study begins in Japan.

1977
Evolutionary biologist Michael Rose of the University of California, Irvine, extends the lifespan of fruit flies through selective breeding. . . . British biologist Thomas Kirkwood theorizes that evolution forced organisms to "choose" between investing energy in producing offspring or living longer.

1984
Elizabeth Blackburn and Carol Greider, then at the University of California, Berkeley, discover the enzyme telomerase that lengthens telomeres, helping to explain why cancer cells become malignant.

1990s-Present

Researchers identify longevity genes and compounds that may promote healthy aging.

1992
Cynthia Kenyon of the University of California discovers that mutations in the gene daf-2 could extend the lifespan of a roundworm.

1997
Frenchwoman Jeanne Calment dies at 122, the longest-lived person on record.

2000
Life expectancy in the United States is about 77 years; the top three causes of death are heart disease, cancer and stroke.

2003
Human Genome Project is completed, giving researchers new tools to study longevity.

2006
David Sinclair publishes finding that the compound resveratrol, found in red wine, improves health and survival of mice on a high-fat diet.

2009
Researchers report that the drug rapamycin, used by transplant patients, extends the lifespan of middle-aged mice. . . . Blackburn, Greiden and Jack Szostak win Nobel Prize for work on telomeres.

2011
Pharmaceutical companies conduct clinical trials of new drugs to combat age-associated diseases. . . . Researchers search for common traits of centenarians.

Futurists Reach for Immortality

"Human life will be irreversibly transformed."

Two scientists have gained notoriety in recent years for predicting that humans will be able to drastically extend their lives — or even become immortal — within 40 to 50 years. Aubrey de Grey, a biomedical gerontologist in Cambridge, England, puts his faith in biological advances, while Ray Kurzweil, a Boston-based inventor and futurist, envisions the melding of artificial and human intelligence in what he calls "the Singularity."

De Grey, a waifish figure who eschews business attire and sports a Rasputin-like beard, has as his life's goal to "defeat aging," which he equates with age-associated disease.

He has written that people in wealthier countries who are born in 2100 could expect to live to be 5000. [1] But in an email he says immortality is not his goal.

"My goal is to keep people healthy as long as they live. Chances are that people will indeed live a lot longer as a result, but we must always keep in mind that that's what it is — a result, a side benefit." He envisions people living to extreme ages in the future, then dying from the same causes as young people do today.

De Grey has developed a research agenda dubbed SENS (Strategies for Engineered Negligible Senescence) that focuses on seven types of therapy to repair an equal number of categories of cellular and molecular damage caused by aging. For example, AmyloSENS is aimed at "destroying junk between cells" that may contribute to Alzheimer's disease and other problems, while MitoSENS focuses on "preventing damage from mitochondrial mutations" that occur through oxidation and metabolic stress. [2]

Research on this agenda is carried out by scientists working at the SENS Foundation lab in Mountain View, Calif., and at universities that have received grants from the foundation.

Although a great many scientists find de Grey's agenda wildly unrealistic, his SENS Foundation has drawn an advisory board of experts from major universities. In 2006, MIT's journal, *Technology Review*, offered a $20,000 prize to any molecular biologist who could demonstrate that the SENS agenda was "so wrong that it was unworthy of learned debate." A panel of independent experts did not deem any of the five entries critiquing de Grey persuasive; at the same time, the panel found de Grey's rebuttals to the critiques "somewhat fanciful." [3]

Kurzweil, meanwhile, unapologetically seeks immortality. In the documentary film "Transcendent Man," Kurzweil says that when he contemplates death, "It is such a profound, sad, lonely feeling that I can't bear it. So I go back to thinking about how I'm not going to die."

Kurzweil invented the flatbed scanner and a voice-recognition tool for blind people to hear books, among many other successful ventures. He was awarded the National Medal of Technology in 1999, the highest honor bestowed by the U.S. president for technological achievement.

The foundation of his theory lies in the exponential growth of human intelligence. For example, he writes, in 1990 it had taken scientists one year to transcribe one ten-thousandth of the human genome. Many biochemists, thinking linearly, assumed it would take a century to complete; it actually took 13 years. Similar exponential growth occurred with the Internet. [4]

Continued from p. 814

regions, races and people with less education and income, say others, and that would lead to longer life for all. Nations that reduce health disparities in the young tend to have higher life expectancy.

