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NATIONAL GEOGRAPHIC

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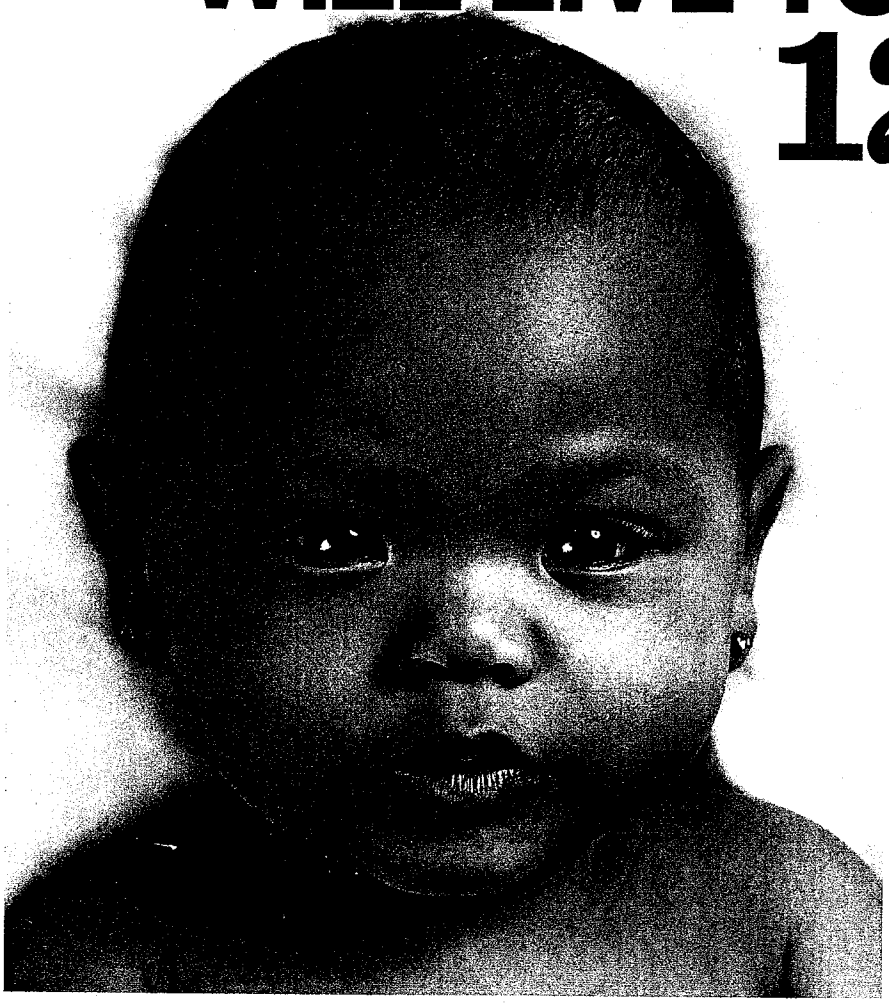

*It's not just hype. **New science could lead to very long lives.**

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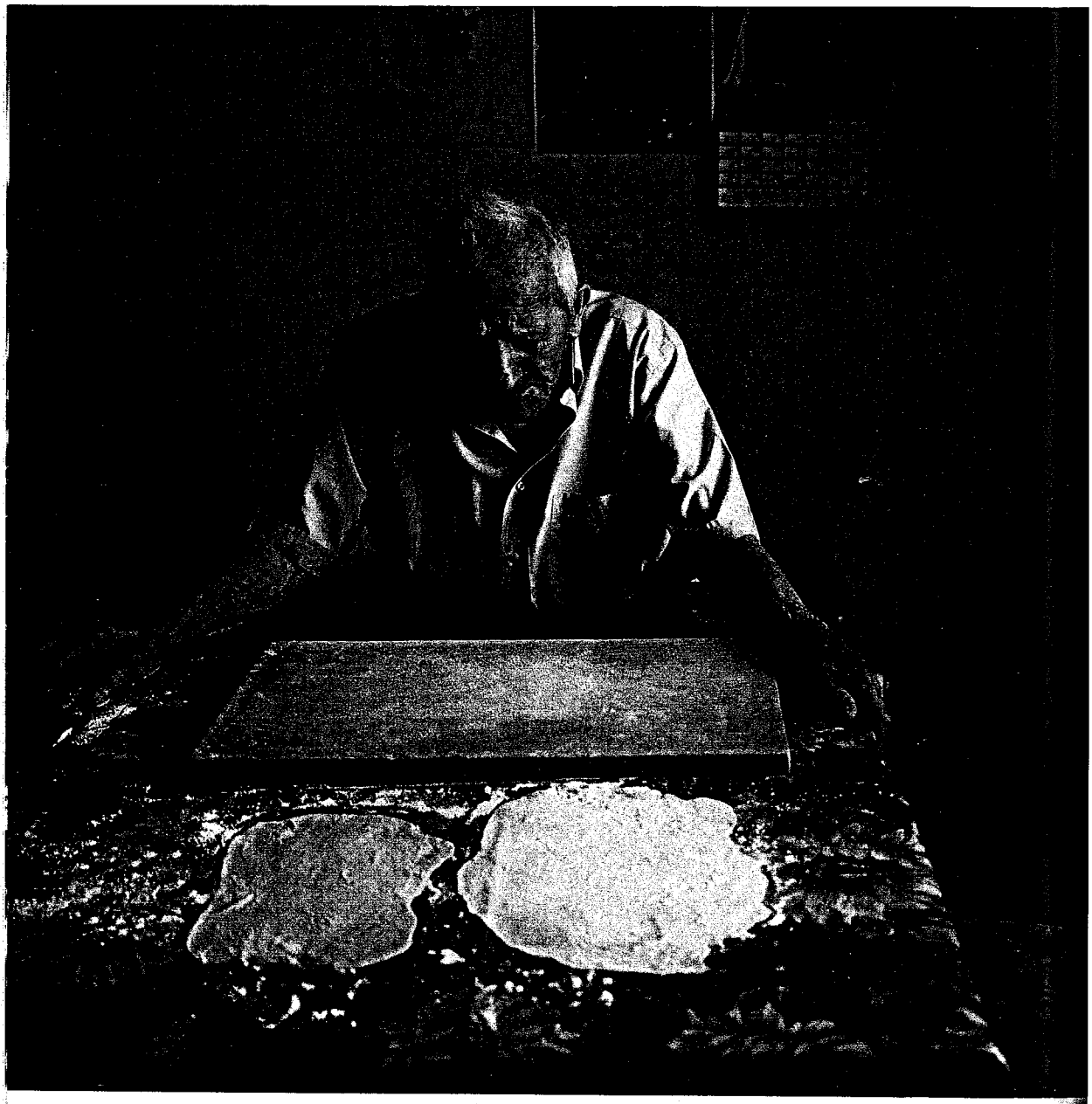


