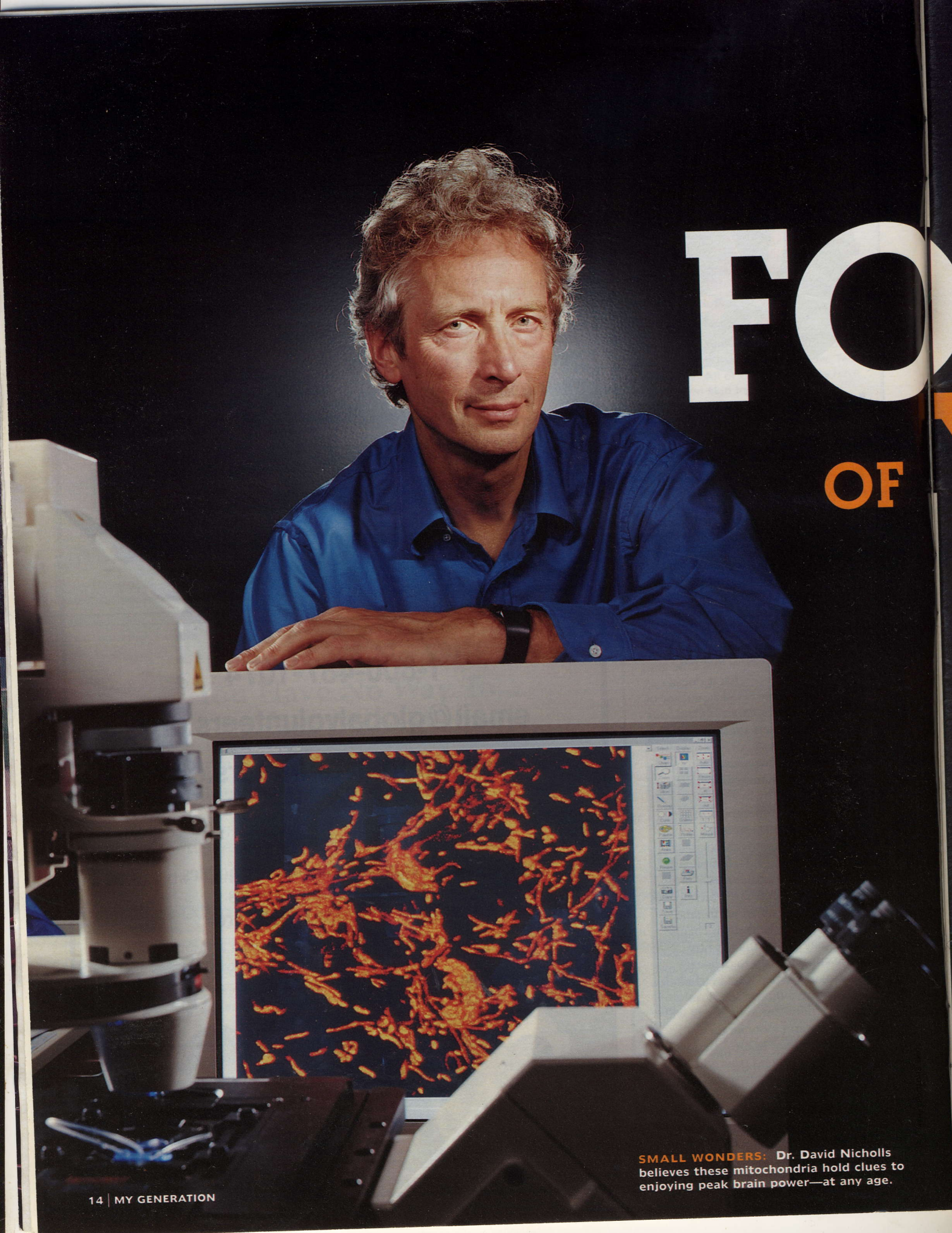


FO

OF

SMALL WONDERS: Dr. David Nicholls believes these mitochondria hold clues to enjoying peak brain power—at any age.

FINDING THE FOUNTAIN OF YOUTH

THESE SCIENTISTS ARE UNLOCKING THE MYSTERIES OF AGING. ARE YOU READY TO LIVE TO 120?