"Healthy longevity is a prime driver of a country's wealth and well-being . . . [and] premature deaths bring little benefit and impose major costs," writes James Vaupel, founding director of the Max Planck Institute for Demographic Research in Rostock, Germany, and also a professor at Duke University. "Moreover, equity in the capability to maintain good health is central to any larger concept of societal justice." [15] ■

BACKGROUND

Lure of Eternal Youth

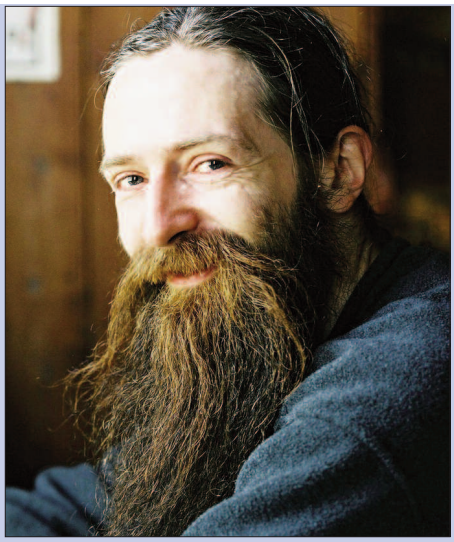
In a Greek myth recounted in Homer's epic poem "The Iliad," the goddess Aurora asked Zeus to grant the gift of immortality to her lover, Tithonus, son of Troy. Tithonus lived forever but grew so old, shriveled and demented that Aurora turned him into a grasshopper. "Even Zeus couldn't stop aging," says geriatrician Thomas, author of *What are Old People For?*

Humans have sought the secrets of eternal youth, long life and even immortality since ancient times. The Babylonian story of Gilgamesh, from 3000 B.C., describes the hero's futile efforts to win immortality. "If the superhuman Gilgamesh was barred from eternal life, it is clear that ordinary men should avoid futile yearnings and accept fate with as good grace as possible," wrote the late Gerald J. Gruman in *A History of Ideas about the Prolongation of Life*. [16] A physician and college professor in Ohio, Gruman coined the term "prolongevity," which he defined as the significant extension of the lifespan by human action.

Some early advocates of prolongevity interpreted literally the Old Testament stories of patriarchs like Adam and Noah living nearly a thousand years

Human intelligence will continue expanding, he says, and within 40 years or so, people will have the ability to reprogram their bodies away from disease and aging. He envisions rapid advancements in genetics, nanotechnology and robotics. In this century, people will back up their brains, as they do now with computers, and will become more of a machine than a biological organism, he claims.

"What, then, is the Singularity?" he writes. "It's a future period during which the pace of technological change will be so rapid, its impact so deep, that human life will be irreversibly transformed." [5]



immortalhumans.com

British scientist Aubrey de Grey says his life's goal is to "defeat aging."

To make sure he's around to take advantage of these breakthroughs, Kurzweil takes some 200 pills a day that he claims reprogram his cells to be young. He regularly has his blood analyzed for levels of nutrients and has a line of supplements he sells. Through this regimen, along with changes in his diet and exercise practices, he said he conquered his diagnosis of Type 2 diabetes.

Kurzweil dismisses the notion that radical life extension would lead to overpopulation and exhaust natural resources. This view "ignores comparably radical wealth creation from nanotechnology and strong [artificial intelligence]," he writes. "For example, nanotechnology-based manufacturing devices in the 2020s will be capable of creating almost any physical product from inexpensive raw materials and information." [6]

In this vision, "nanobots" — tiny robots the size of a blood cell — will patrol the body, repairing cellular damage and "reversing human aging."

Like de Grey, Kurzweil views the effort to end aging as a "war" to be won. Ultimately, the body will become cumbersome and useless, and "humans" (or whatever the new beings would be) will exist on a different plane, connected to the thoughts and feelings of others through a technological, global network. In "Transcendent Man," he prophecies, "We'll look back on having one body and no memory backup as a very primitive time."

— Beth Baker

[1] Aubrey de Grey, "The War on Aging," The Scientific Conquest of Death — Essays on Infinite Lifespans, The Immortality Institute, 2004, p. 38, www.imminst.org/SCOD.pdf..

[2] See the SENS Foundation website, www.sens.org.

[3] Jason Pontin, "Is Defeating Aging Only a Dream," *Technology Review*, July 11, 2006, www.technologyreview.com/sens/index.aspx.

[4] Ray Kurzweil, *The Singularity is Near — When Humans Transcend Biology, Viking* (2005), p. 13.

[5] *Ibid.*, p. 7.

[6] *Ibid.*, p. 13.

as evidence that humans have the capacity for such long lives. Other tales of extreme longevity are found in Persian, German, Japanese and Chinese literature. Some recount a fountain of youth or other special waters that would restore the loss of "vital" moisture associated with old age.