On a crisp January morning, with snow topping the distant Aspromonte mountains and oranges ripening on the nearby trees, Giuseppe Passarino guided his silver minivan up a curving mountain road into the hinterlands of Calabria, mainland Italy's southernmost region. As the road climbed through fruit and olive groves, Passarino, a geneticist at the University of Calabria, chatted with his colleague Maurizio Berardelli,

GIUSEPPE ROMEO

101

Romeo lives in San Fili, Italy. He makes his own pasta and knows how to massage away his own aches and pains—skills he perfected as a prisoner of war after he was captured by the British during World War II. The centenarian also enjoys whittling.

a geriatrician. They were headed for the small village of Molochio, which had the distinction of numbering four centenarians—and four 99-year-olds—among its 2,000 inhabitants.

Soon after, they found Salvatore Caruso warming his 106-year-old bones in front of a roaring fire in his home on the outskirts of the town. Known in local dialect as "U' Raggiuneri," the Accountant, Caruso was calmly reading an article about the end of the world in an Italian version of a supermarket tabloid. A framed copy

Caruso told the researchers he was in good health, and his memory seemed prodigiously intact. He recalled the death of his father in 1913, when Salvatore was a schoolboy; how his mother and brother had nearly died during the great influenza pandemic of 1918-19; how he'd been dismissed from his army unit in 1925 after accidentally falling and breaking his leg in two places. When Berardelli leaned forward and asked Caruso how he had achieved his remarkable longevity, the centenarian said with an impish smile, "*No Bacco, no tabacco, no Venere*—No drinking, no smoking, no women." He added that he'd eaten mostly figs and beans while growing up and hardly ever any red meat.

Passarino and Berardelli heard much the same story from 103-year-old Domenico Romeo—who described his diet as "*poco, ma tutto;* a little bit, but of everything"—and 104-year-old Maria Rosa Caruso, who, despite failing health, regaled her visitors with a lively version of a song about the local patron saint.

On the ride back to the laboratory in Cosenza, Berardelli remarked, "They often say they prefer to eat only fruits and vegetables."

"They preferred fruit and vegetables," Passarino said drily, "because that's all they had."

Although eating sparingly may have been less a choice than an involuntary circumstance of poverty in places like early 20th-century Calabria, decades of research have suggested that a severely restricted diet is connected to long life. Lately, however, this theory has fallen on hard scientific times. Several recent studies have undermined the link between longevity and caloric restriction.

In any case, Passarino was more interested in the centenarians themselves than in what they had eaten during their lifetimes. In a field historically marred by exaggerated claims and dubious entrepreneurs hawking unproven elixirs, scientists studying longevity have begun using powerful genomic technologies, basic molecular research, and, most important, data on small, genetically isolated communities

of people to gain increased insight into the maladies of old age and how they might be avoided. In Calabria, Ecuador, Hawaii, and even in the Bronx, studies are turning up molecules and chemical pathways that may ultimately help everyone reach an advanced age in good, even vibrant, health.

THE QUEST FOR GENETIC answers has brought international scientific attention to people like Nicolas Añazco, known as "Pajarito," Little Bird in Spanish.

