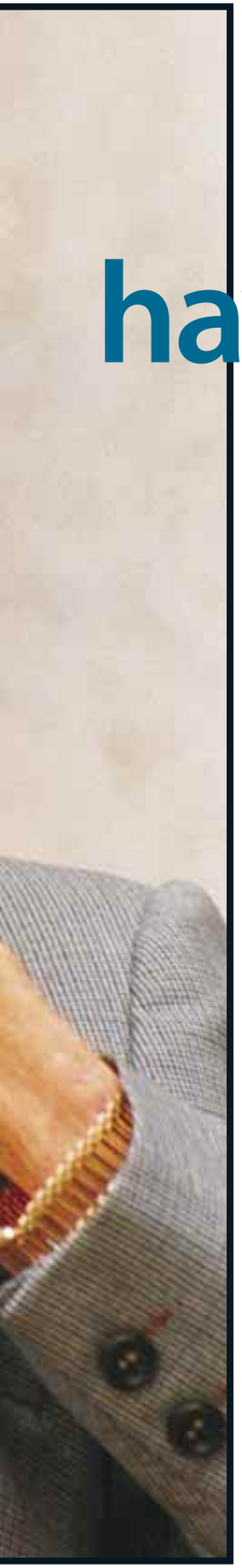
getting ever older

FRED PROUSER *Reuters/Archive Photos*



THE FIRST 150-YEAR-OLD PERSON MIGHT BE ALIVE RIGHT NOW

how long have you got?

BY KATHRYN BROWN

Forget growing old gracefully. For centuries, graying adults have tried all kinds of things to live longer: prayers, yogurt, mystical hot springs—even injections of goat-testicle extracts. Despite it all, the maximum human life span hasn't budged. At best, the statistics say, you can hope to reach about 120 years of age—and precious few actually do.

But don't throw out those birthday candles just yet. Some scientists now say they're about to trump Father Time. Working in the lab, biologists have already reared worms, fruit flies, mice and yeast that live twice as long as normal, thanks to mutations in a mere handful of genes. Other researchers are peering into the increasing molecular disorder that characterizes aging in humans, from damaged DNA to misbehaving cells. And physiologists are finding out why some people do get to celebrate their 100th birthdays. The oldest-known human, Jeanne Calment of France, recently died at 122, leaving researchers to marvel at the possibilities of long life. "Who's to say we couldn't go 10 or 20 years longer?" asks Caleb E. Finch, director of neurogerontology at the University of Southern California.

RACONTEUR: Comedian George Burns lived to 100. When asked if his doctor knew he still smoked, Burns said, "No ... he's dead."

Given the rate at which America is aging, that's a timely question. A century ago only 4 percent of the American population was above age 65. Now 13 percent is [see "From Baby Boom to Geezer Glut," on page 22]. One crowd stands out. According to the U.S. Census Bureau, the number of centenarians doubled over the past decade and may increase more than 11-fold by the year 2050. So far our seniority is mostly attributable to improved public health and modern medicine. But antiaging therapies may soon add even more candles to the cake, says zoologist Steven N. Austad of the University of Idaho. "The first 150-year-old person is probably alive right now," Austad predicts. Will it be you?

Why We Age

Ancient civilizations blamed the gods for old age. Today many scientists blame evolution, which holds that the swift hand of natural selection weeds out genes that hinder reproduction. So genetic traits that cause disease early in life, before our childbearing years, are fairly rare. While we're young, we're usually healthy and strong. "Our bodies are like rented cars," says demographer S. Jay Olshansky of the University of Chicago. "We use them up, and before things start to go dramatically wrong, we pass on our genes to the next generation."

getting ever older

After our baby-bearing time has passed, however, our job is done. Evolution needs us no more. There are two prevailing theories about what happens next. According to the first, developed in the 1950s by British immunologist Peter Medawar of the University of London, harmful mutations of the human genome kick into gear during midlife. Because natural selection is no longer looking out for us, he reasoned, our bodies fall prey to decline and disease.

