

the battle
against aging

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THE ELIXIRS DU JOUR—ANTIOXIDANTS, GENE THERAPY AND AEROBIC
CONDITIONING—HAVE YET TO PROVE THAT THEY DO MUCH BETTER
THAN THE POTIONS AND PATENT MEDICINES OF YESTERYEAR

living longer: what really works?

BY ROBIN MARANTZ HENIG

A *New Yorker* cartoon shows two old geezers creaking in their rocking chairs on the front porch. “I don’t want to live forever,” says the male geezer to the female geezer. “But I damn sure don’t want to be dead forever, either.” We may not want to live forever, but how about for a long, long time? How about for 200 years or 300—two or three times the age that is now considered the outer limit of the human life span? A longer spin on this earth is apparently something that appeals to many of us, but as the checkered history of aging “cures” makes clear, it remains an elusive goal.

Advice abounds about how to beat aging, by which we usually mean either living to the age of 150 or more or staying youthful while living out a life span closer to the biblical threescore and 10. Some of the methods promoted over the years have sounded like sorcery: sleep with virgins, drink the blood of virile youth, get injections of a concoction derived from the testes of dogs and guinea pigs. These techniques have done nothing more

than line the pockets of the people hawking them.

Today more temperate sages offer the same advice our mothers did: eat and drink in moderation, exercise regularly, get enough sleep. All boring, and only marginally effective. Good health habits can make you leaner, more aerobically fit and less liable to suffer some of the worst ravages that aging brings—but they won’t keep you young, and they won’t make you live much longer than you were genetically programmed to live.

The advice that is really getting people excited these days sounds much more scientific, derived as it is from what we are learning about how cells age, how that relates to organisms’ aging and how the process can be forestalled. But even these techniques—hormones, antioxidants, gene therapy, calorie restriction—have not been proved conclusively to make any difference in how long you will live or how well you will age.

It’s true that some laboratory animals who have been exposed to a few of the latest rejuvenating compounds have indeed lived longer—on average,

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from 40 to 100 percent longer when treated with melatonin or calorie-restricted diets. But this does not necessarily translate into a human life span that is 40 to 100 percent longer. As far as gerontologists are concerned, people cannot live beyond the limit of about 120 years, with the occasional exception, such as Jeanne Calment, who was 122 years old—and had the birth records to prove it—when she died in 1997. You and your grandchildren, and probably your great-grandchildren, will almost surely die before you reach that limit. But you, and certainly they, are more likely than any previous generation to achieve a life span of close to 120 years. In other words, scientific progress will enable a greater proportion of the population than ever before to live out the human life span to its fullest.

Centenarian Tsunami

According to the U.S. Census Bureau, more than 800,000 baby boomers will have celebrated their 100th year by the middle of this century. The nearly one million boomers joining the ranks of the oldest old will constitute a swell of centenarians so substantial that the tradition of congratulating them during the morning weather report will go by the wayside. Millions more will reach their 80s and 90s.

But there is no guarantee that the last decades of those 100 or so years will be

healthy ones. Today nearly half of all Americans over age 85 require some sort of help to get through their daily chores. Unless we make great strides in antiaging research, the oldest Americans of the new century may spend their last 30 years in a state of dreadful and debilitating dependency.

Such a spectacle struck horror in the hearts of the ancient Greeks—even though in their day, the average life expectancy was only 18 years. They told the story of Tithonus, a handsome young prince with whom Eos, the goddess of the dawn, had fallen in love. Unable to marry a mortal, Eos asked Zeus to grant Tithonus eternal life. He did so, and Eos and Tithonus lived happily together for many years. But Eos had forgotten to ask Zeus to grant her lover eternal youth as well. So it was Tithonus's fate to age forever. He grew weaker and smaller; he shriveled and shrank; he lost strength in his limbs and power in his voice. As he became more and more wizened, his voice reduced to a mere squeak, Eos hid him in a basket. Tithonus could get no relief from his ceaseless aging. Eventually, he turned into a grasshopper, ignored in the basket, chirping away for all eternity.

