

AGING

Searching for the Secrets Of the Super Old

More and more people are living past 110. Can they show us all how to age gracefully?

They were born when the years still started with “18.” They survived global traumas such as World War I, World War II, and the Great Depression. They didn’t succumb to pandemic flu, polio, AIDS, Alzheimer’s disease, or clogged arteries. Supercentenarians, or people who’ve survived to at least age 110, are longevity champions.

Living to 100 is unlikely enough. According to one estimate, about seven in 1000 people reach the century milestone. And at that age, the odds of surviving even one more year are only 50–50, says James Vaupel, director of the Max Planck Institute for Demographic Research in Rostock, Germany. Making it from 100 to 110 “is like tossing heads 10 times in a row.”

Researchers are keen to investigate these 19th century holdovers. “If we want to better understand the determinants of longevity, we have to look at the oldest old,” says biodemographer Jean-Marie Robine of INSERM’s demography institute in Montpellier, France. With Vaupel, he has recently compiled a demographic database of verified supercentenarians from the industrialized countries.

Two other projects, led by researchers on the opposite coasts of the United States, hope to pin down the traits of these survivors by surveying their genomes for longevity-promoting DNA sequences and by autopsying them when they finally die. Ultimately, work on supercentenarians could uncover “a unique [genetic] variation that explains their longevity that can be the subject of drug development,” says molecular geneticist Nir Barzilai of Albert Einstein College of Medicine in New York City. Such a discovery might not stretch human life span, but it could make our final years less grueling, suggests Barzilai.

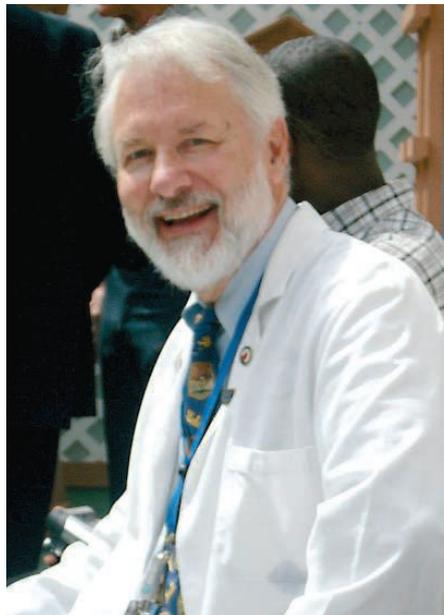
Yet studying supercentenarians is no easy task. Finding these one-in-a-million people is hard enough, and validating their ages can require that researchers become detectives or hire ones.

Come on, how old are you really?

Figures on the number of supercentenarians are shaky. The 2000 U.S. census claimed a total of 1400 living in the country. That number is much too high, says geriatrician Thomas

Perls of Boston University School of Medicine, head of the New England Centenarian Study and its new National Institutes of Health–funded spinoff, the New England Supercentenarian Study. Researchers suspect that some of the oldesters included in the tally had already died and that others—or their relatives—were lying about their ages. Drawing on Medicare enrollment figures, two U.S. government actuaries put the number of supercentenarians in the year 2000 at a mere 105. And in 2002, 139 people claiming to be at least 110 were receiving Social Security payments.

“Claiming” is a key word. A crucial part of studying supercentenarians is proving that they were or are their stated age. No biochemical test or medical exam can peg how old somebody is. So researchers often turn to Robert Young of Atlanta, Georgia, a self-taught documents guru who confirms the ages of the world’s oldest people for *Guinness World Records*. Young comes across like a veteran insurance adjuster who’s seen all the scams. To weed out pretenders,



Cutting for clues. L. Stephen Coles leads a group that has performed most of the autopsies on supercentenarians.



he requires three types of verification: proof of birth, preferably a birth certificate; proof of death, if the person is no longer alive; and “continuity” documentation, such as a driver’s license or marriage certificate, that shows that the putative supercentenarian is the person listed in the birth record. If candidates or their families can’t provide corroboration, Young sleuths through census rolls, school and military records, genealogies, and other types of paperwork.

Using these methods, an organization called the Gerontology Research Group verifies the ages of living supercentenarians and posts a list online (www.grg.org). Young is senior claims examiner for the group, which is headed by L. Stephen Coles of the University of California, Los Angeles, an ob-gyn and computer scientist by training. As of last week, the roster included 10 men and 68 women from 12 countries, ranging up to 115 years old. For reasons that remain murky, most supercentenarians are women. Moreover, of the oldest people ever documented, the majority have been women, including the record-holder Jeanne Louise Calment of France, who died in 1997 at the age of 122.

To obtain a more complete count of supercentenarians for demographic analyses, Vaupel, Robine, and colleagues have dug into national archives, including the records of the U.S. Social Security Administration, to compile lists of candidates in 15 industrialized countries. A team of age checkers then vetted each case. In all, the new International Database on Longevity caches information on nearly 1000 supercentenarians from the past 50 years, although not every country’s records span this entire range. The researchers plan to publish a monograph on the database later this year.