Putting a slightly different spin on life, University of Manchester scientist Thomas B. L. Kirkwood offered the "disposable soma" hypothesis in the 1970s. It suggests that the more energy you spend bearing babies, the less you have for other metabolic feats, such as defending against mutations that cause the battles of aging. If you live fast—having a lot of babies when young—you tend to die younger. Natural selection will gladly make that swap, says evolutionary biologist Linda Partridge of University College, London. In recent years scientists have fleshed out this theory, proposing that some genes act beneficially early in life yet negatively later on.

At first glance, both evolutionary images of aging seem impossible to counter. If our golden years really are determined by mutations or subtle life trade-offs, how can scientists hope to understand aging—much less fight it? The process of aging could be dominated by perhaps 36 genes, although there may be another 200 that fine-tune it, concedes Michael R. Rose, an evolutionary biologist at the University of California at Irvine. "But that doesn't mean it's impossibly complicated," he says.

In fact, Rose has already managed to assemble generations of long-lived fruit flies. In a classic experiment published in 1991, he collected and hatched eggs laid by middle-aged fruit flies. He then collected the eggs of these offspring, but only those laid late in life. On he went, repeating the process, saving only the eggs laid by older and older flies. By doing so, Rose was acting as an evolutionary force: selecting for flies that reproduced late and lived long. If a species consistently delays reproduction until later in life, over many generations, then evolution will select for traits that allow for longer life, so reproduction has the best chance to succeed. After 10 generations, Rose's flies lived twice as long as their original ancestors. "It's possible for evolution to reshape patterns of mortality," Rose concluded.

But demographer Olshansky says we shouldn't expect to see a similar phenomenon at work in humans. It would take huge numbers of older mothers who delayed childbirth—and then dozens of generations of women who did the same—for evolution to even correlate the trend with longer and healthier lives, if indeed that resulted.

Altered Genes Alter Aging

Some molecular biologists contend that these evolutionary theories are wrong altogether. They say we are bombarded with damage from daily life and genetic malfunctions across our entire genome, including the reproductive portion. That means that stopping aging lies in changing our genes. Over the past few years an increasing number of researchers have altered animal life spans by tweaking certain genes. "Evolutionary biologists would have never thought you could change a single gene and double an organism's life span, especially without decreasing fertility," says Cynthia J. Kenyon of the University of California at San Francisco. "But that's precisely what we've done."

In Kenyon's laboratory the longevity gene at hand is called *daf-2*. Worms with a mutated *daf-2* live for a month, twice the norm. Moreover, by tinkering with related genes—*daf-12, daf-16* and *daf-23*—researchers have reared worms that live up to four times longer than the normal span. Kenyon thinks the *daf* genes direct hormones that ratchet up or down a worm's rate of aging in response to environmental challenges such as food supply or temperature. And worms aren't the only ones lingering on the lab bench. Yeast, fruit flies and mice have all eked out far longer lives than normal with the aid of a little genetic manipulation [see "Of Hyperaging and Methuselah Genes," on page 68].

Researchers still debate whether aging is the cumulative result of life's tiny assaults or a more programmed series of events determined at birth. They don't know how all these genes work.

centenarians who made

Charles Greeley Abbot (1872–1973)
Determined that the sun's radiation varies.

Edward E. Kleinschmidt (1876–1977)
Teletype inventor.

Madame Chiang Kai-shek (1897–present)
Anti-Communist crusader.

BETTMANN/CORBIS (*Charles Greeley Abbot* and *Edward E. Kleinschmidt*); CHENG HUI HSU Reuters/Archive Photos (*Madame Chiang Kai-shek*)

a difference

Irving Berlin (1888–1989)
Composer of American song standards.

Grandma Moses (1860–1961)
Folk artist, began painting at 78.

Rose Kennedy (1890–1995)
America's best-known matriarch.

