The Science of Living Longer

SPECIAL 22-PAGE HEALTH SECTION

THREE GENERATIONS
Laila, 7; mother Kristina, 37; grandmother Laila, 65
LIFE EXPECTANCY

Your Kids Could Reach 100

A baby born in the U.S. today can realistically look forward to living to 100, scientists say, despite official life expectancies in the developed world in the high 70s to low 80s.

Confused? It's all in the language. The life-expectancy stat that's so commonly used is not, in fact, meant to reflect our expectations for the future. We can't know what medical breakthrough may come along to extend our lives or what plague may shorten them. Life-expectancy figures instead describe how long we'd live, hypothetically, if today's death rates never changed.

But Danish scientist Kaare Christensen and his colleagues have calculated a different kind of projection, one that assumes longevity improvements will continue at their current pace. In that model, more than half the children in the developed world will be around for their 100th birthday. Now may be a good time to invest in candles.

"I don't envision 1,000-year-old people, but 150-year-old people? That's a pretty modest increase over what we've got now."

—STEVEN AUSTAD, University of Texas Health Science Center, San Antonio

GENERIC

The Importance of Being Female

There's nothing new about the fact that women live longer than men—and nothing uniquely human about it either. The same is true in many other mammals. Japanese scientists may have new insights into why.

Manabu Kawahara at Saga University and Tomohiro Kono, based in Tokyo, compared mice that were engineered from two female genomes—so they had no genetic father—with normal female mice. The bimaternal mice lived an average of 186 days longer, a life-span boost of 30%.

The longevity dividend seems linked to something in the female genome, and though it's not clear what that critical variable is, size of the animal may play a role. The bimaternal mice were much smaller than the other females. In the natural world, males grow bigger, perhaps to improve their chance of breeding, but that investment in growth may affect metabolism and limit longevity. Eliminate the male genome, and you appear to eliminate the penalty. The mice with two moms also had higher levels of eosinophil, a type of white blood cell—which hints at improved immune function.

SCIENCE

Longevity Drugs May Be Coming

Elixirs of youth sound fanciful, but the first crude antiaging drugs may not be so far away. To date, two compounds have sparked scientists' interest: resveratrol, a substance found in grapes, red wine and peanuts; and rapamycin, first isolated in the soil of Easter Island. Both compounds seem to work in animals to mimic the biological response to calorie restriction, an imperfectly understood technique that extends life span in lab specimens, including yeast, mice and, most recently, rhesus monkeys.

Resveratrol is currently available as a dietary supplement. A drug formulation of resveratrol is now being put to a more rigorous test, in clinical trials as a treatment for Type 2 diabetes and cancers. The company behind the drug, Sirtris Pharmaceuticals (bought by pharma giant GlaxoSmithKline in 2008), is touting that compound and two others—chemically unrelated to resveratrol but targeting the same pathway—as drugs that battle aging-related diseases.

Rapamycin, the other
big candidate, has one clear advantage over resveratrol: it's already FDA approved as a drug—but as an immuno-suppressant. Don't expect it to be rolled out to the masses as a miracle drug just yet though. Rapamycin leaves users susceptible to infection—at least in the doses typically used today—and has other harmful side effects too.

**INNOVATION**

**Slowing Aging ... With Semen**

Hold your laughter. It’s not the setup for a joke. Austrian researchers believe that a compound in human semen can have a dramatic impact on life span. Biochemists Frank Madeo and Tobias Eisenberg at the University of Graz led a team to test the effects of a substance known as spermidine. In yeast, spermidine was shown to increase life span by as much as a factor of four; in fruit flies, up to 30%; and in worms, up to 15%. When spermidine was applied to human immune cells, they too lived longer, with three times as many surviving after 12 days as in a comparison batch.

Spermidine works, the researchers show, by promoting the cellular process of autophagy—a kind of self-cleaning that, Eisenberg says, “removes cellular garbage such as clumped proteins or damaged or defective cellular organelles.” Those things might otherwise harm the body.