But that still won’t be the final word. A

Turn of the century. The world's oldest living person is 115-year-old Edna Parker (*right*). Daniel Guzman (*left*), reached 111 before dying earlier this year.

lack of good records in developing nations means that researchers still know little about the numbers of supercentenarians worldwide, says demographer Bertrand Desjardins of the University of Montreal in Canada: "It's anyone's guess how many supercentenarians are living in China."

How to grow old in style

Scientists have gotten a few hints about what keeps centenarians alive for so long—genes associated with a beneficial lipid profile, for example (*Science*, 17 October 2003, p. 373)—but they're just beginning their search for the sources of supercentenarian longevity. Two years ago, Perls and colleagues published the first health survey on these so-called supers, reporting on 32 people between the ages of 110 and 119. "I think it's incredible how well off they are," says Perls. Although almost half of the supers had osteoporosis and almost 90% had cataracts, 41% of them either lived on their own or required only minimal help with tasks such as preparing food, dressing, and bathing. Cardiovascular disease, the leading killer in developed countries, was rare among supercentenarians—only 6% had suffered heart attacks and 13% reported strokes. Diabetes and Parkinson's disease were also uncommon in the group, striking only 3% of the subjects each. Like centenarians, supercentenarians seem to be good at putting off the day when they become disabled, says Perls.

The superseniors deviate from the norm not just in how long they live but in how they die, says Coles, who arranges autopsies of the oldest old as part of his work with the recently established Supercentenarian Research Foundation. Only nine supercentenarians have undergone postmortems—Calment, for example, never agreed to one—and Coles and colleagues have performed six of these procedures, including one earlier this year in Cali, Colombia, on a man who died at age 111.

Coles argues, based on these autopsies, that supers aren't perishing from the typical scourges of old age, such as cancer, heart disease, stroke, and Alzheimer's disease. What kills most of them, he says, is a condition, extremely rare among younger people, called senile cardiac TTR amyloidosis. TTR is a protein that cradles the thyroid hormone thyroxine and whisks it around the body. In TTR amyloidosis, the protein amasses in and clogs blood vessels, forcing the heart to work harder and eventually fail. "The same thing that hap-

pens in the pipes of an old house happens in your blood vessels," says Coles.

Perls and colleagues have also shown that extreme survival runs in supercentenarians' families. Repeating an analysis they did earlier for centenarians, the researchers last year analyzed life spans of the siblings and parents of supercentenarians from the United States. The team compared the relatives' longevity with that of people born in the same year. Brothers of supers gained about 12 to 14 years over their contemporaries, whereas sisters outlasted their counterparts by about 8 to 10 years. A family connection doesn't mean that only genes are responsible for supercentenarians' great age, Perls cautions. Everything from diet to exercise habits can also run in families—the analysis can't distinguish between genetic and environmental factors.

But Perls's current work might. He and his colleagues have collected blood samples from 130 authenticated supercentenarians and have sequenced DNA from 100 of them. As early as this fall, the team could be ready to submit a paper on gene variants that might be stretching supercentenarians' lives, he says. Moreover, because the research team also has data on the supers' past health and lifestyles, it might be able to statistically tease apart environmental and genetic influences on the oldsters' life spans.

The Supercentenarian Research Foundation has similar ambitions. In addition to the autopsies this nonprofit group of doctors and researchers has conducted, Coles and his colleagues have obtained a few blood samples and plan to start collecting more next year. However, the effort, which is operating on donations, won't have enough money to sequence DNA from the samples. They will go into the freezer, but Coles says the shrinking costs of sequencing technology should soon make reading the DNA affordable.

The two projects will be sharing Young's age-checking services but nothing else. Perls says he declined to collaborate with Coles's group in part because some of its members are involved in so-called antiaging medicine, whose practitioners claim to be able to alleviate time's ravages with treatments such as injections of human growth hormone (HGH) (*Science*, 8 February 2002, p. 1032). The

rationale is that the hormone's blood levels normally dwindle as we age. But Perls has blasted this off-label use of the hormone—it's only approved for children with stunted growth and adults with pituitary tumors or other rare conditions—as not only unproven and potentially unsafe but also illegal in the United States.

Working quietly outside that fray, Vaupel and colleagues plan to use their new database to answer a question that's been nagging



Saved by a SNP? Tom Perls (*right*) and colleagues are scanning DNA from people like 110-year-old Mary Marques for longevity clues.

demographers and actuaries: Do the odds of dying in a given year, which rise relentlessly for most of adult life, taper off in the most senior seniors? Demographers want to determine whether the death rate stabilizes so they can test their models of mortality, whereas actuaries need the answer to help governments refine budgets for health care and pensions. If mortality does peak or even begin to decline in very old age, it could mean that people who live past 110 really are super, stronger than the rest of us, Vaupel says.

If centenarians are any guide, researchers will find that supercentenarians have varying backgrounds, lifestyles, and genetic profiles. But as Robine notes, they share one factor: luck. Calment provides a prime example. She outlived her husband, daughter, and grandson. They died from non-aging-related causes—the husband from food poisoning, the daughter from pneumonia, and the grandson in a car accident. So if you hope to reach the big 110, keep a rabbit's foot handy.

—MITCH LESLIE