Longevity research must go hand in hand with research on the effects of aging if the result is to be of any use. These studies focus on adding years to our 120-year life span, whereas other antiaging research tries to slow the progres-

sion of decline within however many years we have. Sometimes the same intervention seems to do both things; calorie restriction, for instance, not only significantly increases the life span of laboratory animals but also makes them measurably more youthful than their contemporaries at every stage along the way. But one intervention doesn't necessarily have to do with the other. The techniques that stave off age-related declines are much further along the road to real-world usefulness than are any methods of helping humans live to be 200.

These methods might not extend the maximum life span, but they do tend to increase the average life expectancy—that is, the number of years within that maximum life span that the average person can hope to attain. When life expectancy increases, it is because medical science has concocted a way to prevent some of the catastrophes responsible for most premature deaths: infections and accidents in the younger age groups, heart disease and cancer after midlife. With the exception of infections, which require medical intervention, most of the biggest killers of adults can be staved off by healthy living. We've all heard the advice, if not from our mothers then from our doctors, our partners or our television newscasters: don't smoke; keep your weight within a normal range; eat plenty of grains, fruits and vegetables; go easy on the red meat and animal fat; drink alcohol only in

the battle against aging

moderation; get some kind of exercise for at least half an hour a day; put on sunscreen when you go outdoors; and wear your seatbelt.

By the same logic, a vigorous exercise program would be good, too. But it can have some real drawbacks for those who revel in their laziness. Let's say, as some gerontologists believe, that a person who starts a program of vigorous aerobic exercise at the age of 40—three times a week for half an hour at a time—will live two years longer than she might have if she had remained sedentary. Those extra two years are just about the exact amount of time she spent exercising—not worth it, ultimately, for someone who hates jogging so much that she'd rather die a little sooner so that she can live a little happier.

Methuselah and Beta-carotene

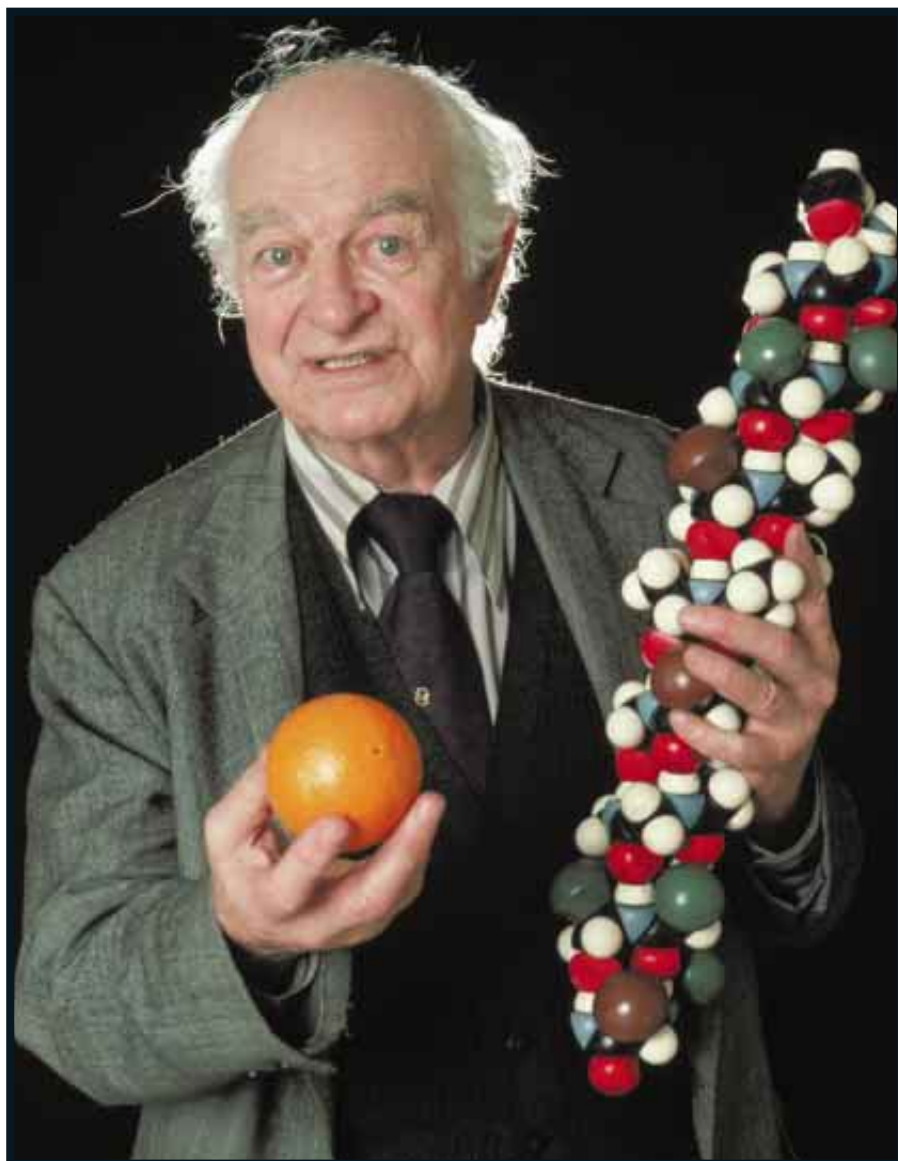
What if there were some easier way toward a longer life, something that did not involve prolonged sacrifice? What if longevity could be packed into a pill? That is the Holy Grail that has driven hucksters and con men for centuries [see box on page 36], and it is the goal of many reputable researchers today. We have always looked for the easy way out; when studies showed that the healthiest people were those who ate the most fruits and vegetables, American industry promptly packaged the active ingredients into a more palatable form, the beta-carotene pill. This proved to be of little health benefit, though; whatever it was about fruits and vegetables that was keeping people healthy was probably not beta-carotene at all, or at least not beta-carotene without the other components of the plant itself.