BY PAMELA WEINTRAUB

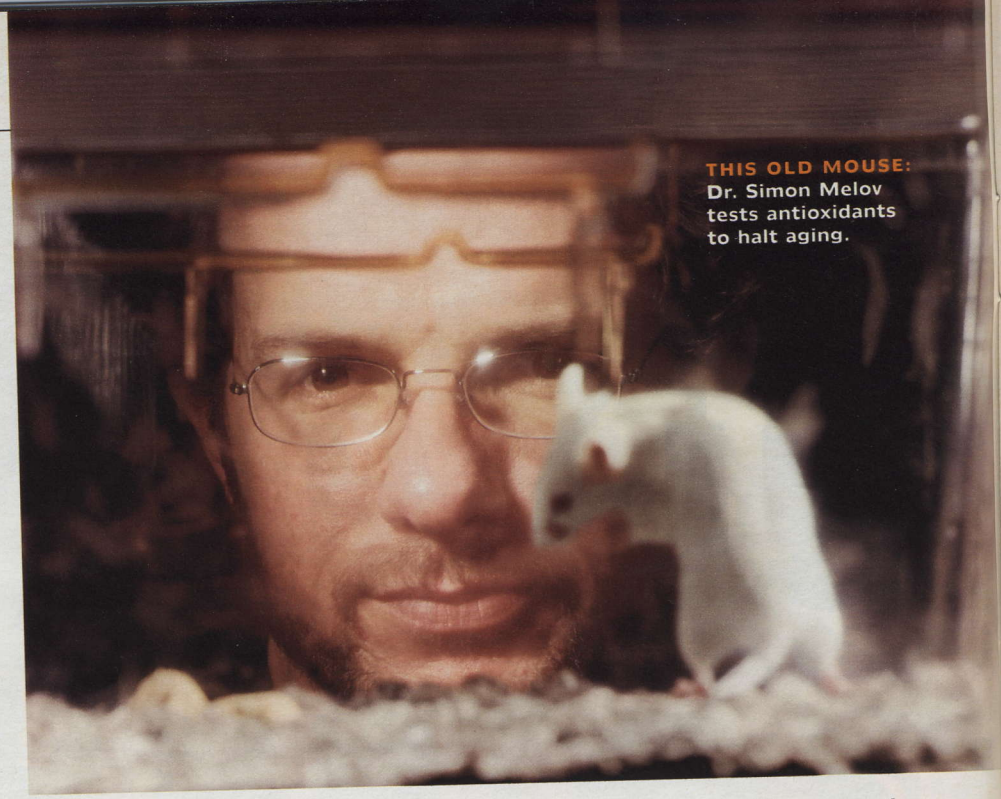
PHOTOGRAPHS BY EVAN KAFKA

FOR 85 YEARS MY UNCLE, ABE WEINTRAUB, WAS THE UNDERachiever of the family. Barely a high school graduate in a clan of lawyers and Ph.D.s, he toiled in a Brooklyn post office while his siblings collected degrees and advised presidents. But now, while his brothers and sisters are slowing down, perhaps vacationing in Florida, Uncle Abe is doing star turns: Said to be the world's oldest male marathoner, at age 91, he can be seen jogging over the Brooklyn Bridge, powering through the streets of London or running along the Martha's Vineyard sand.

As to the secret of his belated success, he has some wacky ideas. Perhaps, he suggests, it's his diet, which consists mostly of gourmet cheeses and creamy soups. Perhaps it is lack of exercise. "I didn't do anything athletic until age eighty," he is fond of telling the newspapers that cover his career, "so my joints are like a baby's—untouched." But I have a theory, too. My hunch is that Uncle Abe has something worth bottling, something I pray I've inherited—world-class longevity genes that supercharge his cells, his muscles, his brain.

There have always been those rare individuals who pushed the outside of the aging envelope: The 100-year-old Russian villagers eating yogurt were not just a joke in a TV commercial, but a symbol of the potential longevity theoretically attainable by all. The average hunter-gatherer, pummeled by the elements and ravaged by childbirth, was lucky to live to 30. With antibiotics, sanitation and the protective cover of technology, our parents can strive for 75, 80 or more. But while the average life span has increased through the millennia, the maximum life span—the point at which we simply hit the wall—has never changed.

"For as long as our species has existed, the oldest known



THIS OLD MOUSE: Dr. Simon Melov tests antioxidants to halt aging.

individuals have made it to about 120 years of age, no more," says molecular biologist Richard Cutler, a pioneer of anti-aging research at the Kronos Longevity Research Institute in Scottsdale, Arizona. "Until we can alter the basic mechanism of aging itself, that is the way it will stay." But once those breakthroughs become a reality, he adds, there will be no limit to human longevity.

