MAKING METHUSELAH

Immortality may not be in the cards, but worms, flies and pigeons may be able to teach us a thing or two about living better longer. **By Karen Hopkin**

"MOST PEOPLE are interested in living long and fruitful lives," begins the TV talk-show host, glancing at his notes.

"Fruit is good," interrupts the 2000-Year-Old Man. "Fruit kept me going for 140 years once when I was on a very strict diet. Mainly nectarines. I love that fruit. Half a peach, half a plum. It's a hell of a fruit."

In their classic 1950s comedy routine, Carl Reiner and Mel Brooks had at least part of it figured out: we all want to live long and fruitful lives. But the answer may not lie in nectarines.

It may lie in worms. Or, more specifically, in what scientists are learning about longevity as they study organisms as diverse as roundworms, fruit flies, monkeys and humans. Their findings lend hope to those who think we might someday be able to slow the process of human aging. "We can markedly increase the life span of simple organisms," reports Judith Campisi of Lawrence Berkeley National Laboratory. Researchers have found mutant worms, for example, that live up to 20 weeks—that's about eight times their normal life span and the equivalent of 600 years for you and me. They have also discovered treatments that can make normal human or animal cells grown in dishes live forever. And they have developed diet regimens that can increase life span while making animals healthier (though not necessarily happier).

"Saying that **in 20 years** we'll all **live to be 200** is utter **nonsense.**"

"We're undergoing a major scientific revolution in our understanding of aging," maintains Michael R. Rose of the University of California at Irvine. But will any of these developments translate into a sip from the fountain of youth? Will scientists ever come up with a simple pill that will keep you looking good and feeling fine into the triple digits? Or—gasp!—even forever?

Questions such as these capture the imagination—and spark heated debate. "Our studies suggest that the rate at which animals age is not fixed in stone or immutable," states Cynthia Kenyon of the University of California at San Francisco. Kenyon has identified mutations that vastly increase the life span of roundworms. "By changing a few genes," she continues, "we can outwit death and keep the worms alive and youthful much longer." Simply mutating genes that control the way these worms respond to hormones that resemble insulin, for instance, enables them to live two to five times longer. A treatment that produced similar results might work for people, too. "If we can make it to 90," she surmises, "I see no reason why, in principle, we couldn't make it to twice that."

Other scientists are less optimistic, though. "Such gene manipulations merely postpone the initiation of the aging process," declares U.C.S.F.'s Leonard Hayflick. "Aging is inevitable. Everything ages, including the universe." In 1961 Hayflick discovered that normal human cells, when grown in a culture dish, divide a limited number of times (about 50) and then die. This ultimate ceiling has been dubbed the Hayflick limit. "Saying that in 20 years we'll all live to be 200 is utter nonsense," Hayflick says.

THE TRIUMPH OF ENTROPY

First off, there's a difference between life span and life expectancy. Life expectancy, the number that appears on an insurance company actuarial table, reflects the average number of years a person can expect to live. Life span represents maximum longevity—the absolute number of years any human could hope to survive. The good news is that life expectancy has been on the rise for some time. People now live into their 70s, on average, which wasn't always the case. "99.99999 percent of the time humans have inhabited this planet, our life expectancy at birth has been no more than 18 to 20 years," Hayflick notes. The increase we enjoy now is largely the result of humankind having conquered many infectious diseases. What is more, studies show that we're living not only longer but healthier, according to Richard J. Hodes, director of the National Institutes of Health's National Institute on Aging. As a population, we are less plagued than ever before by physical infirmity, muscle wasting, osteoporosis and the like.

But how old can we possibly live to be? Tests of simple ani-

CYNTHIA TURNER

Is a fountain of youth in your future? By elucidating the factors that drive the aging process, researchers are hoping one day to postpone the inevitable ravages of age—and perhaps prolong life.