As distinct from the snake-oil salesmen of old, today's life extensionists base their efforts on solid-sounding

theory. They promote "antioxidant" compounds because of the "free radical theory of aging," which states that aging is a matter of cellular oxidation and can be slowed if you can prevent that oxidation. Or they look to hormonal replacement in anticipation that getting certain hormones back to youthful levels will lead to youthful functioning. But it remains to be seen whether any of these supplements or hormones really make any difference, either in prolonging life or in delaying the disabilities of age. So far whenever a "Methuselah factor" pill has sounded too good to be true, it turned out that it was.

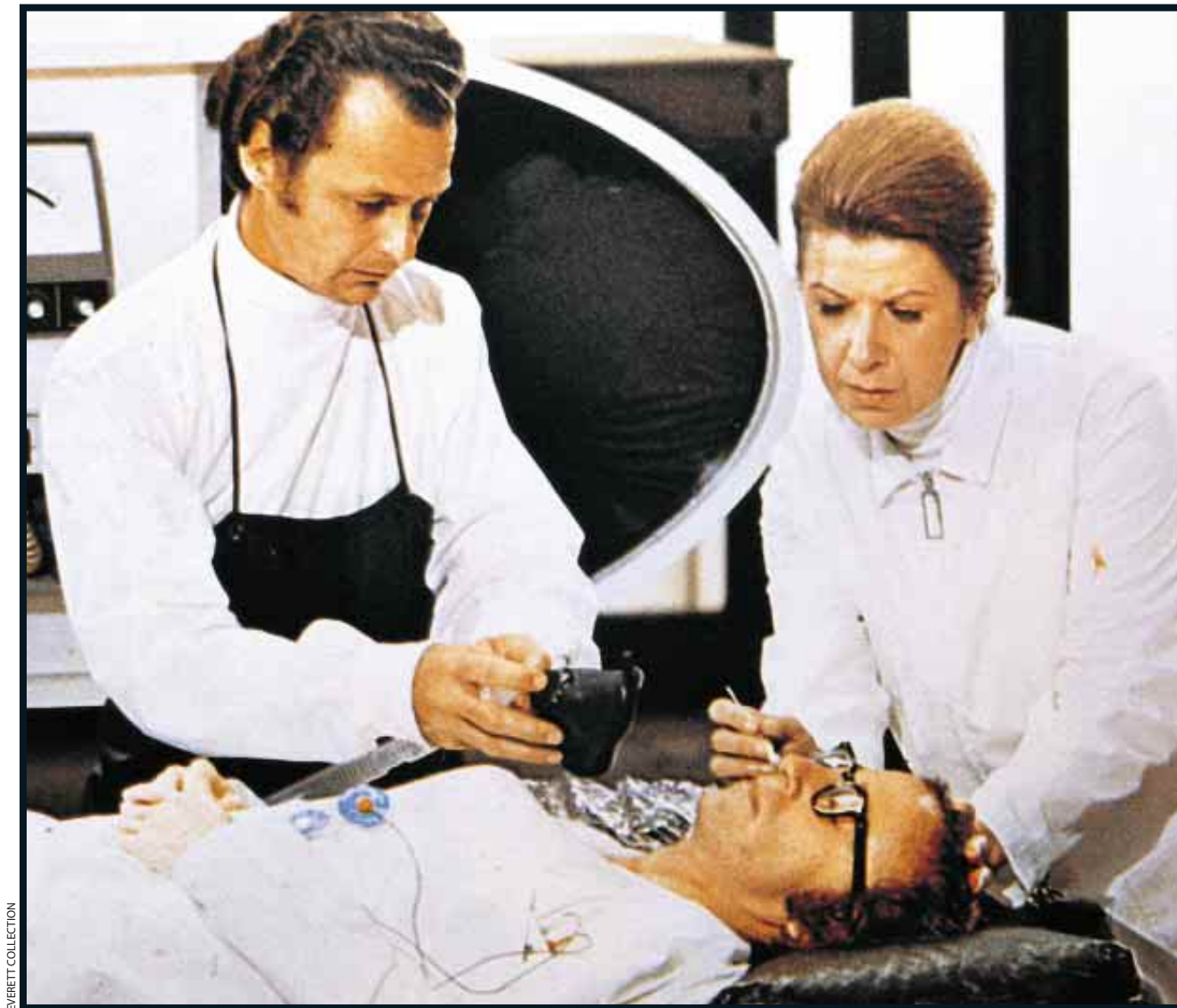
Antioxidants, for instance, started

out full of promise for their antiaging powers, but they still have not proved themselves in careful clinical trials. The most familiar antioxidants are vitamins A, C and E—especially vitamin C, which the brilliant chemist Linus Pauling celebrated in the final decades of his life. (Pauling lived to the ripe old age of 93, attributing his relatively good health to the megadoses of vitamin C he ingested every day.) Their action is thought to relate to what may be a basic underlying mechanism of aging: the buildup in the cell of molecules known as free radicals. Free radicals, the inevitable by-product of cell metabolism, are highly reactive molecules that attach to and re-



ROGER RESSMEYER/Corbis

MEGADOSE OF HYPE: Nobelist Linus Pauling linked high levels of vitamin C to prevention of cancer and heart disease, a claim that has never been substantiated.



EVERETT COLLECTION

THE JOYS OF DEEP FAT: Woody Allen as Miles Monroe in the 1973 movie *Sleeper* is revived in the 22nd century into a world that has discovered that “life-preserving foods” include steak, cream pies and deep fat, not the wheat germ and organic honey sold in his health food store 200 years earlier.