**GENETICS**

**How Do You Spell Longevity? D-N-A**

What if exceptionally long life could be brought about with a single genetic mutation? In a few very simple species, that appears to be the case, and molecular biologists are exploring ways to parlay that knowledge into something that could benefit humans.

In a blockbuster discovery last year, scientists at the University of Washington found a group of genes that seem to affect roundworms’ life span through activation of the hypoxic response, a biological defense against low-oxygen environments. Matt Kaeberlein and his colleagues engineered the worms to have the response turned on at all times, even when there was plenty of oxygen. Result: they lived longer and were healthier. It’s not clear why that worked or whether it would have the same effect in mammals, but Kaeberlein believes the hypoxic response may encourage cells to metabolize more glucose. It may also enhance resistance to stress in some way.

The more such longevity genes that researchers have in hand, the more they can test to see if they work roughly the same way up the chain of lab-organism complexity, from yeast to fruit flies to mice and finally to us. “A lot of genes have been identified that when you perturb their function, you get increased life span,” Kaeberlein says. The challenge is finding ones that will work in humans—something that may not happen soon but, Kaeberlein believes, is likely in the future. “There’s good reason for optimism,” he says.
Feed Your Cells and Keep Them Young

Omega-3 fatty acids—found in fish oil and flaxseed—are already known to help protect you from such age-related illnesses as heart disease. Now research shows they may slow cellular aging.

Doctors followed 608 San Francisco patients with stable coronary-artery disease and found that those with high blood levels of omega-3 fatty acids had less telomere shortening over the next five years. Telomeres are protective caps at the ends of chromosomes (frequently likened to the plastic tips that keep shoe laces from fraying), and telomere length is increasingly seen as a marker for biological aging—entirely separate from chronological age.

In earlier research, cardiologist Ramin Farzaneh-Far, who led the new omega-3 study, helped show that telomere length can be a predictor of death risk in humans. The new finding is exciting because, he says, “it means that telomere shortening is not inevitable.”

A good diet may not just keep you healthy. Perhaps it really can keep you young.

Longest recorded life span in select species (the figures for the whale and the lion are approximate)

- **Bowhead Whale** 200 years
- **Human** 122 years
- **Pigeon** 35 years
- **Lion** 30 years
- **Mouse** 4 years
- **Fruit Fly** 153 days

Trends

Ups and Downs

Lab breakthroughs may help us live long in spite of ourselves. But for now, our life span is still heavily influenced by environment and by how well we behave. Some recent findings from the greatest lab of all, the real world:

**Breathe easy.** Through the 1980s and '90s, U.S. city dwellers gained nearly five months of life expectancy because of clean-air improvements, according to 2009 estimates in the *New England Journal of Medicine*.

**Long life—for some.** Americans made solid life-span gains throughout the second half of the 20th century, but not everyone has shared equally. For roughly 4% of the male population and 19% of the female population, according to a 2008 report in the journal *PLoS Medicine*, life expectancy stagnated or even fell. The main culprits: lifestyle-related diseases like lung cancer and diabetes.

**Perils of the plate.** If all U.S. adults were normal-weight nonsmokers by 2020, a teenager who turned 18 that year could expect to live an extra 3.76 years, according to Harvard economists and a University of Michigan doctor. But given current trends, the life-span boost from our steadily falling tobacco use may be erased by our steadily rising obesity rates.
The Hurlburt Siblings

Peggy
79
WEYMOUTH, MASS.
She's the youngest and has every intention of living as long—and well—as her siblings.

Helen
88
HINGHAM, MASS.
With a newly renewed driver's license, she volunteers at a local hospital.

Millie
93
SHREWSBURY, MASS.
Physically active like the rest of her family, she exercises twice a week for an hour.