In many ways Little Bird is a typical teen. He plays computer games and soccer and has been known to sneak a glance at the pinup calendar that resides beside a framed picture of the Last Supper on the dining room wall of his family's four-room home in the rural uplands of Ecuador's El Oro Province. In this steep and rugged, yet oddly lush, landscape at the foot of the Andes—with a hint of Shangri-La in its exotic mix of bananas, cauliflower, and tamarillo—the young man helps his father process the sugarcane that surrounds the house.

Little Bird, 17, said he became grudgingly aware of the reason for his nickname at age six, when he looked around at his classmates: "I realized that I was going to be smaller than them." Much smaller.

Because of a recessive mutation in a single gene, Little Bird looks like an eight-year-old and is three feet nine inches tall—much shorter than his brother Ricardo, who is a year older. The mutation causes a disease of impaired growth called Laron syndrome. But it may also protect Little Bird from serious diseases that typically ravage humans as they age. And even in this area of geographical isolation and historical poverty, word of that has gotten around.

One afternoon Little Bird and three other Laron syndrome men from the region held court for an interview at the back of an appliance store, their feet dangling in child's-size shoes from their chairs. Freddy Salazar, 39 years old and three feet ten inches tall, had recently had his 1997 Chevy Forsa retrofitted with elevated pedals and a raised seat so he could see through the windshield to negotiate his town's steep hills. Victor Rivera, 23 years old and slightly taller than Salazar, was the subject of a famous photograph, shown at many scientific meetings, taken when he was four—so small that the ear of corn he was holding was a little larger than his arm. Luis Sanchez, at 43 an elder statesman among the group, threw back his head in laughter, which was joined by the others' high-pitched voices, when someone asked if they were aware of the latest scientific reports about their condition.

"We are laughing," he explained, "because we know we are immune to cancer and diabetes."

That somewhat overstates the scientific results to date but reflects a growing interest among researchers to interrogate the genomes of unusually healthy or long-lived groups of people, whose isolation, geographical or cultural, makes it easier to find genetic clues to longevity, disease resistance, and good health at an advanced age.

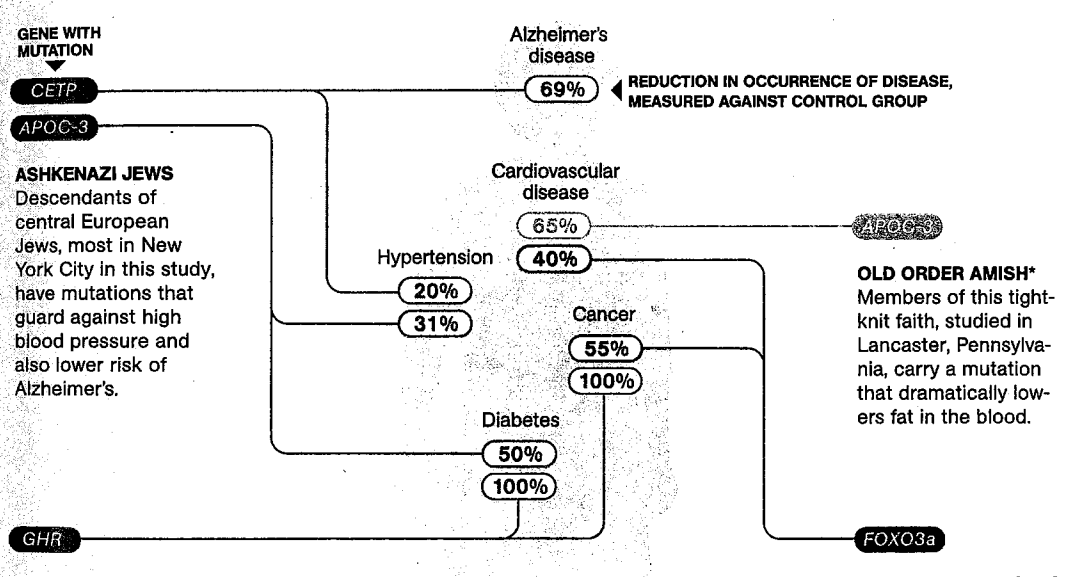
One such scientist is Little Bird's physician, Jaime Guevara, who was born in El Oro Province. Fascinated by the region's "little people," as they have been known since before their condition even had a name, he began to study them around 1987, and during a quarter century of epidemiological sleuthing he identified about a hundred people with the Laron mutation sprinkled through the hills of southern Ecuador.

Meche Romero Robles, a 40-year-old single mother, is also one of Guevara's patients. Just over four feet tall, Robles lives with her teenage daughter, Samantha, in a cinder-block, metal-roofed home perched on a hillside in the town of Piñas. "Look at her!" Guevara cried, giving the elder Robles an affectionate hug. "She should have diabetes. Given her body mass index, she must have diabetes. But she doesn't." Even to a nonmedical eye, Meche appeared obese. Like so many little people, however, she remained free of diabetes. "I realized this in 1994," Guevara said, "but no one would believe me."