act with structures in the cell and damage them. As more and more of these radicals accumulate, cell functioning gradually slows down [see “A Radical Proposal,” on page 38].

Antioxidants reduce the chances that a free radical will turn into an oxidizing menace. The theory is provocative, but it has yet to be converted into any kind of substantive antiaging regime. In fact, studies involving beta-carotene have shown that this powerful antioxidant not only fails to slow aging or increase

longevity but can even be bad for your health. One study designed to examine beta-carotene’s protective effect against lung cancer actually uncovered a higher rate of lung cancer among male smokers who took beta-carotene than among comparable smokers who took a placebo. Another found that vitamin E provided no more protection against heart attack or stroke in high-risk patients than did either a placebo or a popular medication for blood pressure.

One new drug promoted for its anti-

oxidant effect—and for its role as one of the body’s most powerful internal clocks—is melatonin. The main function of this hormone, which is secreted by the pineal gland located in the center of the brain, is to help us differentiate night from day.

For this reason, it is not surprising that melatonin has proved to be useful for treating insomnia and jet lag. But claims have gone far beyond its effects on bio-rhythms. Melatonin is being promoted these days to prevent diabetes, cataracts, cancer, Alzheimer’s disease, schizophrenia and epilepsy. It has also been said to extend life span (up to 20 percent, based on studies on laboratory rodents), treat depression, prevent sunburn and, of

course, revivify an uninspired sex life.