Peter
80
BRAINTREE, MASS.
After teaching himself the piano, he wrote all his children's wedding songs.
Agnes
96
NASHUA, N.H.
She made Christmas dinner last year and bakes scones for her brothers in California

Muriel
89
WEST ROXBURY, MASS.
Always creative, she likes to write poetry and sew quilts for the family

Health Checkup

THE TOPIC A century of life was once a rare thing, but that is changing. Science is slowly unraveling the secrets of the centenarians

How To Live 100 Years

BY ALICE PARK

Photograph for TIME by Jason Grow
Don't write that down! Put your pencil away!” Agnes Buckley is trying in vain to head off an entertaining story her sisters are telling me about how she used to sneak out of the house as a teenager. (She favored boys with motorcycles.) When their father hid her shoes to keep her at home, Agnes simply bypassed the front door and leaped out the window.

“Everyone is going to think I was a troublemaker,” she laments.

Don't worry, Agnes. You may have had some fun as a teen, but there's a lifetime of evidence to prove you've grown into respectability. A lifetime, that is, that already includes a full decade and a half more than the 80 or so years that a girl born in the U.S. today can expect to live. Agnes was born in 1913—the year that Grand Central Terminal opened in New York City and the U.S. Postal Service began delivering packages as well as letters—which makes her 96 years old. Two of her 11 brothers and sisters are nonagenarians too. The other surviving members of the clan are pushing 80 or well beyond it. And, as Agnes points out, “none of us have canes.”

In fact, the entire Hurlburt family is a model of long-lived, healthful vigor, which makes it a perfect candidate for the Long Life Family Study (LLFS), an investigation into the factors that help certain families produce members who live into their 80s, 90s and even 100s. The study—sponsored by the National Institute on Aging, part of the National Institutes of Health—includes investigators from four U.S. research centers and one Danish one. The idea, says Dr. Thomas Perls, the principal investigator at the Boston University Medical Center location, is to figure out which genetic, environmental and behavioral factors contribute to longevity.

“When it comes to rare genetic variations that contribute to longevity, family [analysis] is particularly powerful,” he says. “But just because something occurs in a family doesn't mean it is necessarily genetic. There are lots of behaviors and traditions that happen in families that play a role in longer life expectancies. We want to use these families to ferret out what these factors are.”

There's no denying that longer life expectancy is swelling the number of seniors—people over age 65—in our population. But it's the fastest-growing subset of that superannuated group that proves the most interesting for...
researchers—those over age 85, in particular the centenarians born in the late 1800s, who have lived through the 1918 flu pandemic, the Great Depression and both world wars; have witnessed women's suffrage and the moon landings; and are still here, keeping up with world events during the Administration of the nation's first African-American President.

In the most recent Census, health officials predicted that by 2050, more than 800,000 Americans would be pushing into their second century of life. After the numbers from the 2010 Census are tabulated, some experts believe that figure will grow. By all accounts, these new centenarians are far from the frail, ailing, housebound people you might expect. In contrast, the majority of them are mentally alert and relatively free of disability and remain active members of their communities. They may simply represent a new model of aging, one that health experts are hoping more of us can emulate, both to make our lives fuller and to ease the inevitable health care burden that our longer-lived population will impose in coming decades.

Most people today fall prey to chronic diseases that strike in mid to late life—conditions such as cancer, heart disease, stroke and dementia—and end up nursing disabilities stemming from these illnesses for the remainder of their lives. Centenarians, on the other hand, appear to be remarkably resilient when it comes to shrugging off such ailments; they seem to draw on some reserve that allows them to bounce back from health problems and remain relatively hale until their final days.

Dozens of studies have investigated such individuals, with the goal of picking out the secrets to their salubrious seniority. Those analyses, however, have generally followed two separate if parallel tracks. The traditional approach has been to study the lifestyle and behavioral components of vigorous aging—the good habits, such as a healthy diet, regular
Otis Clark
SEATTLE
He was born in Oklahoma before it became a state and still preaches every Sunday.

physical activity and mental exercises that might keep the elderly vibrant through their golden years. The New England Centenarian Study, which includes 650 people entering their 100s, for example, has identified several behavioral and personality traits that seem to be critical to longevity, including not smoking, being extroverted and easygoing and staying lean.