Science writer Stephen S. Hall's six books include Merchants of Immortality. *For our March 2012 issue, Fritz Hoffmann photographed glacial rocks.*

Genetic clues to long life

Scientists studying groups of people genetically isolated by location or culture have found gene mutations that seem to prevent the diseases that most often shorten life. The mutations aren't limited to these groups, and not all group members have them. Learning how these genes work could help extend life for us all.



ASHKENAZI JEWS
Descendants of central European Jews, most in New York City in this study, have mutations that guard against high blood pressure and also lower risk of Alzheimer's.

OLD ORDER AMISH*
Members of this tight-knit faith, studied in Lancaster, Pennsylvania, carry a mutation that dramatically lowers fat in the blood.

LARON SYNDROME ECUADORIANS
This gene's mutation suppresses an insulin-like growth hormone, causing Laron dwarfism. But it also inhibits diabetes and cancer.

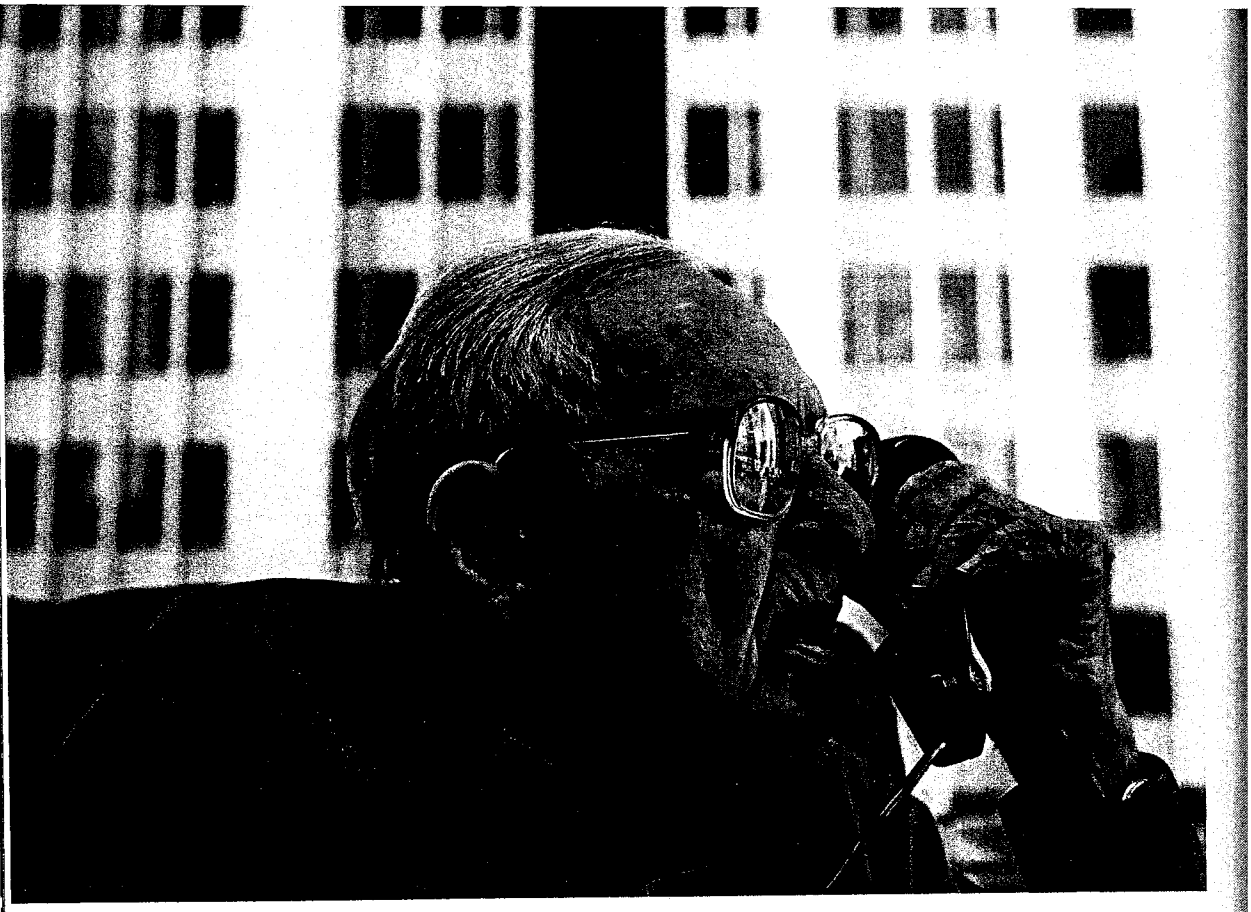
JAPANESE AMERICANS
In males a mutation in this gene lessens the chance of cancer and heart disease. Various *FOXO* genes are suspected to be major factors in longevity.

*A DIFFERENT *APOC-3* MUTATION APPEARS IN ASHKENAZI JEWS.

