To Life!

A TINY FRACTION OF PEOPLE LIVE—AND LIVE WELL—TO THE AGE OF 100. A multidisciplinary team of researchers at Einstein is delving into the genetic and physiological components of extreme longevity, with the goal of devising new therapies to evade or delay life-threatening diseases. If they are successful, the rest of us might one day approach that rare triple-digit milestone and enjoy the long journey.

What is the secret to a long, healthy life? An answer of sorts can be found in two photographs published in the April 2006 issue of *PLoS Biology*, a research journal. The black and white photo on the next page, circa 1910, shows four siblings, ranging in age from about six months to nine years, charmingly posed around a now-antique baby carriage. Ninety-five years later, all four siblings—each looking remarkably chipper—gathered to recreate this family portrait. Revealingly, none of the siblings has led a particularly healthy lifestyle. In fact, the sister (color photo, far left), pictured here at age 104, had been a smoker most of her life, reluctantly giving up the habit after she turned 100. (She still keeps a pack in her desk, just in case).

If ever there were evidence that exceptional longevity resides in the genes, this is it.

Of course, two photos do not a scientific proof make. But a growing number of studies do suggest that centenarians—roughly one out of every 10,000 individuals—owe their long lives primarily to quirks in their DNA and not to being vegetarians, yogurt eaters, teetotalers, marathoners, or eternal optimists. Indeed, some centenarians are downright gluttons or sloths and yet are "immune" to the myriad diseases that send others to an early grave.

The first of these DNA quirks was discovered in 2003 by Nir Barzilai, M.D., who is the director of Einstein's Institute for Aging Research, the Ingeborg and Ira Leon Rennert professor of Aging Research at Einstein, and professor of Medicine and of

> "If we cured cancer, on average we would add just one year to the life span ... But if we found pathways that protect people from all age-related diseases, we could add decades to our lives ..."

(left) Siblings, circa 1910, and (right), 95 years later, participants in Einstein's Longevity Genes Project.

Molecular Genetics. Dr. Barzilai did not set out to be a latter-day Ponce de Leon, the Spanish explorer who wandered the Caribbean 500 years ago in search of a rejuvenating spring. An endocrinologist by training, Dr. Barzilai began his research career studying the metabolic pathways that lead to diabetes, a leading cause of disability and premature death. Over time, he realized he could have a greater impact on overall human health by studying the fundamental processes of aging rather than a specific disease like diabetes.

"If we cured cancer, on average we would add just one year to the life span," says Dr. Barzilai, explaining his evolution as a researcher. "If we cured heart disease, it would add another two years, and so on. But if we found pathways that could protect people from all age-related diseases, then we could add decades to our lives and also increase the quality of those years. The impact on society in terms of decreased health care costs, personal well-being and many other positive benefits would be incalculable."

LONGEVITY GENES

To learn more about longevity, Dr. Barzilai turned to the most logical resource: centenarians. He began by searching their blood for unusual characteristics. Almost immediately, he discovered that super-seniors did not necessarily have favorable levels of high-density and low-density lipoprotein particles (HDLs and LDLs), the body's "good" and "bad" cholesterol. What they did have was abnormally *large* lipoproteins—comparable to those of young, healthy, and vigorously athletic men and women, as he reported in 2003 the *Journal of the American Medical Association*.

Further analysis revealed that individuals with outsized lipoprotein molecules tend to have a lower incidence of heart disease, hypertension, and diabetes. And centenarians with good cognitive function were nearly three-fold more likely to have outsized lipoprotein molecules compared with centenarians with poor cognition.

Despite these tantalizing findings, Dr. Barzilai notes that "the connection between lipoprotein size and disease is still murky." Evidence suggests that larger LDLs are less able to cling to blood vessel walls, which translates into less buildup of arterial plaque, the precursor of heart disease and stroke. As for bigger HDLs, they may carry more cholesterol out of the blood vessels and into the liver for excretion from the body.

Next, Dr. Barzilai and his colleagues traced the genesis of the oversized particles to a variant form of the gene that makes cholesterol ester transferase protein, CETP, which is involved in the regulation of lipoproteins. He has since discovered two more potential "longevity" genes: a variant of the gene coding for apoliprotein C-3 (which is thought to slow the breakdown of trigylcerides) and a variant of the gene for adiponectin (which seems to play a role in improving insulin action and decreasing blood vessel inflammation).

WHITHER SOCIAL SECURITY?

Dr. Barzilai's studies raised the exciting possibility that human life could be extended with drugs that mimic the action of these anti-aging genes and metabolic pathways. A wave of press coverage followed, with stories in *The New York Times* and on CNN, NOVA, and the BBC. (Today, a Google search for "longevity genes" brings up more than 1.7 million hits.)