CORBIS (*Irving Berlin*); ARTHUR ROTHSTEIN *Corbis* (*Grandma Moses*); CORNELL CAPA *Magnum* (*Rose Kennedy*)

Healthy habits now can add years later.

And even if they someday understand the genetic mechanisms, that doesn't mean they'll find a "cure" for aging. We know how cancer works, for example, but we haven't stopped it from commencing in people.

At present, we must be content with the few pieces of the puzzle that are starting to come together. For instance, at least four of the newfound genes affecting the longevity of lab creatures encode antioxidant enzymes. These chemicals disarm harmful oxygen molecules, called free radicals, that emerge whenever cells turn food and oxygen into energy. Like dancers looking for partners, free radicals careen within and between cells, binding to nearby molecules and disrupting normal activity. Over time, scientists suggest, this free-radical damage adds up, causing tissues and organs to deteriorate with age. This oxidizing of our bodies is often compared to the oxidizing—rusting—of metal [see "A Radical Proposal," on page 38].

Lab organisms endowed with certain extra longevity genes seem to fend off damage from free radicals and similar stresses, such as UV radiation, says scientist Thomas E. Johnson of the University of Colorado at Boulder. That molecular trick results in longer life. If researchers can reduce free radicals or boost antioxidant defenses in these animals, he adds, they may be able to design drugs to do the same for humans. "I'm confident we'll find drugs that stimulate resistance to environmental stresses and so increase longevity," says Johnson, who works with GenoPlex, a Denver company he helped to found.

Not everyone is so confident. Genes that contribute to the lengthier lives of certain lab animals may not explain aging in people at all, argues anatomist Leonard Hayflick of the University of California at San Francisco. "Humans are not big flies," Hayflick says. "To extrapolate from flies, mice and yeast to humans is utter nonsense. There are an incredible number of genes related to aging in humans that don't even exist in those organisms."