Ancient Taoism in China sought both extreme longevity and immortality. "An illustrative story is that of a certain Wang Chen, who began Taoist studies at the age of seventy-nine; after some thirty years of diligent practice, he was able to restore his appearance to that of a young man of thirty, but it was not until several hundred years later that he finally became an immortal," wrote Gruman. [17]

Sages such as Wang Chen were said to eat very little, mostly roots, berries and other fruit, and avoid meat, wine and many vegetables. They diligently practiced a physical exercise routine that was frequently interrupted by holding one's breath twice or having a couple of rounds of sexual intercourse. Celibacy, they believed, caused agitation, which led to the spirits becoming fatigued and longevity declining.

By the 4th century B.C., the philosopher Epicurus put forth the idea that death may actually be a good thing. He and others came up with the theory that without the older generation departing, the Earth would soon become overpopulated.

In the 13th century in Western Europe, alchemists in pursuit of longevity began sowing the earliest seeds of modern chemistry. English philosopher Roger Bacon wrote that medicine could only offer people "the regimen of health," while the "experimental art" offered the promise of life extension. [18] Imbibing secret concoctions with precious metals or drinking from a golden goblet were thought to confer long and healthy life.

Some 500 years ago, Venetian nobleman Luigi Cornaro lived to be 98 — remarkable in the 16th century — after, at age 50, going on a diet of small amounts of bread, meat, broth with eggs and new wine. But it was what he didn't eat that mattered most,

he thought. "The food from which a man abstains, after he has eaten heartily, is of more benefit to him than that which he has eaten," Cornaro wrote. [19] He also considered old age an immensely satisfying time, writing, "I have an ardent desire that every man should strive to attain my age, in order that he may enjoy . . . the most beautiful period of life." [20]

In the mid-1930s, Cornell University researcher Clive McCay demonstrated what the ancient Taoists and Cornaro had suggested: that reducing food intake — caloric restriction — could extend life by up to 40 percent, at least in mice. Since then, researchers have observed many changes in other animals put on sharply reduced diets, such as improved sensitivity to insulin, reduced risk of cancer and arthritis and lower blood pressure, not to mention maintenance of sexual activity and cognitive functioning.

AFP/Getty Images/Yoshikazu Tsuno

A Japanese woman celebrates Respect-for-the-Aged-Day in Tokyo with a good workout on Sept. 19, 2011. Life expectancy in Japan is 82, the highest among industrialized nations and about 15 years higher than the global average.

Some studies, though, find a decline in reproductive ability. Studies in humans, while not yet able to demonstrate extended life, have shown some improved health benefits. [21] (Persuading Americans to reduce their calories to 1,500 a day, however, may be hard.)

Other researchers hoped to draw on the vitality of mammals to inculcate humans with youthful vigor — what the University of California's Hayflick calls "scrotum hokum." In the late 1800s, Charles-Edouard Brown-Sequard, a French physician, injected a concoction of crushed testicles from farm animals into his patients and himself. He and others claimed sharper thinking, greater vigor and even better bladder control. Thousands of physicians followed suit with their patients. Brown-Sequard gave away his rejuvenation method, but others began selling it. [22]

Just a few decades later, Eugen Steinach, a Viennese professor of physiology, became rich by giving men vasectomies as a method of rejuvenation. Even electricity and X-rays were applied to the sex organs, to increase vitality. [23]

Such methods may sound preposterous to modern sensibilities, but nostrums to stop or reverse aging continue to flourish in new forms, from melatonin to antioxidant supplements and hormone injections. Indeed, Americans spend an estimated $80 billion a year on anti-aging products, including cosmetic procedures such as Botox injections, with a projected increase to $114 billion by 2015, according to a market research firm. [24]

Scientists from a variety of disciplines reject these modern efforts as no more beneficial than crushed goat testicles. "There are no lifestyle changes, surgical procedures, vitamins, antioxidants, hormones or techniques of genetic engineering available today that have been demonstrated to influence the processes of aging," said a 2002 position statement by prominent scientists. [25] According to the University of Illinois' Olshansky, one of the scientists, nothing has changed in that regard over the last decade.

But scientists like de Grey and Kurzweil are striving to push the lifespan envelope in even more extreme ways. (*See sidebar, p. 816.*) In preparation for the not-too-distant day when they believe humans will be able to choose immortality, some have opted for cryonics — to be frozen after death, with the hope scientific advances will allow them to be thawed and returned to immortal life.