The dream of staving off death has always been with us. The myth of Shangri-la is based on ancient Tibetan legends that describe a paradise where people lived for hundreds of years. The Spaniards searched the New World not only for gold, but also for the Fountain of Youth. If they'd only recognized the ritual snake paintings for what they were—symbols of rebirth—they'd have understood: The Aztec and Inca were looking, too.

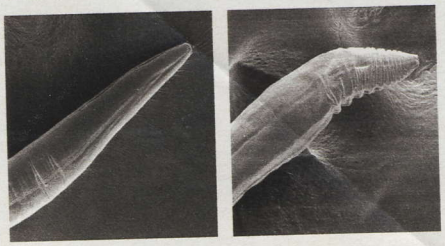
Within the last decade, scientists working in prestigious labs from the University of California to the Massachusetts Institute of Technology have succeeded in doubling—even tripling—the life spans of worms and fruit flies. Encouraged by their success, the federal government now allocates hundreds of millions of dollars a year to various aspects of this quest. And dozens of biotech companies, funded by venture capitalists and staffed by top-tier scientists, now specialize in life extension.

The result: In the next two or three decades, we might significantly increase the average life span by 10 or 20 years. As extraordinary as this sounds, researchers at the vanguard of this new field say it's just a matter of time. Judith Campisi, senior scientist at the Lawrence Berkeley National Laboratory in California, notes that "scientists are now honing in on the basic mechanisms that cause aging, and we will be able to gain power over some of them."

If there is a single destination for modern-day Ponce de Leóns in search of longevity, it is the Buck Institute for Age Research, perched atop Mount Burdell, 20 miles north of San Francisco off Highway 101. Founded in 1999, Buck is the only freestanding facility in the country devoted to finding—and ultimately altering—the mechanisms of how we age. Its curved stone structures, designed by I.M. Pei, house some of the most advanced life-extension experiments in the world.

The basic goal at Buck is to learn exactly how we age. In the last decade, high levels of public excitement were generated by the discovery of telomeres—molecular caps on the ends of chromosomes that prevent them from being degraded. Telomeres shorten slightly each time a cell divides, and scientists found that when the telomeres reach a critically short length, cell division stops. Scientists had hoped that replacing telomeres might allow cells to replicate indefinitely, instead of dying. This concept is still being investigated, but it now appears to be flawed; human cells most prone to the ravages of aging don't undergo cellular division.

Today, notes Buck molecular gerontologist Simon Melov, part of the puzzle has been solved: Most scientists believe that aging can be traced to cellular damage caused by both environmental factors (such as sun, alcohol or psychological stress) and—first and foremost—free radicals, or the trillions of unstable oxygen molecules circulating in our blood that oxidize tissue much as rust attacks metal.



ONE ROUGH WEEK: A nematode worm at 4 days (left) and 10 days old showing the degenerative effects of aging.

COURTESY OF THE BUCK INSTITUTE

"Free radicals, which are the charged, toxic molecules produced with every breath we take, have broad capacity to damage surrounding proteins, fats and genes—essentially, everything they touch," Melov says. "Most free radicals are detoxified by internal defenses, but one tenth of one percent slip through." Our natural antioxidants swiftly repair most of the damage through our reproductive years, but as far as evolution is concerned, there is no reason to preserve youthfulness after that. As our cells and organs age and begin to function less efficiently, the free-radical damage accumulates rapidly. The result: aging. Uncovering this process, scientists say, could be the most significant medical finding since the discovery of the germ.

"By understanding the phenomena of oxidative stress, in which the body literally rusts," says Melov, "we can design effective therapies for intervention, delaying the onset of degeneration associated with age and maintaining the physiology of youth." The bottles of antioxidants lining health-food store shelves can't, however, accomplish that.

A 65-YEAR-OLD MAY BE ABLE TO REGAIN THE APPEARANCE AND HEALTH OF HIS 45-YEAR-OLD SELF, AND A 20-YEAR-OLD MAY STAY 20 FOR AN INDEFINITE PERIOD.

Many don't target free radicals effectively, and others have a more technical drawback: They convert oxidants into hydrogen peroxide, a toxin. At a critical mass of hydrogen peroxide, the antioxidants stop working and oxidation continues.

New research may soon overcome therapeutic shortcomings, though. Enter Eukarion, a tiny, Massachusetts-based biotech company holding patents to a line of antioxidants that not only neutralize free radicals, but also split the resulting hydrogen peroxide into water and oxygen, rendering it benign. Eukarion is now testing its formulas for treatment of age-related diseases such as Alzheimer's and Parkinson's; with FDA approval they could be available to the public in drug form as soon as 2006.