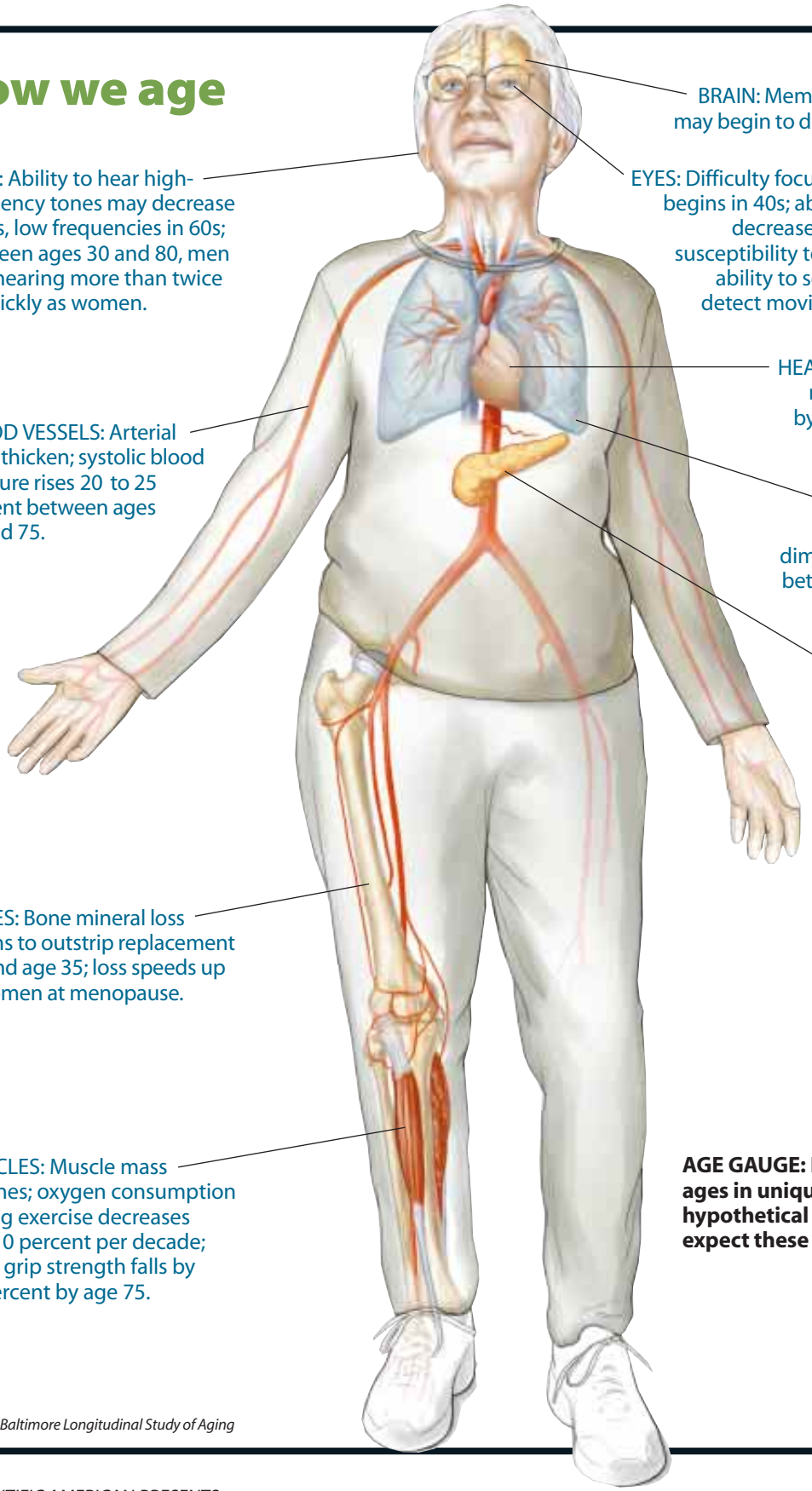
Researchers do agree that oxidative damage is only one possible cause of aging. According to a recent tally, some 300 theories of aging have been proposed—and at the very least, several key processes are involved. In addition to free radicals, for instance, aimless glucose (sugar) molecules attach to proteins, causing those proteins to link up unnaturally and change function, possibly leading to hardened arteries, tougher skin tissue, cataracts and other evils of the silver years.

Furthermore, some cells start misbehaving all on their own. After many years, somatic (body) cells stop dividing, but some don't simply die. Many apparently switch functions—often for the worse. Biologist Judith Campisi of Lawrence Berkeley National Laboratory has found that cells that give youthful skin its smooth elasticity stop dividing and then go awry late in life, breaking down the very same elasticity. "As we start to understand how this works, we have the hope of stopping these altered functions," Campisi says. This work goes hand in hand with studies of cancerous cells that won't stop dividing, as well as studies of multipurpose stem cells that could replace mature cells lost to heart disease, Parkinson's disease and other ills. [Studies on cell senescence are detailed in "Counting the Lives of a Cell," on page 50; "Mother Nature's Menders," on page 56, describes stem cell research.]

Your Number Is Up

The biochemical bits of aging may be the same for everyone, but they certainly add up differently. Your neighbor may have run a marathon at 70, while your landlord was busy having heart surgery. Your great-aunt was a

how we age



BRAIN: Memory and reaction time may begin to decline around age 70.

EYES: Difficulty focusing on close objects begins in 40s; ability to see fine detail decreases in 70s; from age 50, susceptibility to glare increases, and ability to see in dim light and to detect moving targets decreases.

EARS: Ability to hear high-frequency tones may decrease in 20s, low frequencies in 60s; between ages 30 and 80, men lose hearing more than twice as quickly as women.

HEART: Heart rate during maximal exercise falls by 25 percent between ages 20 and 75.

BLOOD VESSELS: Arterial walls thicken; systolic blood pressure rises 20 to 25 percent between ages 20 and 75.