That began to change in 2005, when Valter Longo, a cell biologist at the University of Southern California who studies aging, invited Guevara to USC to describe his research. A decade earlier Longo had begun to manipulate the genes of simple organisms like single-celled yeast, creating mutations that allowed them to live longer. The reasons for this varied. Some mutants could repair their DNA more effectively than normal cells; others demonstrated a heightened ability to minimize the damage from oxidants. Still others became better able to derail the type of DNA damage that would promote cancer in humans.

Others were studying the same processes. In 1996 Andrzej Bartke, a scientist at Southern Illinois University, tinkered with mouse genes that are involved with growth. He showed—not surprisingly—that shutting down the growth hormone pathway resulted in smaller mice.

JOHN TOMANIO AND MATTHEW TWOMBLY, NGM STAFF; MEGAN CASSIDY. SOURCE: NIR BARZILAI, INSTITUTE FOR AGING RESEARCH, LONGEVITY GENES PROJECT, ALBERT EINSTEIN COLLEGE OF MEDICINE



IRVING KAHN
106

Irving Kahn began his career in finance in 1928. He is still chairman of the New York City investment advisory and brokerage firm that bears the family name. Working five hours a day, he has been called the world's oldest active investment professional.

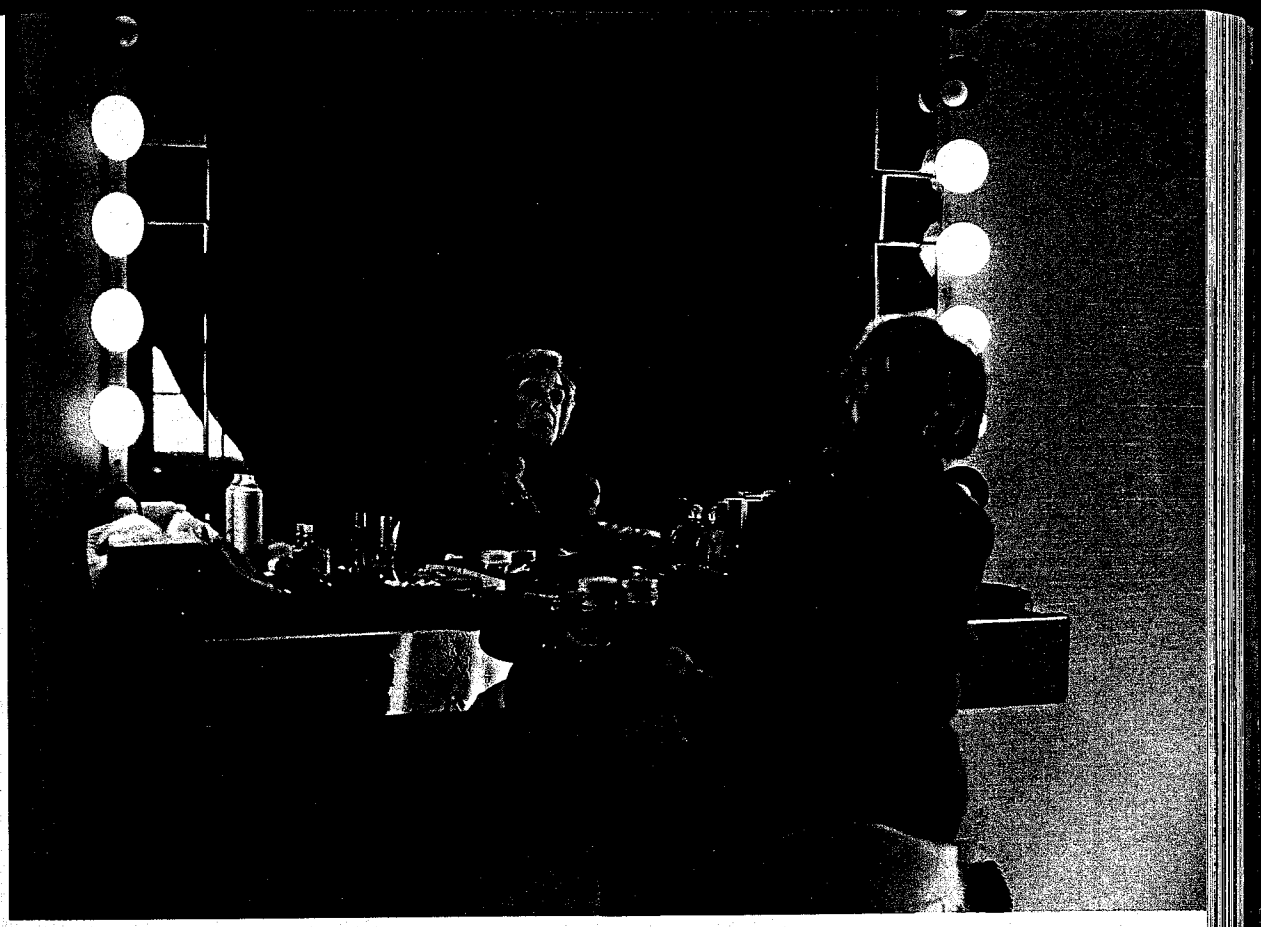
What was surprising was that they lived longer—about 40 percent longer—than normal mice.