In July, cryonics pioneer Robert Ettinger, who wrote *The Prospect of Immortality* in 1964, died at age 92. According to a blog posted on the website of the nonprofit Immortality Institute, Ettinger "believed death

is only for the unprepared and unimaginative. . . . Mr. Ettinger's frozen body is being stored in a vat of liquid nitrogen at a nondescript building outside Detroit, home to more than 100 fellow immortalists — including his mother and two wives — who are awaiting revival. Introducing what he called the Freezer Era, Mr. Ettinger described a world in which people would become nobler and more responsible as they were confronted with the reality of living forever." [26]

Cellular Aging

In 1952 the British biologist Peter Medawar theorized that natural selection — the evolutionary process by which the fittest of a species survive to pass on their genes — accounts for many genes becoming harmful only later in life, after an organism has successfully reproduced. Since most people throughout history did not live to old age, nature did not "care" about eliminating these potentially harmful gene variations.

"For example, if you carry a gene that causes lung cancer but the gene is not expressed until you reach age 120, you probably would not be too concerned, knowing that your chances of living that long are slim. Natural selection would not be too concerned either," write Olshansky and Carnes. [27]

In the 1960s, Hayflick added an important piece to the aging puzzle. Until then, it had been assumed that cells in a Petri dish could be kept alive and dividing indefinitely. This had important implications for aging. "If normal cells removed from animals are 'immortal' when grown in laboratory cultures, the reasoning went, then aging cannot be the result of events that occur inside individual cells. Aging, therefore, must be the result of events that occur outside of cells," Hayflick wrote. [28]

Getty Images/Joe Raedle (both)

How to Age Quickly

Eating foods with high fat content (top) and smoking cigarettes (bottom) are sure ways to limit life expectancy, health experts say. To achieve better health, and a longer life, they recommend such steps as incorporating movement into everyday routines; limiting consumption of meat and processed foods; having a sense of purpose; making family a priority, and staying in touch with others who share those behaviors.

He discovered that normal human cells are not immortal but that cancer cells are. Normal cells can divide only about 50 times, now known as the Hayflick Limit, and die soon after, a process called cellular senescence.

Other researchers added to this knowledge with the discovery of telomeres. Likened to the tips of shoelaces, telomeres are caps found at the ends of strands of cellular DNA that keep the strands from fraying, which leads to disease. Telomeres shorten with each cell division, becoming less and less effective as people age. Cancer cells, however, prevent that shortening by making an enzyme called telomerase, which in some circumstances allows cancer cells to replicate uncontrollably. (*See glossary, p. 811.*)

Another important development came with the "disposable soma" theory of Newcastle University's Kirkwood in 1977 to explain why most cells in the body, called soma cells, are destined to die. (Other cells, called germ cells, are considered immortal in that they are passed on to offspring through eggs and sperm.)

"Under the intense pressure of natural selection, species end up placing higher priority on investing in growth and reproduction — and the perpetuation of the species — than on building a body that might last forever," writes Kirkwood. [29]

More recently, Kirkwood's team discovered that in addition to apoptosis — the process by which damaged cells protect the body by essentially committing suicide — cells have the ability to lock themselves down, stopping perhaps malignant replication, yet continuing their valuable function in the body.

At the same time, other researchers were looking at animal models to learn what role genetics and the environment might play in the aging process. Michael Rose, a professor of ecology and evolutionary biology at the University of California, Irvine, focused on natural selection, not random and progressive cellular damage, as the great driver of aging and longevity.

In 1977 Rose began trying to extend the lives of fruit flies through selective breeding, allowing only those flies to reproduce that were toward the end of their natural reproductive life. This was based on the evolutionary theory that a species will live as long as it can reproduce: the older the age of reproduction, the longer the lifespan. Over many generations, Rose was able to create "Methusalah" flies that lived much longer than normal, with high reproduction rates. His famous experiment has been replicated many times.

More recently, Rose has turned to studying why organisms, including humans, seem to reach a plateau in aging, with their mortality rates leveling off instead of increasing exponentially the older they get. [30]

He says he is now "trying to find environmental manipulations that will stop aging processes early," such as diet. He argues that the modern Western diet is so contrary to the way humans evolved that it affects the aging process and longevity. He favors a diet closer to that consumed by the earliest humans — a "paleo" diet that avoids agriculturally produced foods including dairy, grains and processed food. If you are 70 and begin a paleo diet, he says, "You will stop aging in substantially better health than present day 70-somethings. You might in fact stop aging at a level of health comparable to that of a 50- or 60-something on an industrial diet. That means your life will no longer be an odious burden."

Another important area of research called oxidation or metabolic stress, began in the 1950s, gathering steam in the 1980s. This occurs when mitochondria in the cells convert food into energy, producing oxygen molecules called "free radicals" that can damage proteins and DNA.