LUNGS: Maximum breathing capacity diminishes by 40 percent between ages 20 and 80.

PANCREAS: Glucose metabolism declines progressively.

BONES: Bone mineral loss begins to outstrip replacement around age 35; loss speeds up in women at menopause.

MUSCLES: Muscle mass declines; oxygen consumption during exercise decreases 5 to 10 percent per decade; hand grip strength falls by 45 percent by age 75.

AGE GAUGE: Each person's body ages in unique ways, but a hypothetical average person can expect these changes over time.

SOURCE: Baltimore Longitudinal Study of Aging

TERESE WINSLOW

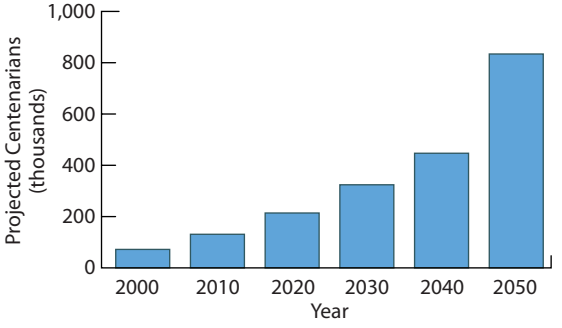
chess champion, but your grandfather couldn't remember his address. Aging is incredibly variable. "Researchers used to believe that the older you get, the sicker you get," says Harvard Medical School physician Thomas T. Perls. "That's completely wrong."

To find out what "normal" aging is, researchers with the National Institute on Aging's Baltimore Longitudinal Study of Aging (BLSA) examine the bodies and brains of volunteers every two years. The longest-running scientific study of human aging in the U.S., the BLSA began in 1958 and now has more than 1,100 active participants. The study is a snapshot of healthy aging, and yes, it does portray a gradual physical decline. As a senior, you probably won't see, hear or breathe quite as easily as you once did. But the study also suggests that life's slings and arrows aren't all outside your control. Without exercise, for example, a 30-year-old woman will lose a quarter of her muscle mass by the age of 70. But a few jaunts around the park or trips to the gym every week can fend off this by-product of aging.

Indeed, Perls says, starting healthy habits now can add years later on. Do you smoke? Keep a positive attitude? Limit red meat? The answers to such questions may affect your likely expiration date. And if you'd like to calculate that fateful moment yourself, try the Life Expectancy Calculator (www.beeson.org/Livingto100/). The tool, presented in Perls's 1999 book, co-authored with Margery H. Silver, *Living to 100: Lessons in Living to Your Maximum Potential at Any Age*, will put a number on your mortality by analyzing your answers to 23 behavior and background questions. Perls says those of us with average genes and healthy habits can expect to live until about 85.

That's pretty good—already almost twice as long as our recent relatives. Since 1900 the average life span in the U.S. has jumped from about 47 to about 76 years, according to the National Institute on Aging. It's not that we're aging more slowly. We're living longer simply because we escape many of the illnesses and events that plagued our ancestors, from death during childbirth to tuberculosis, largely because of better sanitation, cleaner water supplies and basic medical advances such as immunizations. There is new light at the end of the tunnel, too: once you creep far enough along, it

centenarian boom



RAPID RISE: By midcentury the Census Bureau predicts the U.S. could be home to nearly 835,000 centenarians, more than 11 times the number today.

LAURIE GRACE

taking it to the limit

In the good old days, aging wasn't viewed as complex. Some scientists reasoned that, like a car with a full tank of gas, our bodies arrive on earth topped off with some kind of vital substance. As time passes, our tanks drain and our bodies age. Here are a few of the notorious theories about life's limits that have emerged in modern times.

Vital humors — 19th century

Vital humors control all your bodily functions. When these humors run dry, your time is up.

Energy — 1920s–1930s

As you use energy, your cells steadily break down. The faster you live, the faster you burn energy and the sooner your demise, maintains this rate-of-living theory.