Two years ago, an international team headed by Melov contracted with Eukarion to test its antioxidants on worms. "The Eukarion worms lived 50 percent longer than counterparts," says Melov. "It is the most robust pharmaceutical intervention in the aging process anyone has ever seen." Melov is attempting to reproduce the results in mammals. His study with mice is ongoing, and the results aren't formalized yet, but his excitement is palpable. Do they extend the life span of the mice? Melov will not say, but it is easy to read between the lines. "The compounds are remarkably effective in reducing oxidative stress," he states.

Melov also has a hunch that once the oxidative stress is reduced or eliminated, the body's natural repair mechanisms may kick in with a powerful rejuvenating effect—literally healing the tissue damage we now describe as aging.

"We've been able to reverse severe pathologies in many areas of medicine," he notes, "and I don't see why that wouldn't be possible for aging, too."

Given the combination effect of preventing further damage and healing residual damage, the aging process may reverse and then linger in a biological stalemate, predicts Melov. A 65-year-old, for instance, might be able to regain the appearance and health of his 45-year-old self—and maintain it for decades. Even better, a 20-year-old may stay 20 for an indefinite period.

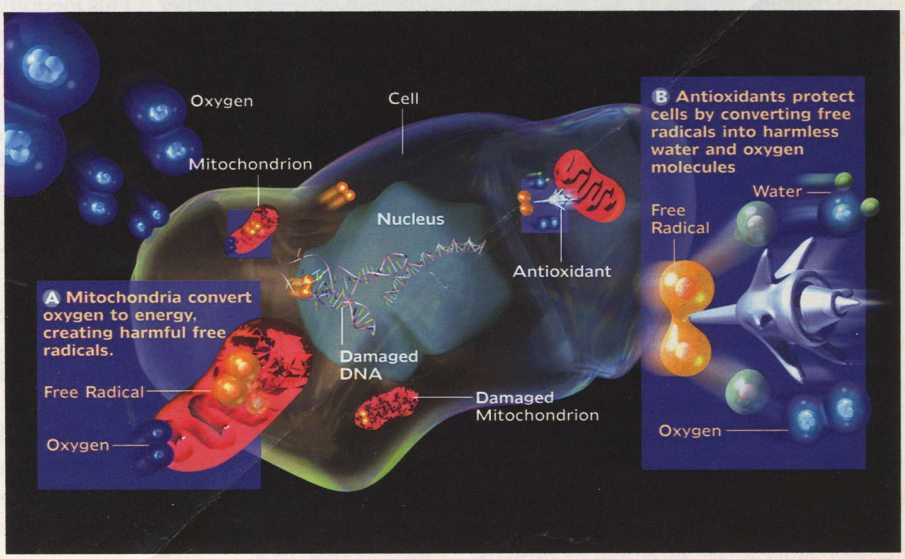
When might this happen? "I'm bullish," Melov states. "Five years from now, Eukarion and perhaps other companies will have drugs that effectively treat such age-related diseases as Parkinson's, Alzheimer's and stroke. These drugs will have an off-label use—significantly increasing the maximum human life span. People will realize they can swallow pills to extend their healthy life span by ten percent, twenty percent, possibly more. There may be some resistance to such tinkering, but the political pressure from the aging boomers will be unstoppable."

And so will the results. Given the compounding breakthroughs in anti-aging research, Melov believes it's quite conservative to expect that Americans will see a long-range boost in the average life span of 30 percent by mid-century—which equates to around 25 years more of healthy, active life. "Since scientists are notoriously inaccurate at extrapolating research trends, it's worth noting that the magnitude of the increase could be much greater," he adds. More incredibly, the throngs who beat Joe Average could see birthday digits that, right now, no scientist will utter for fear of sounding like a sci-fi crackpot. If you're in your 50s, it suffices to say that your chances of getting your pocket picked at a 2076 tricentennial gala may be far better than you'd dare imagine.

Melov's colleague at Buck, David Nicholls, is busy combating another aspect of aging, one that renders a healthy body useless: age-related cell death in the brain. Preventing or reversing this decay will be a cornerstone of any longevity research, because people over 85 suffer at an alarming rate from neurodegenerative diseases—Parkinson's and Alzheimer's—thought also to be caused by free-radical damage. According to estimates, Parkinson's afflicts 10 percent of this group, while Alzheimer's appears in half.

Nicholls is focusing his brain research on mitochondria, the cellular energy factories that generate the molecular nuggets of adenosine triphosphate (or ATP) that power all bodily processes—and a steady supply of toxic free radicals. With each passing year, the aging mitochondria in your cells spew ever more free radicals, and the process begins gradually to destroy brain tissue.