Tobacco smoke and sun exposure also can produce free radicals. [31] Scientists have experimented with altering antioxidant properties in the cells of animals. Although some studies showed health benefits and an increased lifespan, others did not. Many had hoped that if people took antioxidant supplements, such as vitamins C and E, the molecular damage could be reduced. Based on several large-scale clinical trials conducted in the 1990s, however, antioxidant supplements do not appear to have an impact on cancer or on the aging process of humans. [32] Research continues in this area. ■

CURRENT SITUATION

The Magic Pill

Researchers are trying to find drugs that will delay aging, perhaps by mimicking the effects of caloric restriction. Many are backed by pharmaceutical companies.

Resveratrol, a compound found in red wine, received considerable attention in 2006. Obese mice given daily doses of resveratrol were in better health, and their functional decline was delayed, compared to overweight mice in a control group.

"Even more arresting, the animals had shown amazingly youthful vigor as they had aged, as if their fundamental life force had been strengthened and their aging process slowed down," science writer David Stipp notes in *The Youth Pill.* [33]

In August, the NIA announced similar results from a study involving the compound SRT1720. Mice that normally lived three years were put

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At Issue:

Will U.S. life expectancy rise until the end of the century?

WOODRING E. WRIGHT, M.D., PH.D.
SOUTHLAND FINANCIAL CORP. DISTINGUISHED CHAIR IN GERIATRIC RESEARCH, UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER

WRITTEN FOR *CQ RESEARCHER*, SEPTEMBER 2011

yes

Increasing lifespan during the 20th century was accomplished by preventing people from dying prematurely, without affecting the fundamental processes that cause aging. Further advances in preventing the major causes of death in industrialized societies, such as heart disease and cancer, will make progressively smaller contributions to lifespan because they occur at later ages.

Preventing one late-onset disease doesn't make much of a difference in overall lifespan in the face of the general aging process that is causing many tissues to function less effectively. From this perspective, U.S. life expectancy is unlikely to make dramatic increases during the next 90 years. However, the rules of the game are changing.

A new perspective on the evolution of aging has emerged from the realization that our bodies invest a lot of resources in maintaining healthy tissues, and that it is wasteful to invest enough to keep us healthy for 200 years if most of us would be dead by 35 under Stone Age conditions. As a consequence, evolutionary forces have acted to limit many "quality control" systems, so that we are reasonably healthy during our expected lifespan in the wild, but not forever.

Dramatic advances in our understanding of these systems have been made over the past several decades. Many of these stem from genetic studies in model organisms such as roundworms, flies and mice. These organisms possess feast-and-famine strategies: When times get tough and the probability of offspring surviving is small, it makes sense to shut off reproduction and invest as much as you can in keeping yourself healthy enough to survive until times get good again.

This is why dietary restriction (severe enough to mimic tough times) has been found to induce a large number of stress resistance/repair/quality-control pathways and extend lifespan in many different species. Phenomenal advances have been made in defining the molecular pathways that regulate these responses. Given the rate of progress, it is almost inconceivable that over the next 90 years we will not be able to intervene and manipulate these pathways, slowing the aging process and producing both increased years of health span and life expectancy.

We face many challenges, and global disruptions due to climate change, limited fossil fuels, famine and war all have the potential to derail optimistic future predictions. However, if we can avoid these catastrophes, the prospects for increasing human health span/lifespan by at least 20-30 percent in the 21st century are very rosy indeed.

S. JAY OLSHANSKY, PH.D.
PROFESSOR OF PUBLIC HEALTH, UNIVERSITY OF ILLINOIS AT CHICAGO

WRITTEN FOR *CQ RESEARCHER*, SEPTEMBER 2011

no

No matter how hard we try or wish it to be so, life expectancy in the United States won't continue to rise. Here's why:

Biodemographic forces: Raising life expectancy by one year today is far more difficult to accomplish than it was a half-century ago, and it will inevitably become exponentially more difficult as time goes by.

Biological clocks: Evolution could not have given rise to aging or death programs orchestrated by genes, but we do have fixed genetic programs for growth, development and reproduction. Biological aging is an inadvertent byproduct of these fixed programs for early life developmental events. By way of example, there is no genetic program that limits how fast we can run; yet no one disputes such limits exist. Upper bounds on rising life expectancy exist for the same reason.

Biomechanical constraints: Our body parts wear out at varying rates with time and use. Our Achilles' heels are non-replicating cells that make up muscles and neurons — implying that living machines have a biological warranty period, and most of us already live beyond it.

Observed worsening health: Forecasting life expectancy based on linear extrapolation is like driving a car by looking in the rear-view mirror. If we look in the right direction, health indicators for the U.S. suggest that younger cohorts today are less healthy than their predecessors. This is especially true among minorities, where recent declines in life expectancy have already been observed — a drag on life expectancy that is likely to increase.