The media attention was understandable if perhaps premature. As Dr. Barzilai points out, his studies have demonstrated only an *association* between longevity genes and


© DiMaggio/Kalish/CORBIS

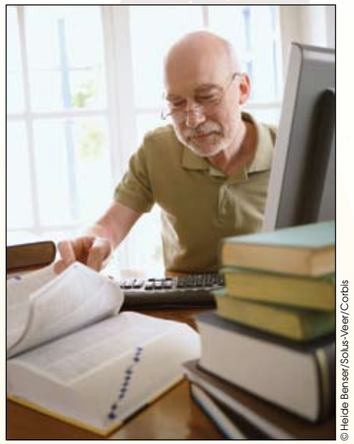
protection against age-related diseases—not cause and effect. That would require other research methodologies, including long-term studies of individuals with and without the putative longevity genes, plus various laboratory tests and statistical analyses aimed at understanding what is happening at the molecular and genetic levels.

Nonetheless, the very idea of longevity drugs was enough to energize baby boomers—and cause managers of pension funds and the Social Security Administration to lose sleep.

"From the Federal government's perspective, the best thing that could happen is that you work until you're 65, retire, and die the next day—this is the most economical outcome," he says with a laugh. "I'm just thankful that I don't have to rely on the folks at Social Security for my research grants. But since the goal of our work is to keep people healthy, having older people feeling well enough to work longer might actually help to curb Social Security payouts."

Fortunately, another part of government—the NIH—is highly supportive of Dr. Barzilai's research. In August of 2007, the National Institutes of Health (NIH) awarded Dr. Barzilai and his colleagues a five-year, $9.25-million grant to further explore the biological factors that underlie longevity.

The study comprises four integrated projects. The first study, led by Aviv Bergman, Ph.D., professor of pathology, will continue the search for additional genes, and genetic variations within genes, that are associated with longevity. A second project will focus on the growth hormone/insulin-like growth factor (IGF) signaling pathway, which plays a role in the growth and function of almost every organ in the body. Genetic variations in the IGF pathway have been associated with exceptional


© Heide Benser/Sola-Veer/Corbis


© RCWW, Inc./Corbis

longevity. This project is led by Dr. Barzilai and Dr. Yousin Suh, associate professor of medicine and molecular genetics at Einstein.

The remaining two projects are long-term longitudinal studies. One, led by Richard B. Lipton, M.D., professor of neurology and principal investigator of the Einstein Aging Study, will determine if people who possess longevity genes are less likely to experience cognitive decline as they age. The other study, directed by Clyde Schechter, M.D., associate professor of family and social medicine, will determine whether the three longevity genes that are already identified confer protection against cardiovascular disease.

But how can long-term studies be conducted on centenarians, who presumably don't have too many more years to live? And who would serve as the control group? (The logical controls would have died decades ago—and would, of course, be among the centenarians if they had lived.) Dr. Barzilai has sidestepped these problems by matching the offspring of centenarians (constituting the test group) with the offspring of parents who lived usual lifespans (the controls). His research has shown that the offspring of centenarians are healthier than their control peers—and more likely to possess longevity genes.

All told, the four longevity studies at Einstein's Institute for Aging Research occupy 17 co-investigators, primarily from Einstein, with expertise in gerontology, endocrinology, neurology, genetics, statistical genetics, advanced statistical analysis, bioinformatics, nutrition, and metabolism. "This work could not be accomplished by any single investigator," emphasizes Dr. Barzilai. "I think of myself as the promoter, the one bringing the best researchers together to accomplish the goals we have set for ourselves."

In addition, Dr. Barzilai has assembled a separate multidisciplinary research team for a second NIH-funded program to investigate environmental factors that may contribute to successful aging. The project is now focusing on resveratrol, the ingredient in red wine that has been shown to extend the lives of mice and other animal models.

WHAT ABOUT HEALTH CARE COSTS?

Dr. Barzilai doesn't believe that spending on health care will necessarily rise as the lifespans of Americans increase. He notes that the average senior citizen lives approximately three to six years after developing a fatal illness and, during that time, there is a greater need for health care and related services. In contrast, centenarians generally pass away just three to eight *months* after falling terminally ill.

"Centenarians live longer because they tend not to get illnesses like cancer and heart disease, or else they develop these diseases far later in life," Dr. Barzilai explains. "When they eventually do get sick, it is with a terminal illness. With their very advanced age, illness rapidly overtakes them, and the end of life comes relatively quickly. This so-called compression of morbidity translates into lower use of health care resources. These savings in Medicare and other health costs would very likely exceed any possible increase in Social Security payouts to Americans living longer."

Dr. Barzilai cites data from the Centers for Disease Control and Prevention (CDC) to support his case: In 1993, the CDC found that, for a person who died between the age of 60 and 70, the average health-care expense for the final months of life was about $24,000. However, the health care expense for individuals who died at age 100 was two-thirds less, or about $8,000.

ADDING NEW LIFE TO YEARS

Decades ago, President Kennedy sent a special message to Congress about seniors, noting, "It's not enough for a great nation to have added new years to life; our objective must be to add new life to those years."

Dr. Barzilai echoes this sentiment. "It is not the extension of life *per se* that compels us; we seek to increase health span along with life span," he says. "If we are healthier, we will naturally live longer. But more importantly, the length of our days will be enhanced by good physical and mental functioning. This is the reason we search for longevity genes."

> "...the length of our days will be enhanced by good physical and mental functioning. This is the reason we search for longevity genes."


© Veer


© Corbis