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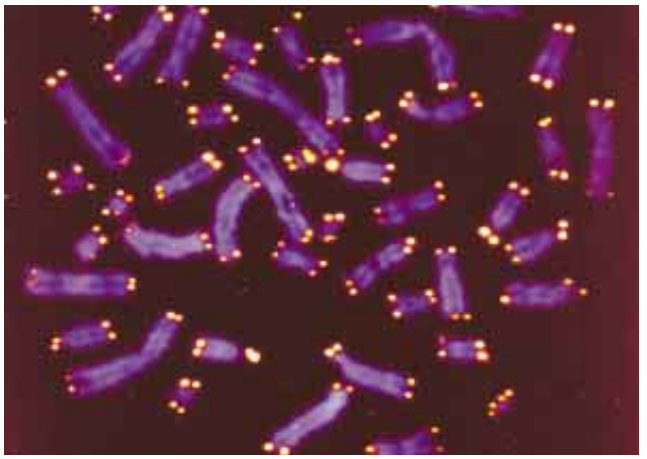

COURTESY OF GERON CORPORATION

Telomeres, which show up as glowing caps on the chromosomes above, may be the molecular timekeepers of the body. Each time a cell divides, they get a little shorter; at a crucial limit, the cell dies.

mals such as Kenyon's worms suggest there may be no upper limit, observes Rose, who studies aging in flies.

"It's hard to imagine, though, that we could live past 200," says Leonard P. Guarente of the Massachusetts Institute of Technology, who has correlated a mutation that accelerates aging in yeast with a premature aging syndrome in humans. "If we extend life span even a few years, cancer will kill everybody." And even if we duck cancer, he continues, wear and tear will weaken our veins and arteries, and our organs will eventually have to be patched up or replaced.

Even eliminating the diseases that now kill us would not increase our life expectancy substantially, Hayflick argues. Cure heart disease, add a dozen years; cancer, two or three more, he claims. "So if you cured both tomorrow morning, you'd only increase life expectancy by another 15 years. That's it, period. End of sentence." Hayflick believes that the human life span may be fixed by our genes at an upper limit of about 125 years.

Our maximum life span may have become set during evolution, because there is really no need for any creature to live beyond its reproductive years. Humans escape this seemingly cruel contract, generally speaking, because we have no natural predators hunting down the infirm or elderly members of our society. As far as evolution is concerned, by the time an animal bears children, it has fulfilled its biological destiny to pass on its genes and is just taking up space and sponging off its kids.

In any case, evolutionarily speaking, there must be a price to be paid for longevity, suggests Steven Austad of the University of Idaho, who studies aging in wild mice, opossums and birds. "Otherwise we'd all be long-lived."

But maybe we only make that argument because we're one of the longest-lived animals around, Kenyon counters. "If we were dogs, we'd look at humans and think, 'Hey, they live for a really long time, why can't we?' "

Even if natural selection did not favor the evolution of humans with the longest life spans, Hodes declares, "there's no reason why we can't change that." But to come up with potential therapies to slow or halt aging, we first need to understand why we age.

BEGINNING AT THE END

By now almost everyone has heard of telomeres—the bits of repetitive DNA sequences that cap and protect the ends of our chromosomes. Even the border guard who checked Kenyon's passport as she crossed into Canada to attend a recent conference on aging emitted a knowing "Ah, telomeres" when she described the purpose of her visit. But how do telomeres relate to aging?

There's no doubt that telomeres are important for keeping cells alive in culture dishes in a laboratory. Allow connective tissue cells called fibroblasts to grow in culture and their telomeres get shorter and shorter each time the cells divide. And when a cell's telomeres shorten enough, they signal the cell to stop dividing. Activate telomerase—an enzyme that rebuilds telomeres—and cultured cells become immortal. Cancer cells can keep dividing in part because they reactivate their telomerase.

But is telomere shortening involved in aging in the body? It's debatable. In the body, telomeres do dwindle in size as cells age, eventually shrinking to a length that would signal the same cells to stop dividing in a culture dish. But there's no direct evidence that human cells stop growing in the body because their telomeres are too short, Guarente points out. "Cells from old people grow just fine in culture," he says. And as far as we know, Austad adds, "animals don't typically die because their cells don't divide any longer."

Still, researchers who earn their living studying telomeres are hedging their bets. "It's simply too early to judge," asserts Titia de Lange of the Rockefeller University. "We just do not know enough about telomeres and aging in humans."