Could similar processes be at work in humans? Could genetic anomalies protect against diseases of age? Zvi Laron, the Israeli endocrinologist who in 1966 first described the dwarfism that came to be named after him, had found dozens of people scattered through central and eastern Europe with the rare syndrome. Longo thought Guevara's patients might represent an experiment of nature—an isolated population with a condition that linked genetics to longevity.

THE ECUADORIAN LARON PEOPLE can be traced, researchers believe, back to the late 15th century, when Jews traveled from the Iberian Peninsula to the New World with a very specific piece of baggage: a genetic misspelling known as the E180 mutation in the growth hormone receptor gene, which produces the molecule that receives the body's growth signals. This distinctive misspelling in the genetic code has also turned up in Israel.

"The presumption is that Sephardic Jews were desperate to leave Spain and Portugal because of the Inquisition," says Harry Ostrer, a medical geneticist at Albert Einstein College of Medicine in New York City who has collaborated with Guevara. "They went to North Africa, the Middle East, southern Europe. Many ventured to the New World as well, but the Inquisition followed them. So it was in their interest to get out of cities like Lima and Quito, where the church maintained its strongest presence."

They settled in small towns and villages sprinkled across 75 square miles of rural Ecuador, where until the 1980s there were few roads, no phones, and no electricity. Over the centuries the



LILLY PORT
99

"I could have been put away in a concentration camp, and nobody would have known the difference," says Port, who fled her native Vienna after the Nazis took over. The retired consumer advocate lives in New York but loves to travel, most recently to Machu Picchu.

mutation lurked and spread in the population, amplified by isolation and inbreeding. "Theoretically we are all from the same family," says Christian Asanza Reyes, an economist in Balsas, whose tall frame belies the mutation he and his wife passed on to two of their three children.

Guevara and Longo began to collaborate in 2006. Guevara had found a homogeneous group in one geographic location with a known genetic mutation that seemed to block the development of diabetes and cancer in individuals. Within the Laron group there were no cases of diabetes and only a single, nonlethal malignancy. In a control group of people the same age living in the same area, Guevara and Longo found that 5 percent developed diabetes and 20 percent died of cancer. Follow-up experiments conducted by Longo at USC showed that blood taken from the Ecuadorian patients seemed to protect human cells from laboratory-induced cancers. What was the magic ingredient in their blood?

"Nothing," Longo says.

Nothing? In fact, it was the absence of something—a hormone known as IGF-1, or insulin-like growth factor. The blood was protective, Longo says, because it had unusually low levels of IGF-1, which plays an important role in childhood growth but has also been implicated as an accelerant of cancers and as a powerful regulator of metabolism. Could controlling the presence of one hormone in human blood postpone the diseases of old age? It's probably not quite that simple, but the insulin–IGF-1 connection keeps popping up in longevity research.

IN CALABRIA the hunt for hidden molecules and mechanisms that confer longevity on people like Salvatore Caruso begins in

RAE KLINE
83

"A perpetual motion machine" is how Kline, of Solana Beach, California, describes herself. An early advocate of yoga in the U.S., she demonstrates a knees-to-ears pose. Her daily exercise includes a mile swim, an hour of biking, and a four-mile beach walk.

places like the Ufficio Anagrafe Stato Civile (Civil Registry Office) in the medieval village of Luzzi. The office windows here offer stunning views of snow-covered mountains to the north, but to a population geneticist the truly breathtaking sights are hidden inside the tall file cabinets ringing the room and on shelf after shelf of precious ledgers numbered by year, starting in 1866. Despite its well-earned reputation for chaos and disorganization, the Italian government, shortly after the unification of the country in 1861, ordered local officials to record the birth, marriage, and death of every citizen in each *comune,* or township.

Since 1994 scientists at the University of Calabria have combed through these records in every one of Calabria's 409 *comuni* to compile an extraordinary survey. Coupling family histories with simple physiological measurements of frailty and the latest genomic technologies, they set out to address fundamental questions about longevity. How much of it is determined by genetics? How much by the environment? And how do these factors interact to promote longevity—or, conversely, to hasten the aging process? To answer all those questions, scientists must start with rock-solid demographic data.

"Here is the book from 1905," explained Marco Giordano, one of Giuseppe Passarino's young colleagues, opening a tall, green ledger. He pointed to a record, in careful cursive, of the birth of Francesco D'Amato on March 3, 1905. "He died in 2007," Giordano noted, describing D'Amato as the central figure, or proband, of an extensive genealogical tree. "We can reconstruct the pedigrees of families from these records."