Nicholls has uncovered an interesting cause of this neural damage: When an older person suffers a stroke or, he



AGING, UNMASKED: The mitochondria within the cells use oxygen to produce energy, creating unstable free radicals as a by-product. These free radicals then rampage throughout the cell, damaging cellular DNA and mitochondria. At right, antioxidants neutralize mitochondrial free radicals to prevent this damage.

ILLUSTRATION BY BRYAN CHRISTIE

speculates, experiences even mild physical stresses such as drug and alcohol use, a certain neurotransmitter, glutamate, leaks from nerve cells and allows calcium to accumulate in brain cells. While attempting to absorb the calcium, the mitochondria generate massive quantities of free radicals, which damage neurons. Over a period of decades, this microscopic chain reaction may be a key cause of Parkinson's, Alzheimer's and garden-variety senility. In the near future, Nicholls predicts, effective antioxidant supplements or synthetic versions of brain neurotransmitters may stop this toxic avalanche before it causes irreversible damage.

Rather than making the elderly spry, the first effective anti-aging therapies will likely work best when administered to healthy young persons who are at high risk for certain diseases. "Up until now, we have done what I call reactive aging. We wait for something to go wrong, and then we call our doctor to report a pain or a lump. But in the near future, we'll be able to use genetic profiling to predict something as specific as the likelihood of getting Parkinson's at age fifty-seven, plus or minus five," says Dr. Dale E. Bredesen, Buck president and CEO. Preemptive treatments could delay the onset of these diseases for decades. His facility is busily working to uncover those biological markers; a staff of robots continually etches the genetic codes of whole species onto gene chips, allowing scientists to scrutinize and compare the countless genetic alterations that occur through aging.

Of course, the wonders being unraveled at Buck and other research havens will need to have practical applications to be useful to us. And most of the biotech companies struggling to achieve that lucrative goal can still show results only in tiny nematode worms akin to the long-lived ones squirming in Melov's lab—most no bigger than a comma on this page.

Still, scientists maintain that it's just a matter of time before many of these advancements are effective in humans. What's more, insurance companies will have a strong financial motivation to cover the cost of the resulting anti-aging drugs; they could significantly reduce the astronomical medical costs incurred by people who live in sickly, frail old age. And the current research has banished at least one long-standing fear: that extending longevity would burden society with armies of infirm, helpless elderly people. "The animal data tell us that we cannot extend decrepitude," says Melov. "Extending life span means extending health span. The years we add will be years of health, vigor and productivity, not years of decline."

AN OUTSTANDING FUTURE: Buck CEO Dr. Dale Bredesen says genetic profiling will conquer disease.

Still, the notion that we all may routinely live to be 120 years old—an inevitable reality, according to leading anti-aging researchers—is terrifying to many.

"In the beginning, the anti-aging treatments might be too costly for most people, especially those in the underdeveloped nations of the world," says bioethicist John Harris of the University of Manchester in England. "We face the prospect of mortals and immortals existing alongside one another." This inequity would be staggering, Harris fears—one that would literally give new meaning to the phrase "haves and have-nots."

More philosophically, Ben Bova, author of *Immortality: How Science Is Extending Your Life and Changing the World,* believes that an extremely long—or indefinite—life span could crumble the Judeo-Christian religions.

"If men and women can achieve immortality here on Earth," he says, "motivation for following the ethical teachings of religion will be greatly, perhaps fatally, weakened. Good people will not go to Heaven, they'll stay here on Earth. Bad people won't be punished in Hell, they'll go on in their evil ways as long as they like."

In the end, however, Harris points out that all the objections regarding human ethics, altering nature or exhausting the Earth's resources simply won't hold up. "If increased life expectancy is good, should we deny palpable goods to some people because we cannot provide them for everyone?" he asks. "We don't deny everyone liver transplants because they are only available to some." He adds that people should remember that life extension is associated with preventing and curing a host of human diseases. "It is one thing to wonder whether we should increase people's life spans and quite another to ask whether we should make people immune to heart disease, cancer and dementia—and to decide that we should not."

Given all the potential financial windfalls and the scientists toiling this minute at Buck and elsewhere, it's very likely that we'll see new drugs, supplements and gene therapies that significantly increase active life—by at least another 10 years—before the presidential election of 2012. So keep a pair of running shoes on hand. You, too, may have the chance to run a marathon at age 90, if that's your pleasure. And you won't need Uncle Abe's genes. ■

How long will you live? Take our long-life poll at *www.mygeneration.org*.