That's where the mice come in. To examine more directly the link between telomeres and aging, Ronald A. DePinho of the Dana-Farber Cancer Institute in Boston has generated mice that lack telomerase and found that as these animals age their telomeres shrink. They also go gray and lose their hair—a result that de Lange deems "remarkable." The rodents do not, however, develop many of the other maladies generally consid-

CYNTHIA KENYON, DELIA GARIGAN AND JAVIER APFELD
University of California, San Francisco

What a difference a gene makes. An elderly, two-week-old nematode worm (*left*) is sluggish and stiff compared with a two-day-old adult (*center*). In contrast, a mutant worm (*right*) lacking a gene that allows it to respond to hormonal signals continues to look youthful, even at two weeks.

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ered hallmarks of aging, such as cataracts, osteoporosis and cardiac disease. DePinho's conclusion: "Telomere shortening is not the cause of overall aging as we know it."

But certain cells or tissues—especially those that are dividing rapidly—probably do become crippled by shortened telomeres, suggests Calvin L. Harley of Geron Corporation in Menlo Park, Calif. Withered telomeres might help weaken the immune system, bones or skin, for example, all of which contain rapidly dividing cells and all of which are compromised as we age. In these cells, telomere shrinkage may reach a critical point, after which chromosomes begin to break. So someday doctors might boost immune function or strengthen bone or skin by turning on telomerase in the appropriate cells. Telomerase might also help extend the lives of the rapidly dividing endothelial cells that line blood vessels, allowing them to repair the wear and tear caused by a lifetime of vigorous blood flow.

Having long, luxuriant telomeres also seems to help animals deal with stress, DePinho posits. In his telomerase-deficient mice, old age and telomere loss act together to reduce the animals' ability to handle and survive stress, such as chemotherapy. Dwindling telomeres, he concludes, might explain why older people tend to have trouble recovering from surgery, infections or wounds. In the future, DePinho foresees, perhaps cancer patients scheduled for chemotherapy will also receive telomerase to prevent the treatment's side effects and enable their blood cells to survive and proliferate.

But would switching on telomerase all over the body allow people to live to the ripe old age of 150? "I doubt it," Harley declares. "When it comes to maximum human life span, so many other factors could be involved."

OXYGEN: A DEADLY GAS

Take free radicals, for example. Scientists have hypothesized since the 1950s that destructive molecules called free radicals might contribute to aging. These molecules—which are generated as byproducts of breaking down oxygen—can damage almost every critical component of cells, including DNA, proteins, and the fatty compounds that make up the inner and outer membranes of cells.

"Oxygen is toxic," declares Rajindar Sohal of Southern Methodist University. And the rate at which an animal ages may relate to how well it detoxifies oxygen radicals. Sohal finds that aged flies accumulate specific types of free-radical damage in their mitochondria—the tiny subcellular organelles that provide power to cells and tissues, including a fly's flight muscles. Martin Chalfie of Columbia University recently found that worms that lack a newly discovered form of an enzyme called catalase do not live as long as normal worms. Catalase disposes of hydrogen peroxide, a chemical that cells generate as they are converting oxygen into water. Further, Irvine's Rose has bred flies that live twice as long as normal. He finds that they show, among other things, an increase in the activity of superoxide dismutase (SOD)—an enzyme that destroys toxic oxygen radicals called superoxides.

Free radicals might also explain why pigeons live 35 years, 12 times longer than rats, animals that are about the same size. For the amount of oxygen they take in, pigeons produce fewer free radicals than rodents do. Perhaps we should be studying these animals to see how nature solves the aging problem, Austad suggests.

In the case of free radicals and aging, researchers need to be mindful of whether they are seeing cause and effect or simply a correlation, Guarente warns. Sure, oxygen radicals and cellular damage increase with age. But just because antioxidants increase life expectancy does not mean that free radicals cause aging. Banning motor vehicles would increase our life expectancy by about six months, Hayflick notes: "But that doesn't mean cars cause aging."

Free radicals can't be the bottom line when it comes to aging, Campisi agrees. "Mice and men live in the same toxic world."

So is SOD therapy likely in our future? "There's no guarantee it will work in humans," Rose admits. How about taking megadoses of antioxidants, such as vitamins C and E? That may not be good either, cautions Hodes, who recalls a study in which a group of smokers given the antioxidant beta carotene actually developed more cancers than a group of control subjects did.