Any single compound that is supposed to do all these things should raise a few eyebrows. It may turn out that melatonin does have some beneficial age-retarding and possibly even life-extending effect, but no one has proved this yet. We would be well advised to wait for some rigorously conducted studies before putting too much faith in this hormone, now sold over the counter in grocery and health food stores as a “natural” dietary supplement.

Other chemicals in the body are, like melatonin, present at significantly lower levels in

the film, which takes place in the latter part of the 22nd century, talks of the health foods of the day—steak and cream pies—while expressing astonishment that denizens of the late 20th century consumed such unwholesome fare as wheat germ and organic honey.

The only intervention ever shown to

preliminary results indicate that with a 30 percent caloric restriction—once again, in a diet that emphasizes undernutrition without malnutrition—monkeys age more slowly and possibly live longer. The calorie-restricted monkeys have measurements of lean body mass, fat, blood pressure, triglycerides and in-



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Enter your health food store with extreme caution.

old people than in young ones. Applying the logic that putting back what has been lost must be rejuvenating, people have been pushing supplements of “anti-aging hormones” like DHEA, human growth hormone, estrogen and testosterone as the newest and most scientific-sounding form of youth-restoring nostrums.

But any one of these in too large a dose can be dangerous. DHEA, for instance, has been associated with increased risks of breast and prostate cancers, liver problems, and masculinizing effects in women (acne, facial hair, voice changes and a more dangerous profile of blood lipids). For now, the jury is still out as to whether restoring hormones to a more youthful level bears any relation at all to making an older body look, feel or act like a younger one.

Perils of Wheat Germ

The message here is that you should enter your local health food store with extreme caution. From vitamin E to DHEA, the fickle wisdom of nutrition lore seems to mutate ceaselessly. In his 1973 movie *Sleeper*, Woody Allen spoofed the absurdity of the eternal quest for dietary elixirs. A scientist

extend maximum life span reliably, at least in laboratory animals, is calorie restriction—a strict dietary regimen also known as “undernutrition without malnutrition.” Scientists have used this method to extend significantly the life spans of experimental rodents, insects and fish. In mice, for instance, limiting food intake to one-third fewer calories than normal increased a mouse’s maximum expected life span of 39 months by more than 40 percent. This would translate in humans to a maximum life span of nearly 170 years [see “The Famine of Youth,” on page 44].

Not only do calorie-restricted animals tend to live longer, but they tend to look and act younger every step of the way. They are leaner and more active than their fully fed agemates; their fur loses its pigment more slowly; they are less likely to develop cancer and other diseases of old age. Even at the age of two and a half—advanced old age for lab rodents—calorie-restricted mice tend to look young.

The question now is whether this approach will work in primates, including humans. Early results in monkeys appear promising. In the late 1980s gerontologists began calorie-restriction studies on 200 rhesus and squirrel monkeys;

sulin that are typically associated with their younger brethren. And their levels of the hormone DHEA decrease more slowly than expected.

But even if these monkeys live way beyond their normal life spans—and we will not know if they do for another decade or so—it is unclear that this can be translated into a benefit for humans. And without such assurance, who would willingly put himself on a diet of 1,500 calories a day? One of the few who has done so is Roy L. Walford, a respected gerontologist at the University of California at Los Angeles, who for the past 13 years has been limiting his food intake to about one third less than the rest of us.

In 1991 Walford signed on to the highly publicized “experiment” known as Biosphere 2. As the official team doctor, he expected that he would be called on to take care of injuries and infections for the other seven “biospherians” who lived together for two years in a self-sustaining greenhouse in the Arizona desert. But he ended up doing something quite different. Because of problems in the climate and agricultural parts of the experiment, food was scarce in Biosphere 2, and team members were restricted to about 1,500 calories a day, made up primarily of vegetables, beans, grains and fruit (mostly bananas). This was, in essence, the same calorie-restricted diet Walford had been following for four years. And here he was able to measure the effect of such a

fountains of youth

In the summer of 1889 the highly respected Parisian neurologist Charles-Édouard Brown-Séquard made a stunning announcement to the Société de Biologie. At the age of 72, he had concocted an emulsion drawn from the testicles of dogs and guinea pigs and had injected himself with it. He said he felt great—and he lived on, still feeling great, for another five years.

