



The Secret of
Living to

100

(Choose your parents wisely)

BY GARY GOLDENBERG

“If I had known I would live so long, I would have taken better care of myself.”

—GEORGE BURNS (AND OTHERS)

George Burns’ famous quip may defy ordinary logic, but it actually touches upon an emerging truth about exceptional longevity. Simply put, the secret of living to 100 is out of our hands and in our genes. Centenarians—one out of every 10,000 individuals—live as long as they do in large part because of quirks in their DNA, not because they are vegetarians, teetotalers, marathoners, or eternal optimists. In fact, some centenarians are downright gluttons and sloths, yet they are immune to the myriad diseases that send others to an early grave.

Life is not fair—but it may become fairer. Studies of the oldest of the old are beginning to identify rare genetic variations that promote healthy aging, raising the possibility that drugs can be made to do what run-of-the-mill genes cannot.

The first of these variant human genes was discovered in 2003 by Nir Barzilai, MD, director of the Institute for Aging Research at Albert Einstein College of Medicine. Dr. Barzilai found the gene by trolling for unusual characteristics in the blood of centenarians. Much to his surprise, these super-seniors did not have better-

than-average cholesterol profiles. What they did have, however, was abnormally large high-density and low-density lipoprotein particles (HDLs and LDLs), the “good” and “bad” cholesterol particles that carry fat throughout the body, he reported in the prestigious *Journal of the American Medical Association*.

“Large particle size seems to give people an extra twenty years of life, with very little disability to go along with it,” Dr. Barzilai was quoted as saying in *The New York Times*. Individuals in general with outsized lipoproteins have a lower incidence of heart disease, hypertension, and diabetes, according to the researcher. He has observed that people with a mutation in their cholesterol ester transferase protein (CETP) gene tend to score higher on cognitive ability tests.

Why lipoprotein size matters is still murky. Mounting evidence suggests 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, it’s possible that they carry more cholesterol out of the blood vessels and into the liver for excretion from the body.

Dr. Barzilai, an associate professor of medi-

cine (endocrinology and geriatrics) and molecular genetics at Einstein, traced the oversized particles to a mutation in a gene that controls CETP, which is involved in regulating lipoproteins. As luck would have it, CETP is well known to heart disease researchers, and one major pharmaceutical company is already testing a drug that suppresses the action of the protein.

REPAIRING THE WORLD

Dr. Barzilai did not set out to be a latter-day Ponce de Leon, the Spaniard who wandered the Caribbean a half millennium ago in search of a tonic spring. Born in Israel in 1955 into a family of health professionals, Dr. Barzilai naturally gravitated to the healing arts. He began his career as a medic in the Israeli army, eventually rising to the position of chief medic. This inspired him to study medicine and work in a refugee camp in Cambodia and at a clinic in the Kwazulu homeland in Africa—his interpretation of *tikkun olam* (the Kabbalistic concept of repairing the world through social action). “In many ways, these were very good experiences,”

Eating right, getting regular exercise, and avoiding smoking might get you to 80 or 85, but living a full century appears to depend more on your genes than on your lifestyle. Researchers at Albert Einstein College of Medicine are learning how centenarians differ from the rest of us, with the ultimate goal of developing therapies that will give everyone a chance to live long and prosper.

“If we found pathways that protect people from all age-related diseases, we could add decades to the life span.”

he says. “Never since have I saved so many lives. But in the end, it was very frustrating. The problems facing these unfortunate people were political.” A healer, not a politician, he resolved to find other ways to repair the world.

Back home, he completed his medical studies and started investigations into glucose and insulin metabolism, following in the footsteps of his father, an endocrinologist. In 1993, Dr. Barzilai joined the Einstein faculty. Around this time his focus began to shift from the study of specific diseases that are associated with aging, such as diabetes, to the study of the fundamental processes of aging itself. “If we cured cancer, we would add just one year to the average life span,” he explained, illustrating the evolution of his new direction as a researcher. “If we cured heart disease, it would add another two years, and so on. But if we found pathways that protect

people from all age-related diseases, we could add decades to the life span.”