NO SEX + LESS FOOD = LONG LIFE

Arguably the most striking results of studies examining ways to boost longevity come from investigations of the simplest organisms. Kenyon, for example, looks at worms that live two, three or four times longer than average. The creatures' longevity seems to boil down to the way they respond to hormones similar to insulin. Somehow mutations in this pathway allow these worms to stay frisky and svelte way past their prime, explains Kenyon, who adds, "I don't think, at the molecular level, we have much idea how."

Interestingly, she finds that removing the animals' sperm and egg cells does the same thing. Mature sex cells accelerate aging, perhaps by producing the insulinlike hormones that seem to control longevity in worms, Kenyon observes. Such an arrangement may allow animals that mature slowly to remain healthy long enough to reproduce.

This dovetails nicely with what Rose finds in his flies. He breeds longer-lived flies by delaying when the insects reproduce. "Like 'good' teenagers, they don't waste their energy on sex," he reports. As a result, they have more verve left for later. When these

RICHARD H. WEINDRUCH *University of Wisconsin*

Which of these mice is oldest? Actually, they're all the same age—39 months—which is beyond elderly in rodent-years. The two in the middle look sleek and healthy because they've been maintained on a diet containing half the calories eaten by their scraggly companions. Researchers are trying to find out how such calorie restriction can lead to long life.

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flies are 40 or 50 days old—over the hill in human terms—"they're flying around, fornicating and having a good time while the regular flies are dying," Rose says.

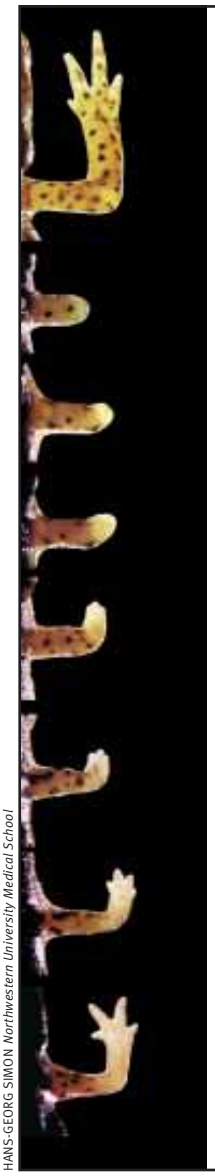
Does that mean people should put off having kids? "Oh, no, that's totally impractical," Rose responds. "What I'm doing to these flies is much more severe than what career women are doing." Besides, delaying parenthood would not affect your own life span—although it might help your descendants live it up 100 generations down the line.

The caveat? Scientists need to be certain that they are not looking at interventions that merely decrease metabolic rate, which also increases life span. Put a fly in the fridge, and it will live eight or nine times as long, Sohal states. But humans probably would not want to live longer if they had to chill out and hibernate. Although Rose's flies appear to have the same metabolic rate as adults, DePinho insists, "we need to bring these findings back to mammalian systems to see how relevant they are."

So far the only intervention that has been proved to slow aging in mammals is calorie restriction. Mice and rats raised on a diet high in nutrition but reduced in calories by 30 to 60 percent live about 30 percent longer—and by all accounts are healthier to boot, reports Richard H. Weindruch of the University of Wisconsin. In addition to his work with rodents, Weindruch has been following a colony of rhesus monkeys that have been on a restricted diet for 10 years. Compared with nondieting animals, these middle-aged monkeys have low insulin levels and are better able to regulate their glucose. They also have lower triglyceride levels, which means they are probably less prone to developing atherosclerosis, another benefit that might allow them to live longer.

The food-restricted monkeys also have less free-radical damage to their skeletal muscles than animals that are allowed to eat their fill. Together, these results suggest that the researchers who are finding that insulin regulation and oxygen radicals are important in aging in flies and worms are on to something.

But calorie restriction won't necessarily lead to another new "miracle" diet. "Nobody proposes that we starve people so they live to be 150," Campisi counters. And the truth is that this diet would not be easy for people to pull off, Weindruch admits. It's tricky to cut



HANS-GEORG SIMON *Northwestern University Medical School*

TALKIN' 'BOUT REGENERATION

FORGET THE fountain of youth. Slowing down aging may be less of a priority when we are able simply to replace faulty body parts as they wear out.