With Brown-Séquard's self-experiment, claims for "organotherapy" took off, and the testes of all kinds of animals—as well as their prostates, ovaries, pancreases,

Soon special potions were developed that also promised a longer and more fruitful life. During the Tang dynasty in seventh-century China, for instance, a "golden elixir" that took nine months to prepare was said to guarantee immortality. It was made mostly of cinnabar, combined with the red sulfate of mercury, a red salt of arsenic, potassium and mother-of-pearl. When you drank it, the story went, you turned into a crane, took up residence with the gods and lived forever.

In our own century, there have been dozens of treatments that were supposed to make you live forever. Yogurt was one. Remember the village of centenarians in the Caucasus Mountains of Georgia, the ones who appeared on the Dannon commercials with their ancient craggy faces, faded babushkas and cartoons of supermarket yogurt? It turned out that not only was the theory of yogurt as an antiaging food—propounded by Nobel Prize-winner Elie Metchnikoff in the early 1900s—based on the mistaken assumption that aging was caused by intestinal toxins, but the villagers weren't nearly as old as they claimed. They just looked it.

Then there were restorative sea algae; the dried cells of fetal pigs, sheep or rabbits; and Gerovital. This last concoction was promoted in the 1970s by Romanian physician Ana Aslan. Aslan herself always looked younger than her age, and when she died in 1988 she had reached the respectable age of 91. Her spas and research institute had made her into one of the richest women in Romania, all from the sales of Gerovital—which turned out to be nothing more than simple Novocain, the painkiller you get in the dentist's office.

And how about amino guanidine? The drug attracted some attention in the mid-1990s for its ability to clear out the bulky sugar-protein molecules called AGEs, which were thought to age cells in the same way that oxidized free radicals do—by clogging cells and preventing them from doing their work.

Amino guanidine seems to have fallen off the antiaging radar, much the way that deprenyl, bioflavonoids and centropfenoxene have done. But never fear. New variations on old-fashioned snake oil—most of them dressed up in long scientific names ending in "ine" and "oid"—continue to gush through the pipeline. And, of course, they will keep on coming as long as people continue to look for the latest shortcut to the ever elusive fountain of youth.

—R.M.H.



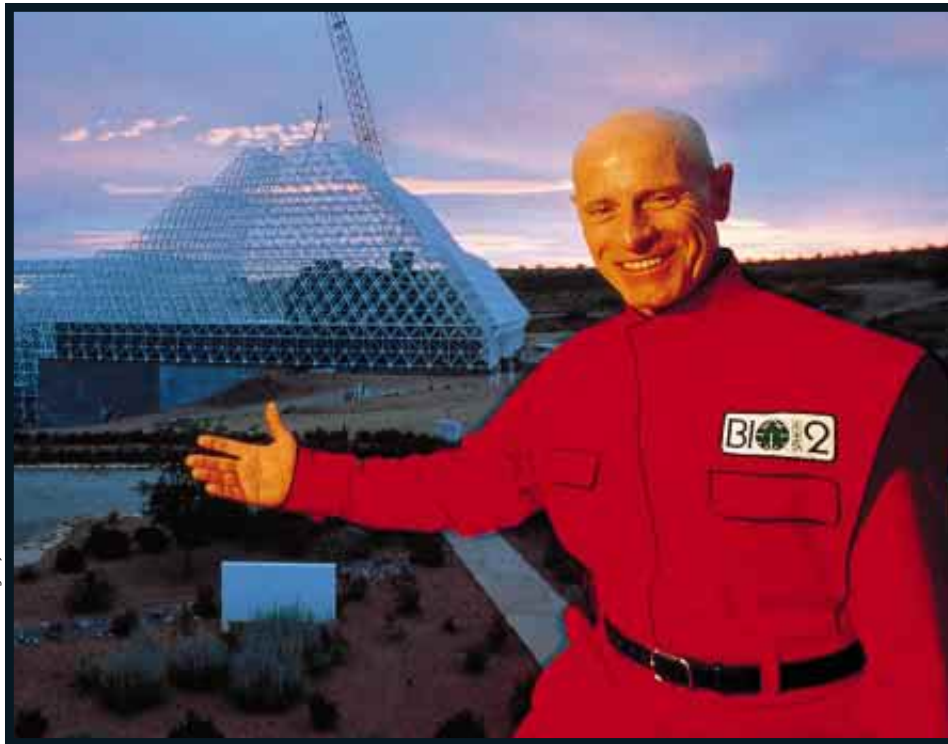
EAST PHOTO/ROMPRES

RICH, RED QUACK: Ana Aslan became one of the richest women in Communist Romania during the 1970s by selling Gerovital, a tonic that turned out to be nothing more than ordinary Novocain.

thyroids and spleens—were cut out and ground up for the sake of rejuvenating a gullible public.