Cross-checking the ledger entries against meticulously detailed registry cards (pink for

women, white for men) going back to the 19th century, Giordano, along with researchers Alberto Montesanto and Cinzia Martino, has reconstructed extensive family trees of 202 nonagenarians and centenarians in Calabria. The records document not only siblings of people who lived to 100 but also the spouses of siblings, which has allowed Passarino's group to do a kind of historical experiment on longevity. "We compared the ages of D'Amato's brothers and sisters to the ages of their spouses," Giordano explained. "So they had the same environment. They ate the same food. They used the same medicines. They came from the same culture. But they did not have the same genes." In a 2011 paper the Calabrian researchers reported a surprising conclusion: Although the parents and siblings of people who lived to at least 90 also lived longer than the general population, a finding in line with earlier research, the genetic factors involved seemed to benefit males more than females.

The Calabrian results on gender offer yet another hint that the genetic twists and turns that confer longevity may be unusually complex. Major European studies had previously reported that women are much likelier to live to 100, outnumbering male centenarians by a ratio of four or five to one, with the implication that some of the reasons are genetic. But by teasing out details from family trees, the Calabrian researchers discovered an intriguing paradox: The genetic component of longevity appears to be stronger in males—but women may take better advantage of external factors such as diet and medical care than men do.

In the dimly lit, chilly hallway outside Passarino's university office stand several freezers full of tubes containing centenarian blood. The DNA from this blood and other tissue samples has revealed additional information about the Calabrian group. For example, people who live into their 90s and beyond tend to possess a particular version, or allele, of a gene important to taste and digestion. This allele not only gives people a taste for bitter foods like broccoli and field greens, which are typically rich in compounds known as polyphenols that promote cellular health, but also allows cells in the intestine to extract nutrients more efficiently from food as it's being digested.

Passarino has also found in his centenarians a revved-up version of a gene for what is called an uncoupling protein. The protein plays a central role in metabolism—the way a person consumes energy and regulates body heat—which in turn affects the rate of aging.

"We have dissected five or six pathways that most influence longevity," says Passarino. "Most of them involve the response to stress, the metabolism of nutrients, or metabolism in general—the storage and use of energy." His group is currently examining how environmental influences—everything from childhood diet to how long a person attends school—might modify the activity of genes in a way that either promotes or curtails longevity.

ANOTHER CONTINENT, another genetic island. It was a gray day in the Bronx, and 81-year-old Jean Sisinni paced back and forth on a gray carpet in a third-floor room on Morris Park Avenue. As she walked, Sisinni struggled to recite every other letter of the alphabet ("B, D, F, H"), while the sensor on her forehead measured activity in her prefrontal cortex, and the carpet simultaneously registered the location, path, and velocity of every step.

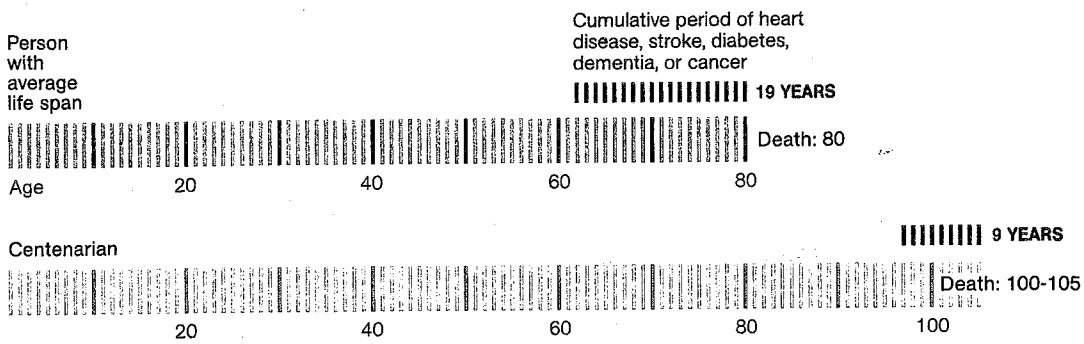
"You're doing great!" said Roee Holtzer, a neuropsychologist at Albert Einstein College of Medicine who has been conducting studies of brain function and mobility in the elderly.

If this sounds like a scientific variation on the old joke about being able to walk and chew gum at the same time, go ahead and laugh. In a series of studies over the past several years Holtzer and neurologist Joe Verghese have shown that the amount of thinking people are able do in the executive, prefrontal part of the brain while they walk and talk predicts the risk of dementia, loss of mobility, and falls.

These experiments complement research at Einstein led by Nir Barzilai, an Israeli doctor with a mop of gray hair atop a youthful face who

Getting to 100 candles

Centenarians reach that milestone because they're healthier, by virtue of genetics, common sense, or luck. In people with an average life span, diseases of old age strike earlier and last longer.



in 1998 began a study of three New York centenarians. The Einstein project has since grown to include more than 500 centenarians in and around New York City—all from central Europe and all Ashkenazi Jews, a historically isolated and culturally insular population. In this homogeneous group, research has again revealed a set of genes related to longevity, some of which have also turned up in Italy.

As they gathered more and more data, the Einstein researchers noticed that the Ashkenazi centenarians had exceptionally high levels of HDL, often called the good form of cholesterol, and that the children of these centenarians had even higher levels. This sent them off to analyze the DNA of about a hundred genes known to be involved in cholesterol metabolism. What they found was a variant, a distinct genetic subtype, of a gene known as *CETP* (cholesteryl ester transfer protein) that was more common in centenarians than in others.