Okay, ordering Dad a new liver from Hammacher Schlemmer may not be in your immediate future. But right now biotech companies are placing stock in the idea that researchers and physicians may one day be able to direct the formation of spare body parts—be they bone, liver, pancreas or skin [see "Growing New Organs," on page 10].

To do that, scientists are taking tips from embryos. Cells and organs can be regrown, it stands to reason, with the same molecules that the embryo used to grow them in the first place. It is "unlocking the body's capacity to repair and regenerate," declares Doros Platika, president and CEO of Ontogeny in Cambridge, Mass.

Researchers at Ontogeny are treating animals with proteins with names as fanciful as Sonic hedgehog, Indian hedgehog and Patched—which all play an important role in the development of neurons, bone, cartilage, skin and hair—to stimulate the growth of the corresponding tissues in an adult. The dream is to get organs to regenerate in place inside the body, not implant a new part grown on the outside. "It may not be as sexy as a brain pulsing in a dish," Platika admits. But growing organs inside the body is better, he says, because it would allow molecular signals to be delivered in the correct context, directing organs to grow to the proper size and shape and to make the right connections with blood vessels, nerves and other tissues.

Cut off a newt's leg, and it grows back weeks later (and, in this sequence, in a lighter color). Why can't humans regenerate limbs and other body parts the same way? Enquiring scientists want to know.

"I don't think it's complete fantasy," comments Hans-Georg Simon, who studies regeneration in newts at Northwestern University Medical School. "The human body has quite remarkable capabilities for repair and regeneration." The problem is that we tend to lose that capacity as we age.

Very young children can regrow their fingertips—even up to the first knuckle, notes Clifford J. Tabin, a developmental biologist at Harvard Medical School. The trick is not rushing to heal the wound. Forming a scar is a quick and dirty way to prevent infection, but it eliminates the potential for growing new parts.

At least that's what happens in newts. Of course, these tiny creatures are at liberty to burrow into the muck for two months until they grow a new limb. Or pretty much a new anything, Tabin says. "Chop off any part of a newt, and if the animal survives, it'll grow back," he claims. It appears that adult newts retain something of the embryo's ability to allow all its cells to divide—something humans shut down, probably to avoid the runaway cell division that is characteristic of cancer.

In the next decades, regeneration might allow doctors to repair hearts, livers, skin and even injured spinal cords. But we might think twice about trying to regrow, say, a leg. "It took you 18 years to grow your leg to the size it is today," Tabin observes. "To wait 15 years to grow the right size leg is probably not as important as healing the wound to protect yourself from infection."

It's not a stretch to think that such techniques could be used to treat some of the disabilities associated with aging, according to Platika. Being able to regrow bone, for example, could save a woman with osteoporosis from getting a hip fracture that could keep her laid up in a nursing home instead of playing with her grandkids.

Ultimately, keeping people looking and feeling fit into their old age will be "more important than greatly extending life span," Platika asserts. "We want to be a bunch of gorgeous hunks and babes that are 100 years old." —*K.H.*

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that many calories and still maintain a nutritious diet. But if scientists can catalogue the physiological changes that occur in these animals, they may be able to design an intervention that accomplishes the same thing in humans who won't give up their Häagen-Dazs.

PILL ME

What does all this presage for potential antiaging therapies? The findings in calorie-restricted mammals suggest that to some degree longevity hinges on the hormones that control glucose metabolism, notes Richard A. Miller, a pathologist who studies aging mice at the University of Michigan School of Medicine. And the worm studies reveal that related hormonal pathways might regulate aging in all organisms. Animals that burn glucose more efficiently—extracting more energy from less blood sugar—somehow manage to live longer and healthier lives, Austad adds. This raises the possibility that therapies aimed at manipulating hormones might put the brakes on aging—or perhaps stave off aging-related ills such as osteoporosis, muscle loss, heart disease and cancer.