But that 19th-century craze was only the most scientific-sounding approach in the quest for long life that dates back to ancient Greece and Rome, when the practice of "gerokomy"—the injunction for old men to sleep beside young virgins to regain their youthful vigor—was widely and quite enthusiastically entertained. Proof of the value of such a remedy was said to be long-lived Hermippus, headmaster of a Roman school for girls who supposedly lived to the age of 150. The reason? A lifetime spent breathing in the air around all those maidens.

the battle against aging



VOULGARPOULOS/Leison Agency

DIETARY GUINEA PIG: Gerontologist Roy L. Walford was both participant and observer in an informal experiment in calorie restriction—the most promising antiaging approach—during the two years he spent in the self-sustaining Biosphere 2 greenhouse located in the Arizona desert (seen in background).

diet on the physiological changes of seven young people over the course of two years in their confined home.

“It happened just by a freak of chance that I should be positioned inside, taking care of these people, when the same kind of diet was forced on them,” Walford has said. “So this, then, was an experiment of nature.” His findings were that many of the physiological measurements that get worse with age—such as cholesterol, blood pressure and glucose metabolism—improved among the calorie-restricted biospherians.

Even if a calorie-restricted diet does ultimately add years to your life, is it worth sticking to, given the fact that it doubtless subtracts life from your years? Is it worth it to you to spend most of your life being vaguely hungry to gain another 10, 20 or 30 years?

Eating less to live longer may not be the only strategy to deal with the perils of aging. A significant stride toward renewal of fading flesh and organs may come from a small section at the end of

chromosomes that seems to resemble an internal hourglass, counting off the number of times a cell divides until it reaches a kind of molecular old age and the relentless divisions halt. The telomere is a region at each end of the chromosome that acts like an aglet, the little hard tip at the end of a shoelace. Just as the aglet keeps the shoelace from fraying, the telomere keeps the chromosome intact. But it gets progressively shorter with each cell division, until it ultimately all but disappears. When that happens, the cell stops dividing—unless it is a cancer cell, which divides and grows in a way that becomes completely out of control [see “Counting the Lives of a Cell,” on page 50].

Recently scientists have rejuvenated old cells by inserting the gene for telomerase, an enzyme that maintains the length of telomeres, and thus preventing the aglets from wearing away. In the laboratory, cells approaching the end of their natural lifetimes, a milestone called the Hayflick limit, begin di-

viding again, in some cases continuing to multiply indefinitely. Scientists still have no idea whether any of these cellular changes will ultimately translate into a longer life span for humans, but some researchers are optimistic that manipulating telomeres may serve as a treatment for reviving tired tissue.

It might sound like a dream come true—a world where nobody ages and where people live for 200 years or more—but such a world is still a long way away. This is a good thing, basically, because it gives us time to think about whether this is really a world we want to live in or whether there’s something useful, in terms of maintaining the social balance to which we’ve become accustomed, in replacing the older generation at least every 100 years or so. In the meantime, each of us can do a tiny bit of “life extension” for ourselves if we so desire. If you set your alarm clock half an hour earlier every morning, you’ll be awake for

that much longer each day. At the end of 60 years, you’ll have gained a year and a quarter of extra conscious moments during which you would otherwise have been asleep—about as many months as would be added to the average life span if we eliminated stroke as a cause of death. That is one way, only partly facetious, to obtain the grail of all these other longevity quests: to make you feel as if you’ve lived each day allotted you, however many that might be, to its absolute maximum.

Robin Marantz Henig is author most recently of *The Monk in the Garden: The Lost and Found Genius of Gregor Mendel, the Father of Genetics*.

Further Information How and Why We Age.

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