When they investigated the centenarian version of the *CETP* gene, they confirmed earlier research showing that this particular variant protects against cardiovascular disease, and they have gone on to show that many people with this genetic subtype—not just centenarians but other Ashkenazi Jews and even non-Jewish residents of the Bronx—perform better on cognitive tasks like the "walking while talking" experiments. Two major pharmaceutical companies are now testing drugs that inhibit the amount of *CETP*, as the centenarian gene variant does.

Barzilai and his colleagues have also focused on the mitochondria of centenarians. Mitochondria are the cell's power plants, with their own DNA, their own genes, their own genetic variants—all with key metabolic responsibilities. Barzilai and his team have identified several mitochondrial proteins, which they dubbed mitochines, associated with people who live into their 90s and 100s. One of these molecules, humanin, looks especially interesting, at least in animal experiments. Barzilai says that giving a single shot of humanin to a diabetic rat normalizes its glucose levels and essentially erases diabetic symptoms in a few hours. It also prevents arteriosclerosis and Alzheimer's in mice prone to these diseases and somehow limits coronary damage when researchers induce heart attacks in the experimental animals.

Einstein's large and ambitious longevity program is part of a sea change sweeping human genetics research, where the prevailing emphasis for the past 20 years has been on the search for so-called disease genes. "Everybody is looking

Society Grant Biologist Valter Longo's research on Laron syndrome was funded in part by your National Geographic Society membership.

NGM ART. SOURCE: THOMAS PERLS, NEW ENGLAND CENTENARIAN STUDY, BOSTON UNIVERSITY

for genes for diabetes and obesity and things like that," says Barzilai. "I think one reason we are not finding them is because we also have protective sets of genes." Many researchers are now focused largely on the search for those protective genes, which seem to override genes associated with disease or aging.

One of the most intriguing genes is called *FOXO3*. In yet another study of an isolated, homogeneous population, University of Hawaii researchers have found variants of the gene in long-lived Japanese-American men on the island of Oahu. This gene is in the same insulin–IGF-1 pathway that has popped up both in studies of yeast and worms and in the Laron population in southern Ecuador.

Protective genes are also the target of a study at the Scripps Translational Science Institute in La Jolla, California, where physician Eric Topol and colleagues are riffling through the DNA of about a thousand people they call the wellderly. These are people over the age of 80 who have no chronic diseases, such as high blood pressure, coronary artery disease, or diabetes, and have never taken prescription drugs for them. "There must be modifying genes that explain why these individuals are protected from the deleterious genes that affect the aging process," Topol says. "The hunt is on."

The race to find the keys to longevity has even led scientists to a place that looks increasingly important in setting every individual's rate of aging: the womb. Researchers at Einstein now suspect that our pattern of aging may be set very early, perhaps before we're born.

To study this hypothesis, Francine Einstein and John Greally have been examining subtle chemical markings on the DNA of stem cells recovered from the umbilical cord blood of babies born in the Bronx and comparing differences in infants who were, for their gestational age, small, normal, or large. They have found that the pattern of DNA markings in both small and large infants is significantly different compared with that of normal-size babies. These results form part of a hot new field of biology called epigenetics, which studies how environmental influences can etch chemical modifications in DNA and thus introduce lifelong changes in the activity of genes. As Barzilai explains it, "There might be influences in the uterus that affect genetic mechanisms that somehow set your rate of aging." The fetus, in other words, may be father of the old man.

IF NOTHING ELSE, the plethora of new studies indicates that longevity researchers are pushing the scientific conversation to a new level. In October 2011 the Archon Genomics X Prize launched a race among research teams to sequence the DNA of a hundred centenarians (dubbing the contest "100 over 100").

But genes alone are unlikely to explain all the secrets of longevity, and experts see a cautionary tale in recent results concerning caloric restriction. Experiments on 41 different genetic models of mice, for example, have shown that restricting food intake produces wildly contradictory outcomes. About half the mouse species lived longer, but just as many lived less time on a restricted diet than they would have on a normal diet. And last August a long-running National Institute on Aging experiment on primates concluded that monkeys kept on a restricted-calorie diet for 25 years showed no longevity advantage. Passarino made the point while driving back to his laboratory after visiting the centenarians in Molochio. "It's not that there are good genes and bad genes," he said. "It's certain genes at certain times. And in the end, genes probably account for only 25 percent of longevity. It's the environment too, but that doesn't explain all of it either. And don't forget chance."

Which brought to mind Salvatore Caruso of Molochio, now 107 years old and still going strong. Because he broke his leg 88 years ago, he was unfit to serve in the Italian Army when his entire unit was recalled during World War II. "They were all sent to the Russian front," he said, "and not a single one of them came back." It's another reminder that although molecules and mechanisms yet unfathomed may someday lead to drugs that help us reach a ripe and healthy old age, a little luck doesn't hurt either. □