Heartbeats — 1950s

Mammals get about one billion heartbeats. As you near that limit, your heart breaks down.

DUSAN PETRICIC

world's
oldest creatures

Hiding inside rocky crevices 1,800 feet below the Pacific Ocean, rockfish stubbornly persist well past 100 years, far surpassing their peers. Giant 10-foot-long tube worms sway in the dark depths of the Gulf of Mexico for up to 250 years. Blanding's turtles can slosh through Midwestern U.S. wetlands for at least 70 years, and certain giant tortoises push 300. Defying even greater odds, some bristlecone pines high in the California and Nevada mountains have lived almost 5,000 years!

How do these remarkable creatures do it? Scientists are trying to find out, hoping to learn more about how nature's organisms age and thus how we might lengthen human life. "The natural world offers hundreds of lessons in longevity," says University of Southern California gerontologist Caleb E. Finch.

One lesson: find an environment free of predators. Researchers have identified yelloweye and rougheye rockfish as old as 118 and 149 years, respectively, at great ocean depths. They endure partly because many of their predators prefer shallower waters, says Allen H. Andrews, a research associate at California State University. Blanding's turtles may outlive soft-shelled varieties because their rough, hard exterior deflects the bite of hungry critters, explains ecologist Justin D. Congdon of the Savannah River Ecology Laboratory in Aiken, S.C.

The record-breaking bristlecone pines have also found a safe haven; they prevail at around 11,500 feet above sea level, too high for the comfort of many insects or competing trees. One pine at Nevada's Wheeler Peak was estimated to be 4,900 years old, based on its annual growth rings, before it was cut down in 1964. Amazingly, Finch says, the trees seem to reproduce just as well in their 4,000th year as in earlier days.

For a long time, scientists didn't bother to study the longevity of animals and plants. They assumed that most creatures would die before their time because of predators, competition, natural disasters, insects or disease. But that idea is changing. To measure more precisely the effect of environment on aging and longevity, University of Idaho biologist Steven N. Austad turned to an animal that normally lives fast, breeds madly and dies young: the opossum. Austad reasoned that opossums living without the evolutionary pressure of many predators—such as owls, coyotes and wolves—would age and breed more slowly, ultimately living longer. About a decade ago he found that very situation on Sapelo Island, a scrap of land off the Georgia coast. There opossums live up to 50 percent longer than on the mainland—and actually age more slowly along the way, according to Austad's measurements of their tissues over time. Austad is now looking for similar longevity in island mice, considerably easier creatures to study in the lab.


Bristlecone pine


Galápagos giant tortoise


Yelloweye rockfish

GALEN ROWELL *Peter Arnold, Inc. (bristlecone pine)*; GERALD LACZ *Animals Animals (Galápagos giant tortoise)*; DOUG WECHSLER *Animals Animals (yelloweye rockfish)*

Austad's research underscores the flexibility—or "plasticity"—of aging, suggesting that the right environment can increase life span. The question now at hand is: Once predators and competition are removed, do biological processes take over and cause aging in animals, even those that live a squeaky-clean lifestyle?

For clues, Austad and University of Idaho ecologist Donna J. Holmes are looking skyward. Five years ago they proposed birds as the ideal animal to use in aging studies. After all, birds are closer to humans, biologically speaking, than are worms or fruit flies, the favorite subjects of aging-study labs. They are warm-blooded, like us, so they don't lapse into periods of dormancy or hibernation, as do fish and turtles. Moreover, some birds live for decades against all odds.

This is even more remarkable because, to rev up for flight, birds generate extremely high levels of blood sugar. The 150 parakeets twittering around a basement lab at the University of Idaho have blood sugar levels so high they should be diabetic. They have elevated temperatures and burn energy at feverish rates. Yet they live to 20, old for parakeets. These bird traits defy a primary theory of aging—that increased metabolism creates higher levels of oxygen molecules, called free radicals, that oxidize cells, damaging tissue in ways normally associated with aging. Rather than rapidly growing weak and dying, birds carry on in good health, year after year.