Separately, biologists and geneticists have pursued the secret to longevity on a cellular or molecular level, first in animals and more recently in people. The goal is to identify genes associated with slowing normal aging and avoiding the chronic illnesses that accompany it.

But with advances in genomic technology that allow scientists to scan thousands of genes from a single sample at a time and then link them to specific functions in the body, researchers on aging can finally begin to knit together their two strands of inquiry. The result is an intricate tapestry that is starting to reveal exactly how we can best push the limits of life span. These findings in turn could eventually lead to drugs or other compounds that mimic such natural mechanisms, stretching lives a bit longer by keeping the genome in good repair, for example, or by boosting the body’s defenses against free radicals. If we can’t stay chronologically young, the scientists reason, we can at least live and feel as if we are.

“We are going through a revolution,” says David Sinclair, a professor of pathology at Harvard Medical School, who has studied aging in animals and co-founded Sirtris, a biotech company developing antiaging compounds. “I think we might have our first handle on the molecules that can improve health.” Even if we are not endowed with the genes that can ease us into our 100s, most of us can certainly learn something from families like the Hurlburts, who apparently are.

Of Yeast and Men
UNTIL RELATIVELY RECENTLY, THE BEST clues about the factors involved in growing old came not from healthily aging humans but from other, decidedly less interesting species. Take, for instance, yeast. These organisms provided the first hints about how much of aging was due to genes and innate biology and how much was the product of other variables. It was yeast and, later, flies and rodents that provided the first findings about caloric restriction, the intriguing hypothesis that a drastically reduced intake of calories can extend life span. (See page 78.)
While there is no firm evidence that the same phenomenon occurs in humans, researchers like Leonard Guarente at the Massachusetts Institute of Technology found yeast genes that appear to cause a food-restricted metabolism to use energy more efficiently, burning through caloric inventory at just the right rate to maintain life-sustaining processes while keeping something around for future use. Sinclair calls these survival genes. When they’re activated, he says, they stabilize DNA and, in the yeast’s case, extended survival 30% beyond what is normal. So far, Sinclair and others have identified a dozen similar genes in people. What they are hoping to do is find a way to turn these pathways on without forcing the rest of the body to hunker down in survival mode.

But while genes are certainly an important component of aging, they may not be the most relevant factor, if only because we don’t have much control over them. The good news is that according to animal studies, only about 30% of aging is genetically based, which means that the majority of other variables are in our hands. Not only can getting such factors under control help slow the aging process before it starts, it can also help those who are already in their golden years improve their fitness and strength. Recent studies have shown, for example, that when seniors from ages 65 to 75 exercise with resistance weights, they can improve their scores on cognitive tests of memory and decision-making. Other research, in Germany, found that regular physical activity lowers the risk of developing cognitive impairment in people over age 55.

The 70%-30% split between environment and genes, however, doesn’t apply to everybody. For lucky oldsters like those who qualify for the LLFS study, the reverse seems to be true. Perls has found that in centenarians, it’s principally genes that are the secret to extra years. That’s not surprising, since these people represent the extreme limit of our species’ life expectancy. But the centenarians’ happy accident of
Like other elderly people, centenarians get sick, but they log less time in intensive care and require less-expensive treatment.
Leonard McCracken

106
TAVARES, FLA.

A survivor of the 1918 flu pandemic, he attributes his longevity to eating oats.

identified no fewer than 440 genes that start to slow down after age 40. Using that set as a starting point, Yankner’s group is trying to determine just what those genes do to affect individual aging processes.