Life expectancy does not rise unabated: There has never been an entire century in recorded history when life expectancy rose steadily — including the century in which we now live. Fluctuations in death rates are a normal and consistent part of human mortality dynamics. The fact that life expectancy failed to rise unabated even in this century suggests we're in for a rocky ride ahead.

Duration of life is fundamentally driven by our biology, not by past trends. I am optimistic that many of the dampening effects on life expectancy can be ameliorated through behavior modification, biomedical technology and the development of interventions that slow aging. However, until these miracles of the 21st century are invented and disseminated, available evidence suggests that life expectancy in the United States will soon level off and perhaps even begin declining. It most certainly will not continue unabated throughout the remainder of this century.

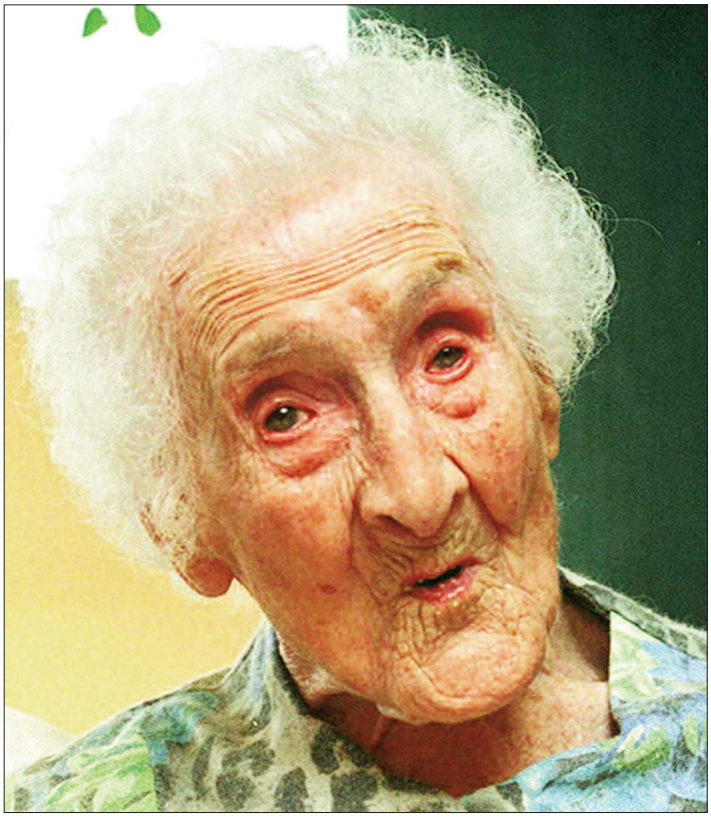
Continued from p. 820

on a high-fat diet at 1 year, along with daily doses of SRT1720. "The damage induced in the liver [by the high fat diet] was almost obliterated by the compound," says Rafael de Cabo, a researcher with NIA's Laboratory of Experimental Gerontology, who led the study. There was also a beneficial reduction of the inflammatory response.

What really surprised de Cabo was the effect on lifespan. "We got a tremendous effect on the mean lifespan and also the maximum lifespan — much greater than with resveratrol," he says. (Although the obese mice lived longer than expected, they still died sooner than mice fed a normal diet.) Both resveratrol and SRT1720 are being developed by Sirtris, a start-up founded by Harvard University researcher David Sinclair and now owned by GlaxoSmithKline. Sirtris researchers were among those collaborating on the study.

Another compound that mimics caloric restriction is rapamycin, a drug approved for organ transplant patients that acts on a different genetic pathway than reseveratrol. A study by the NIA's Intervention Testing Program in 2009 found rapamycin extended the lifespan of mice by about one-third. The mice were not given the treatment until they were 20 months old — late middle age for this species. But in humans, rapamycin has serious side effects, suppressing the immune system in complex ways.

Although mimicking the effects of caloric restriction is a hot area of research, NIA's Hodes urges caution. "If one looks at multiple species, it's not a universal effect," he says. "It extends lifespan in a fraction of mice species, and in some it has a deleterious effect. How do we know when it would have a positive effect in humans or when negative? It emphasizes the need to be cautious."



AFP/Getty Images/Georges Gobet

Frenchwoman Jeanne Calment celebrates her 120th birthday in 1995. When she died at 122, she was the world's longest-lived person. "She was someone who, constitutionally and biologically, was immune to stress," a biographer wrote. "She once said, 'If you can't do anything about it, don't worry about it.' "

Scientists are also identifying longevity genes, some of which accelerate aging, while others slow it down. Researchers have identified three "pathways" in a cell by which genes seem to influence longevity: insulin/IGF-1, sirtuins and mTOR. In an NIA-funded study of 30 genes associated with the insulin/IGF-1 pathway, researchers found that variants of some of the genes were more common in women over 92 than in those under 80. Researchers say there are likely many, many genes that influence aging and other processes and that the likelihood of being able to increase longevity by tinkering with just a few genes is slim.