But even manipulating hormones may not be the whole answer. At the very least, we will need two different antiaging interventions, Guarente proposes: one for the brain and heart—cells that do not divide much—and another for cells that divide rapidly, such as skin. That is, unless you just want to look good. Adding telomerase might stretch the lives of skin cells, for example, but heart cells may need to be protected from the ravages of free radicals by somehow shoring up antioxidant defenses or regulating glucose metabolism.

"There's not going to be a magic bullet" to beat Father Time, Rose predicts. Campisi agrees. "To think that a single pill would slow all aging is extremely naive," she says. But someday certain interventions may be used to help particular systems of the body last longer and to prevent some age-related disorders. Retarding the death of neurons may not dramatically extend life span, for instance, but it might delay the onset of neurodegenerative diseases such as Alzheimer's disease so that they do not appear until age 90 or 100.

And as with anything, living longer may have its price. So-called dwarf mice, which are about one third the size of normal mice and live 50 to 70 percent longer, are sterile. Calorie restriction delays puberty in rats, mice and monkeys. And the maggots produced by long-lived flies die in greater numbers than those of normal flies do. "So we're never going to see childhood immunization against aging," Austad advises. But therapy later in life, after childbearing, might be an option.

Just beware the quick fix, Miller warns. Most of the people who will tell you that we can prolong the human life span are "quacks who have something to sell." If Austad were less scrupulous, he might be among them. "I like the royal jelly idea," he comments. People eat this gooey substance because bees feed it to their queens and queens live longer than drones, he says. "But mostly it's just bee poop." Perhaps the fact that researchers who study aging aren't getting rich hawking antiaging therapies suggests that they haven't found the answers—yet.

"Right now aging is still very much a black box," Guarente admits. "But we're standing on the brink of understanding." Chalfie predicts that "we'll learn a staggering amount about the biology of aging in the next 50 years. What we'll be able to do with that information, it's hard to say."

VONNEGUT'S VIEW OF AN AGELESS FUTURE

THE YEAR was 2158 A.D., and Lou and Emerald Schwartz were whispering on the balcony outside Lou's family's apartment on the seventy-sixth floor of Building 257 in Alden Village, a New York housing development that covered what had once been known as Southern Connecticut. Em and Lou weren't without their troubles, and they were out in the nippy air of the balcony because of them.

"Sometimes I get so mad, I feel like just up and diluting his anti-gerasone," said Em.

"That'd be against Nature, Em," said Lou, "it'd be murder. Besides, if he caught us tinkering with his anti-gerasone, not only would he disinherit us, he'd bust my neck. Just because he's one hundred and seventy-two doesn't mean Gramps isn't strong as a bull."

"Against Nature," said Em. "Who knows what Nature's like anymore? Ohhhhh—I don't guess I could ever bring myself to dilute his anti-gerasone or anything like that, but, gosh, Lou, a body can't help thinking Gramps is never going to leave if somebody doesn't help him along a little. Golly—we're so crowded a person can hardly turn around, and Verna's dying for a baby, and Melissa's gone thirty years without one."

"He's going to leave, Em. Just give him time.... He's talking about giving up anti-gerasone right after the five-hundred-mile Speedway Race."

"Yes—and before that it was the Olympics, and before that the World's Series, and before that the Presidential Elections, and before that I-don't-know-what. It's been just one excuse after another for fifty years now. I don't think we're ever going to get a room for ourselves or an egg or anything."

"All right—call me a failure!" said Lou. "What can I do? I work hard and make good money, but the whole thing, practically, is taxed away for defense and old age pensions."

Em put her arms around his neck. "Lou, hon, I'm not calling you a failure. You just haven't had a chance to be anything or have anything because Gramps and the rest of his generation won't leave and let somebody else take over."

"Yeah, yeah," said Lou gloomily. "You can't exactly blame 'em, though, can you? I mean, I wonder how quick we'll knock off the anti-gerasone when we get to Gramps' age."

"Sometimes I wish there wasn't any such thing as anti-gerasone!" said Emerald passionately. "Sometimes I wish folks just up and died regular as clockwork, without anything to say about it, instead of deciding themselves how long they're going to stay around. There ought to be a law against selling the stuff to anybody over one hundred and fifty."

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KAREN HOPKIN is a freelance science writer who lives in suburban Washington, D.C. She, too, believes in nectarines.

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