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How to Live 100 Years

By Alice Park

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 physical activity and mental exercises that might keep the elderly vibrant through their golden years. The New England Centenarian Study, which includes 850 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.

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 birth may benefit the rest of us too, if Perls and his colleagues are successful in their work. Their first goal is to draw a complete map of their subjects' genomes, to figure out what makes their mortality clocks tick so slowly and for so long. "We think centenarians are going to be really powerful when it comes to genetic variations or combinations that are important to living to really old age," says Perls.

The challenge for researchers is to identify those genes that contribute not just to longevity but to healthy longevity in particular. Based on its unique collection of genetic data from the New England Centenarian Study, Perls' team is close to identifying such a suite of genes. From the evidence gathered so far, it appears that for the most part, people who live to 100 and beyond do not necessarily avoid the chronic diseases of aging that normally claim the rest of us after midlife. About 40% of centenarians have experienced one of these illnesses in their lifetimes, but they seem to push through them without long-term problems or complications. And when they do get sick, according to a study Perls conducted in 1996, they are less likely to log time in the intensive-care unit (ICU) and often require less-expensive care per admission — at least compared with the cardiac surgery, chemotherapy and other ICU procedures that many of their younger elderly counterparts need.

Even as the LLFS investigators look for the full sweep of genes behind such resilience, other researchers are focusing on individual areas of the body — particularly the brain. Dr. Bruce Yankner at Harvard Medical School is studying what distinguishes brains that make it to 100 with limited cognitive decline from those that succumb to the ravages of Alzheimer's disease or other forms of dementia before age 85. Yankner zeroed in on genes in the frontal cortex — which is involved in higher learning, planning and goal setting — of people ages 24 to 106. That's a big chronological span, and it netted a big genetic haul: the research 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.

"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 — vitally important, 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 noncentenarians the same edge.

That work might also begin to explain the growing body of evidence behind the use-it-or-lose-it hypothesis, which suggests that people can improve their odds of remaining mentally alert by keeping their minds engaged. Learning a new language, picking up a hobby and maintaining a rich network of social connections are all ways to keep brain neurons firing. Yankner and others hope to isolate which brain circuits seem to be most active in this process.

A Different Kind of Youth

If everyone could begin to mimic what the centenarians do naturally, we'd all benefit — as the Hurlburts vividly illustrate. Agnes was mentally nimble enough as she aged that she learned to drive when she was 63, and she only recently gave up her license ("I was a very fast driver, but they never caught me," she confesses); Walter, 84, is an accomplished painter; Muriel, 89, writes poetry and sews quilts; James, 91, is also a poet; Peter, 80, taught himself to play the piano and ice-skate after midlife; Millie, 93, burns through half a dozen books every few weeks ("I like exciting books with a lot of action," she says); Helen, 88, sews intricate dolls, complete with period costumes; and Peggy, the baby at 79, loves to cook and read. Even when they're watching Jeopardy!, says Peter's granddaughter Nicole, they're calling out the answers — in the form of a question, of course.

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 hawkers 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.