The virtue of such an approach is that it gives you a look at the entire developmental trajectory of the key genes throughout the adult life span. The disadvantage is that it lacks specificity: you can’t ever know which 24-to-80-year-olds will actually make it to 90 and beyond, so you can’t be certain from looking at their brains which genes are really at work in extreme old age and which eventually deteriorate. For that reason, Yankner’s team—like the LLFS investigators—is also studying the brains of a separate group of people who have already achieved extreme old age. Coming at the data from two different directions could better pinpoint the genes that are truly in play and lead to a reasonable library of targets for deeper research.

Newly discovered genes regulate the connections between brain cells—and it’s healthy connections that keep neurons alive.

“It’s a work in progress, but we believe that the expression of genes in the brain and how they are regulated is at least an indicator of how well someone is aging,” Yankner says. “It may play a causal role as well.”

Indeed, a causal role is precisely what the early results suggest. The key function of the collection of brain genes Yankner has identified is to regulate the connections between neurons—vital importance, since it’s healthy connections that keep neurons alive. Among the first ones to go when brain cells start dying are those involved in learning and memory. This may help explain why even the sharpest oldsters are prone to so-called senior moments, a tendency to forget newly learned information or repeat stories or questions, sometimes over and over again. Other genes in the collection have more-precise repair duties, fixing small nicks and mistakes in DNA. Without such maintenance work, normal genetic activities are slowly compromised.

Yet despite his excitement over his genetic findings, Yankner too is adamant that DNA is not destiny. Just as you can
keep your body fit with good lifestyle habits and by avoiding pollutants, toxins and carcinogens, you may be able to keep your genes healthier. Environmentally triggered alterations in genes—known as epigenetic changes—can affect when a gene is activated, how robustly it is turned on and how it interacts with neighboring genes. Free radicals provide a very good case study of how epigenetic processes play out.

As the brain ages, it weathers a constant onslaught from these destructive oxygen ions. The body is able to patch over tiny dings and cuts in the genome, but over time, the genetic fixers can no longer keep up, and the function of the gene is compromised. The balance between wear and repair may be the key to a healthily aging brain. By scanning the genomes of centenarians, Yankner hopes to isolate the genes—and the biological processes attached to them—that help them stay ahead of the damage. Those might then be harnessed to give non-centenarians the same edge.

The first step to longer life spans is to get back some of what we lose by living our overfed, overstressed, underactive lifestyles...

If studies are going to determine how adopting such behaviors can influence and strengthen genes, they're going to need a lot of volunteers, and the LLFS, like the New England study, is ready. So far, the trial includes 840 families like the Hurlburts, with 4,800 siblings who were at least 79 when they enrolled in 2006—and many of their children. All of the participants signed on knowing they'd be sitting still for in-depth interviews, recounting family histories and providing blood and DNA samples. And all have happily done their part. “I am interested to see if their influence can carry over to our generation,” says Janet Kinnally, 61, who joined the study along with her mother Helen. “I hope the research leads to things that are helpful for generations to come.”

None of this means that centenarian studies will produce a youth pill for the rest of us anytime soon—or ever, despite all the overblown claims made by hawks of antiaging compounds such as human growth hormone or resveratrol, an ingredient found in red wine. The goal, at least at first, will be merely to give us back some of what we lose by living a modern—which is to say, overfed, overstressed and underactive—lifestyle. “One misconception of aging research is that we are looking to prevent aging,” says Sinclair. “What we are hoping to do is to come up with something that will give us a lifestyle that now only centenarians enjoy.”

That's an idea that certainly appeals to the Hurlburts' three dozen children, who like to believe that their parents' genes give them a leg up but aren't taking any chances. “Our lifestyles are more stressful than theirs were,” says Maureen Miraglia, 62, one of Agnes' daughters. “But I am trying to change to be more like my mother. Most of my friends are talking about retiring, but I look at my mother, and I'm looking forward to my next decade and trying to figure out what I want to do.”

As studies of the longest-lived among us continue to reveal more secrets to living well into old age, we can hope that's a happy dilemma that more of us will have.