The Holy Grail is to find drugs that will not just prevent a particular disease but also buffer the body's vulnerability to all major age-related conditions, including cancer, heart disease, Alzheimer's and diabetes. "The idea is to postpone the onset of all these chronic diseases as much as we can, all at once," says de Cabo. "We are now very good at treating a particular disease, but there is no disease called aging — and this is a problem when a drug company and investigators are trying to develop interventions that affect aging. There's nothing in the FDA [Food and Drug Administration process] that will allow you to do a clinical trial on aging." To win FDA approval for clinical trials, researchers must target a potential drug toward a disease.

De Cabo's NIA lab is studying not only the effects drugs might have on the aging process but also the role exercise and genetics play.

The Oldest Old

Researchers are studying very old people in search of lifestyle patterns that contribute to healthy aging.

One hopeful finding, says Perls, the director of the New England Centenarian Study, is that it appears "the older

you get the healthier you've been. We found that 90 percent of our centenarians are independently functional at 93."

Even if they have age-related diseases, he says, they are able to manage them well for 20 years or more. The study participants fall into three categories: "survivors" of a life-threatening illness before the age of 80, "delayers" of a serious health problem until late in life and "escapers" who reach 100 without any serious medical problem. [34]

Increasingly, many researchers believe that the oldest-old have some genetic protection. "It's like the lottery that's so hard to win because you've got to get all seven numbers right," says Perls. "But in our case it may be 200 or 300 numbers. And it's not just the interaction of genes but the interaction of genes with each other and with the environment — and then throw in a little luck."

Lifestyle is important, though. Perls points out that Seventh-day Adventists, whose life expectancy is in the high 80s, demonstrate what may be an optimal lifestyle for longevity. "Their religion dictates healthy habits," he says. "God has endowed people with this wonderful body, and they feel it's a sin to not take care of it. They don't smoke or drink, they're generally vegetarian, they regularly exercise and spend a lot of time with family and religion, which may help them manage their stress well. You put all that together and you get those average life expectancies that are eight years longer than the rest of the country."

Similar lessons come from communities around the globe where people are known to live far longer than average. In his 2008 book on these communities, *The Blue Zones*, author Dan Buettner identified nine behaviors that he believes contribute to healthy longevity:

- incorporate movement into your everyday routine;
- eat about 80 percent of your normal diet;
- limit meat and processed foods;
- regularly have a drink or two of wine or beer;
- have a sense of purpose;
- make time for relaxation and socialization;
- join a spiritual community, and
- make family a priority and surround yourself with others who share these behaviors.

Seventh-day Adventists "don't smoke or drink, they're generally vegetarian, they regularly exercise and spend a lot of time with family and religion, which may help them manage their stress well. You put all that together and you get average life expectancies eight years longer than the rest of the country."

— Thomas Perls

Associate Professor of Medicine and Geriatrics, Boston University

A Japanese woman from Okinawa epitomized this lifestyle, Buettner wrote. At 104, Ushi Okushima had recently taken a job bagging fruit at a nearby market. She spent plenty of time with her grandchildren and three close friends, ate a dinner of mostly vegetables and then drank a cup of mugwort sake before bed. [35] Working hard, sleeping well and drinking sake were the secrets to longevity, she believed.

The 122-year-old Frenchwoman Calment, the world's longest-lived person, still rode a bike at 100 and "walked all over Arles to thank those who congratulated her on her birthday that year," a public health researcher wrote in a book about her. "She was someone who, constitutionally and biologically speaking, was immune to stress. She once said, 'If you can't do anything about it, don't worry about it.' " She also kept a sense of humor. At age 117, "when somebody took leave by telling her, 'Until next year, perhaps,' she retorted: 'I don't see why not! You don't look so bad to me.' " [36]

The lessons from "the blue zones" confirm what Stanford geriatrician Bortz argues: that having meaning, along with regular exercise, are keys to a long, healthy life. Octogenarian Bortz is a marathon runner and has treated and studied older people for decades. "I plan to be 100," he says. Bortz maintains that genetics and accidents play only a small role in living long and well.