One potential pathway to longevity involves insulin resistance. As we age, we gradually lose the ability to utilize insulin (a hormone secreted by the pancreas to help the body metabolize glucose). Nothing good comes of this. Insulin resistance plays a role in a host of serious diseases, ranging from diabetes to obesity and hypertension to atherosclerosis. This would suggest that tinkering with metabolic processes would be a fruitful way of increasing the life span. As a matter of fact, a host of calorie-restriction studies, including experiments conducted by Dr. Barzilai, support this idea. In these studies, animals given just enough food to survive, but not enough to maintain their usual body weight, lived significantly longer than those on normal diets. What works for mice and worms will not

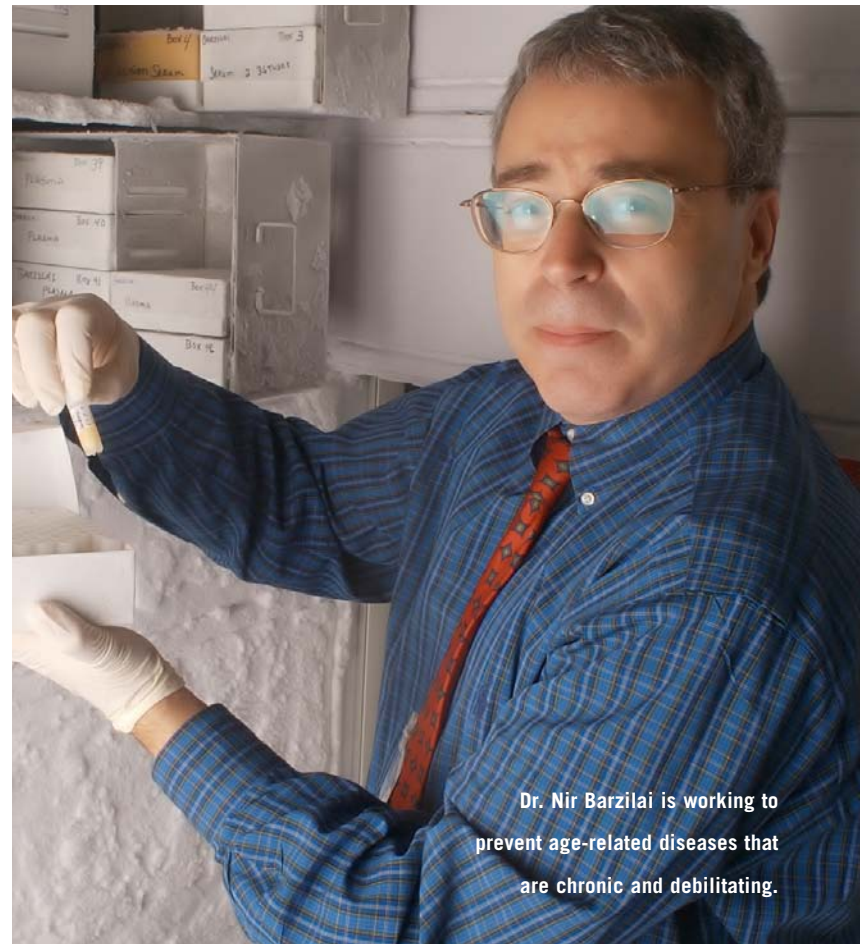
necessarily work for humans, of course. And even if it does, who would want to follow a diet that reportedly leaves you feeling perpetually cold and hungry? Nevertheless, the researchers are obviously tapping into fundamental links between metabolism and longevity.

AGING AND ABDOMINAL OBESITY

Another intriguing key to longevity concerns a phenomenon called abdominal obesity. The older we get, the more fat we tend to accumulate inside our abdomen. The classic example is the skinny middle-aged guy with a beer belly. He’s not overweight in the classic sense; it’s just that all his extra fat has settled in one place. But he’s not exactly healthy, either. In recent years, studies have found a cor-

The average life expectancy

is now inching toward 80 years, up from a mere 45 years in 1900, thanks to “environmental” advances such as safer drinking water, better diets, vaccines, antibiotics, and therapies for such major killers as heart disease and hypertension. Those were the “easy” gains, however. Most experts in the field agree that comparable leaps in longevity will not occur unless researchers can decipher the very basic processes of aging, down to the genetic and molecular levels.



Dr. Nir Barzilai is working to prevent age-related diseases that are chronic and debilitating.

relation between excess abdominal fat and a higher incidence of insulin resistance, among other serious ailments. However, the studies did not establish cause and effect—that is, they did not resolve whether metabolic changes of aging lead to a change in fat distribution or, conversely, whether changes in fat distribution lead to metabolic changes of aging. The distinction is critical, for if the latter is true, it might be possible to affect aging by altering the distribution of body fat.

