LONGEVITY

Living to 120

Drugs we already use for some medical conditions show surprising abilities to keep aging cells healthy. Scientists have new hope that they can develop medicines able to slow aging

By Bill Gifford

In March 2016, officials from *Guinness World Records* traveled to Haifa, Israel, to visit a retired candymaker named Israel Kristal. They came to proclaim him, at the age of 112 years and 178 days, the world's oldest man. Kristal, who has since turned 113, has led an extraordinary life. When he was born, in 1903, life expectancy for a boy in Poland was only about 45 years. As a child, he remembers throwing candies to Emperor Franz Josef of Austria-Hungary. As an adult, he ran a candy factory near Lodz. He lived through two world wars and survived nearly a year in various concentration camps, including a three-month stint at Auschwitz. His wife and two children were killed. After remarrying, he immigrated to Israel, where he made artisanal confections by hand. He now has something like 20 great-grandchildren. Born in the era of gas lamps, the centenarian now lives in the age of Twitter.

"Mr. Kristal's achievement is remarkable," said Marco Frigatti, head of records for Guinness, in an official statement. Indeed, the average life expectancy of a male in the developed world is close to 80 years. Only about two in 10,000 people live to age 100, and the vast majority of centenarians are female. At 113 and change, Kristal is near the limit of maximum observed life span for men. No human being has ever outlived Jeanne Calment of France, who died in 1997 at the age of 122.

What if, instead of dying at 80 or 85, the average person lived to be 100 or even 113 like Kristal? False promises of longer lives, even immortality, date back to the days of the alchemists, of course. So far there has not been much evidence to support such optimism. But some scientists believe centenarians such as Kristal really do age more slowly than the average person. Legitimate findings of current biological research hint that periods of extreme calorie restriction—perhaps like those experienced by the candymaker—affect the life spans of cells. This research is showing more precise ways to stretch those limits, not with diets, but with drugs.

Half a dozen medications or supplements, all of which have already been approved for human use for other purposes, turn out to target mechanisms within our cells that seem to improve internal damage control and thus help to prolong life. Some of these substances, including an anticancer drug, have already been shown to increase average and maximum life span in mice and other laboratory animals. A popular diabetes drug called metformin is headed for the first clinical trial ever designed to reveal whether a medication works to slow aging in people.

IN BRIEF

Diets and other strategies, despite promising results in simple organisms and even mice, have failed to reliably extend healthy life spans in humans and other primates.

Mechanisms within cells triggered by dietary deprivation, however, are proving to be promising life-extension targets.

Drugs, including an antidiabetes medication and an anticancer drug, aim at these mechanisms and are now being tested for antiaging potential.

Because of this activity, a small coterie of well-established aging researchers is beginning to say that serious life extension could become a reality within the lifetimes of people reading this magazine. "There's been so much crazy talk about living forever and 'hacking' aging that it kind of drowns out what we know is possible now," says Matt Kaeberlein, a leading biogerontologist at the University of Washington. "The way the research is going, I see maybe 25 to 50 percent increases in healthy longevity as plausible in the next 40 or 50 years."

"There's been a huge response and huge interest and a feeling that something big is going to happen," says Nir Barzilai, a leader of the metformin trial and director of aging research at the Albert Einstein College of Medicine. "I think we'll get significant results. And the next drugs will be better."

BEYOND DIET

AGING, AT LEAST IN PART, is rooted in our appetites. Scientists have known since the 1930s that underfeeding lab animals such as mice and rats can enable them to live longer—in some experiments, as much as 40 percent longer. Even nonscientists like Kristal think that the episodes of hunger in his life, during and after World War II, may have contributed to his longevity. In an interview with the newspaper *Haaretz,* he said, "I eat to live, and I don't live to eat. You don't need too much. Anything that's too much isn't good."

Unfortunately—or fortunately, depending on one's point of view—experiments with extreme caloric restriction in monkeys, animals more similar to people, have had mixed results. Low calorie consumption seemed to work well in one study, but then another well-designed trial showed that simply eating a more natural, whole-foods based diet, with a low sugar content, seemed to help just as much, regardless of calorie count. And in any event, very few humans can stick to a diet that requires cutting calories by 25 percent.