"The rest of it is decisions made and not made," he says. "Most of it is choice." His plan includes not costing Medicare "anything," because he will take no pills, get no medical tests and maintain his passion about life. In his book, *Next Medicine*, he argues for a paradigm shift

that would dramatically lower medical spending by focusing on wellness and prevention, rather than disease. ■

OUTLOOK

Many Unknowns

As the Social Security Administration looks to the future, it must balance many unknowns. What new breakthroughs that manipulate the aging process or cure major chronic disease might appear? Will increased access to health care, promised in the 2010 Affordable Care Act, improve longevity?

Demographers disagree on what to expect. Olshansky, the University of Illinois professor of public health, is among those who believe life expectancy will reach a plateau. (*See "At Issue, p. 821.*) In 2005, in a study published in *The New England Journal of Medicine*, he predicted that life expectancy might actually go down in the future because of long-term effects of childhood obesity. Already more than 60 percent of adults in the United States are overweight or obese. [37]

"Those who forecast indefinite increases in life expectancy close their eyes to the living population," he says. "They look only at historical trends."

Max Planck Institute demographer Vaupel predicts life expectancy will continue to rise indefinitely at about three months per year. "Experts like me have a deep knowledge of the past," he says, "but we're remarkably bad at forecasting the future." But because there are so many unknowns, the only tried and true way is to extrapolate from the past, he says. "The future is going to be turbulent, but the past was also turbulent," he says. "In the 20th century we had a smoking epidemic that killed a lot of people — many more than obesity will. Nonetheless, life expectancy went up by a lot."

Meanwhile, Stanford's Bortz and others are working to persuade insurance companies to offer incentives to their customers to adopt lifestyles that would bring many more years of good health to older people.

Others suggest disincentives for unhealthy behaviors that reduce life expectancy. "We can put a tax on french fries," says psychiatry professor Gary Small, director of the UCLA Longevity Center at the University of California, Los Angeles. "When you have a tax on cigarettes, cancer rates go down. It's not rocket science. Make it harder for people to do bad things to our bodies. It's going to save health-care dollars."

On the research front, drugs are already in clinical trials that may mimic caloric restriction. [38] In other areas, NIA expects the field of epigenetics — an emerging science that looks at the interplay between genes and the environment — to shed light on aging. What people eat, drink and smoke and what toxins they're exposed to in the air and water, for example, influence their genes and how they age. Researchers also will try to move forward with "regenerative medicine," with the hope of using stem cell therapy to restore function in damaged tissue.

Although much remains unknown, says NIA's Hodes, "There's an incredible, dramatic, unthinkable amount we have learned. We have the skills and technical abilities that are capable of sustaining quite an incredible pace of discovery. We are going to learn how it can be translated into more practical applications. It won't be simple, but that doesn't mean it's not going to be accomplished." ■

About the Author

Beth Baker is an award-winning freelance journalist in Takoma Park, Md., whose articles appear in numerous publications, including *The Washington Post*, *AARP Bulletin*, *Ms.* and *BioScience*, where she is features editor. She has received two National Mature Media Awards for her reporting on aging and media fellowships to study aging and cancer issues from, respectively, Case Western Reserve University and the National Press Foundation. Her books include *Old Age in a New Age — The Promise of Transformative Nursing Homes* (Vanderbilt University Press, 2007). She is a former hospice volunteer.

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FOR MORE INFORMATION

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Caloric Restriction Society, 187 Ocean Dr., Newport, NC 28570; (877) 511-2702; www.crsociety.org. Promotes low-calorie diets as a means of increasing lifespan.

Duke Center on the Demography of Aging, Social Science Research Institute, Duke University, P.O. Box 90420, Durham, NC 27708; (919) 681-1972; www.dupri.duke.edu. Examines the "biodemography" of aging, including papers on human health and survival and on the biology of aging in plants and animals.

Eden Alternative, P.O. Box 18369, 1900 S. Clinton Ave., Rochester, NY 14618; (585) 461-3951; www.edenalt.org. Nonprofit working to change the traditional nursing home culture by introducing more development and growth opportunities for residents.

International Longevity Center, 722 W. 168th St., New York, NY 10032; (212) 305-3927; www.mailman.columbia.edu/academic-departments/centers/international-longevity-center. Columbia University research center conducting studies on healthy aging, ageism, caregiving, financial longevity and health care.

National Institute on Aging, National Institutes of Health, Building 31, Room 5C27, 31 Center Dr., MSC 2292, Bethesda, MD 20892; (301) 496-1752; www.nia.nih.gov. Provides information on the biology of aging and the latest on healthy aging and many age-associated diseases.

New England Centenarian Study, Boston Medical Center, 88 E. Newton St., Robinson 2400, Boston, MA 02118; (888) 333-6327; www.bumc.bu.edu/centenarian. Ongoing research about individuals who live 100 years or more.

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