Dr. Barzilai found some tantalizing clues to this riddle in a study of overweight rats. When fat was surgically removed from the rats' abdomens, their insulin resistance normalized. Removal of fat from other parts of the body, however, had no effect. Unfortunately, such surgery is probably not feasible in humans, due to potential injury to the intestines. However, there's no reason a drug couldn't be developed to accomplish the same result. Said the researcher, "We are looking at peptides [chains of amino acids] that could remove the fat, and we are making some progress."

He has a tough task ahead. Humans are designed to accumulate excess fat, not shed it. Eons ago, back on the savannah, our ancestors were repeatedly subjected to food shortages. Those who were energy efficient and good at storing fat had a significant survival and reproductive advantage over those who weren't. "For example, a young girl who had a mutation in the beta-3 adrenal receptor gene, which controls energy expenditure, would be able to store fat while her girlfriends were dying from starvation," said Dr. Barzilai. "When spring came and food was plentiful, she would get even chubbier. That means her menarche would come sooner and she would have, on average, more children, since obese women become fertile sooner than lean women. You can see a major genetic force at work here."

While the beta-3 mutation offers a survival advantage, it predisposes its carriers to obesity, diabetes, and heart disease. The mutation is a prime example of an evolutionary theory called antagonistic pleiotropy. "This refers to something that protects you early on, that gets you to the age of reproduction, but then makes you age faster," reported Dr. Barzilai. Today, with our calorie-rich diets and sedentary lifestyles, energy efficiency is a decided disadvantage. "The fat we accumulate, and how it is distributed, is a real time bomb," he says.

But why would we have genes for longevity, a post-reproduction phenomenon? What would

be the evolutionary advantage? Once you've had your children and raised them, does it matter if you live to 50 or to 100? Possibly. One explanation is the grandparent theory. "Having a grandparent was unusual thousands of years ago," said Dr. Barzilai. "A surviving grandparent probably had life experiences or money or possessions that he could pass along. Or he might have had a large family, which could offer a protective environment. So, if you had a living grandparent, you might have several advantages over those who didn't."

NOT ALL CENTENARIANS ARE ALIKE

In the months and years ahead, Dr. Barzilai hopes to find additional longevity genes by comparing subsets of centenarians. Not all 100-year-olds are alike. "There are some who look very old and some who look relatively young," he pointed out. "Most of my centenarians don't see well or hear well, but there are a few who don't need glasses or hearing aids. Not only are they not getting age-related diseases, but somehow they are not aging physiologically. When we have enough study subjects, perhaps we'll be able to see more genetic differences among centenarians." This, in turn, could lead to the development of more drugs that mimic the genes that confer exceptional longevity.

A scientist with a philosophical bent, Dr. Barzilai admitted that he is a little uneasy about developing pills that people could view as incentive to abuse their bodies. "I don't want to find something that would allow everybody to smoke and overeat," he said. "My goal is to prevent age-related diseases that are chronic and debilitating."

Curiously, Dr. Barzilai's office at Einstein is littered with more than a few chocolate bars, an odd choice of snack for an endocrinologist with a family history of diabetes and heart disease, not to mention modestly sized lipoprotein particles. "I am unable to stem the temptation of certain foods," he admitted, "so I exercise a lot and stay lean, which my studies show increase the chances of living longer. Yes, I do like chocolates, especially Israeli chocolates. That is what sustained me through the Israeli army."

Those lucky to have the right genes for longevity don't have to worry much about chocolate addictions and other deleterious habits. "The rest of us have two choices," said Dr. Barzilai with a sly grin. "One is to support my studies of longevity. The other choice is to go back and choose other parents." ■



At Einstein's Institute for Aging Research

Aging research had a late start compared to other areas of medical science, but with the rapid growth in the elderly population and a new awareness among scientists that aging is a complex biological phenomenon, interest in the field has mushroomed in recent years.

One of the most recent and most unusual additions to the field is the Einstein Institute for Aging Research. While most research programs in aging are rooted in traditional geriatric programs, Einstein's Institute emerged from a diverse group of basic and clinical scientists focused on specific organs or physiologic systems.

Directed by Dr. Barzilai, the Institute consists of three collaborative programs, Biology, Cognitive Function, and Human Genetics, with some 19 investigators and more than \$6 million in annual NIA funding. The Biology program focuses on the metabolic syndrome of aging, addressing such issues as the influence of calorie intake and fat storage on aging. The Cognitive Function program addresses risks for decline in cognitive function (see p. 8). The Human Genetics program specializes in the study of genes that confer longevity.

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