In 1998 Holmes, Austad and their colleagues reported that the cells of three bird species—canaries, European starlings and budgerigars (a.k.a. parakeets)—can endure a battery of oxidative stresses with surprisingly little damage. The scientists exposed these bird cells, along with the cells of mice, to baths of hydrogen peroxide, bolts of radiation, chambers of oxygen and doses of pesticide. Under these assaults, the DNA inside the mouse cells often unraveled, broke or stopped replicating, typical signs of free-radical damage. The bird cells, on the other hand, divided normally and repaired much of the induced DNA damage right away. "We don't have any idea yet how the bird cells are doing it," Holmes says. "But it appears that birds have special enzymes that dispose of free radicals. If free radicals are a primary mechanism of aging, then this may explain why these birds live so long."

If the scientists find the genes responsible for birds' resistance to free-radical damage, they might someday apply them to humans. "Ultimately," Holmes continues, "it's possible that gene therapy could transfer a gene from the bird genome to the mammalian genome." As U.S.C.'s Finch puts it, "We're in a major discovery phase now." If researchers can understand the endings of other species, we just might learn how to rewrite our own. —*K.B.*

seems, your chances of dying actually begin to ease. Demographers have found that death rates steadily climb until about 85—and then begin to slowly edge back down again. The same phenomenon holds true for some fruit flies, wasps, worms and yeast in studies led by researcher James W. Vaupel of Duke University and the Max Planck Institute for Demographic Research in Rostock, Germany. It's as though we all decline to a certain point, rest, get our second wind and rally back.

And some people *really* rally. As the number of centenarians in the U.S. climbs, scientists hope to learn the secrets of their success. Already Perls has a few hints, gathered as head of the New England Centenarian Study, which tracks more than 450,000 older adults in Massachusetts to see who reaches 100 and why.

So far 169 centenarians have participated in the study; there is data on 250 others. They are a motley crew: Some exercise. Some smoke. Some brazenly defy the notion of a healthy lifestyle. Nevertheless, almost all have lived free of cancer, and up to a fourth have escaped any form of dementia.

How do they do it? With luck—and a few "genetic booster rockets," Perls says. Studying half a dozen families that include 10 or more centenarians, he is closing in on chromosome regions with genes linked to long life. Isolating the genes won't be easy, but drugs to mimic their effects could one day prevent some deadly diseases of old age. "In the future, we may be able to look at your genetic profile, determine your risk for various diseases, and give you vitaminlike pills to delay or prevent those diseases," Perls forecasts. Blessed with centenarian-style health, you too may live to well over 100. ["Design for Living," on page 18, relates more about what scientists have learned from studying centenarians.]

Whether you will live *many* years beyond 100, though, remains to be seen. No one knows when or how scientists might extend our life spans. It's been more than 60 years since researchers first discovered that lab animals that consume fewer calories than normal—a regimen known as caloric restriction—tend to live unusually long. But scientists still don't know how caloric restriction works or if it can slow aging in humans [see "The Famine of Youth," on page 44]. There are other dilemmas as well. Could the U.S. afford legions of elderly people? Would you be alive but ridden with ailments at age 130? At 150? "This research raises all kinds of ferocious social and economic questions," University College's Partridge observes.

We just might find ourselves answering these questions. "People tend to underestimate how fast the aging field is moving," claims biologist Leonard P. Guarente of the Massachusetts Institute of Technology. "We're uncovering the molecular basis of aging. No, we're not at a point where we can intervene in humans yet. But we have every reason to be hopeful that day will come."

Kathryn Brown *is a writer at* Science News.

Further Information

Life Expectancy Calculator can be found at www.beeson.org/Livingto100/ on the World Wide Web.

Why We Age. Steven N. Austad. John Wiley & Sons, 1997.