But experiments in lower organisms have revealed specific, beneficial cellular pathways—chains of molecular interactions—that are triggered when nutrients are scarce. These pathways evolved to allow organisms to survive long periods without food. In theory, activating such pathways with drugs could yield the same benefit without the pain of starving oneself. One example involves the enzyme AMPK, which acts as a kind of cellular fuel gauge. When nutrients are low, as happens during intense exercise or caloric restriction, AMPK jumps into action, transporting glucose into cells for energy and increasing cells' sensitivity to hormones that aid in this transport, such as insulin. It also helps break down fat for more energy. During exercise, AMPK stimulates the creation of new mitochondria, the energy producers within cells. All of these things improve health.

There is compelling evidence that aging and the rate of metabolism—the process by which a body converts food to energy—are directly linked. In 1993 Cynthia Kenyon of the University of California, San Francisco, discovered that mutations in just one specific gene called *DAF-2* could double the life span of the *Caenorhabditis elegans* worm. That gene is also linked to metabolic rates. But scientists still know relatively little about the genetics of aging, so for now their preferred targets are the higher-level mechanics of the cell.

One of the most promising antiaging mechanisms was discovered by accident. In 2001 biologist Valter Longo of the University of Southern California went away for a weekend and forgot to feed yeast cells that he was using in an experiment. He was surprised to discover that starving them completely for a time made them live longer than usual. The reason, he learned, lay in a cascade of molecular actions usually referred to by the enzyme at its center, which is called mTOR.

This pathway was originally discovered years earlier thanks to a drug called rapamycin, which was found in soil bacteria. The drug, scientists learned, affected a major pathway regulating growth and division in the cell, like the circuit breaker in a tiny factory. Researchers named the path mTOR because it is a "mechanistic target of rapamycin." When mTOR is activated, the "factory" (that is, the cell) is humming along, producing new proteins, growing and ultimately dividing. When mTOR is blocked, such as by rapamycin—or by short-term fasting—cell growth and replication slow down or stop. This is why rapamycin has been effective as an immunosuppressor to protect transplanted organs and more recently as a cancer therapy; these conditions involve runaway cell division.

Longo's work led to the revelation of mTOR's crucial role in aging. When nutrients are scarce, mTOR is inhibited, and the factory goes into a more efficient mode, recycling old proteins to make new ones, ramping up the production of cellular cleaning and repair mechanisms, and hunkering down to wait out the famine. Cell division slows down. And the animal is better able to survive until its next meal.

"What mTOR really does is, it senses the environment, and if there's lots of food around, then it gets cranked up—and in simple organisms, it causes them to develop really quickly and reproduce," Kaeberlein explains. "That makes a lot of sense because when there's lots of food, that's a really good time to make babies." No wonder the mTOR mechanism has been such a big evolutionary hit, used and reused by creatures up and down the tree of life, from single-celled yeast all the way up to humans and whales.

The activity change affects survival. In 2009 a team of scientists reported in *Nature* that rapamycin made lab mice live longer. This was a stunning finding: No other drug had ever lengthened the life span of mammals in this way in a controlled experiment. And this was not just one group of mice but *three* sets of genetically heterogeneous animals. All groups lived longer and not only on average: the animals' *maximum* life span was lengthened, which some considered clear evidence that the drug was slowing the aging process itself.

The mice given rapamycin generally seemed to stay healthier and more youthful for longer than rodents that did not get the drug. Their tendons, for example, stayed more flexible and elastic. So did their hearts and blood vessels. Even their livers were in better shape than the control mice's. They remained more active, even as they got older. What is more, rapamycin extended average and maximum life span even though mice only got it starting at the age of 20 months. It was like giving 70-year-old women a pill that let them live past 95. Or to put it another way, imagine a drug that would let Kristal live into his 130s.

Other labs were able to reproduce the results and to extend them. Mice given rapamycin throughout their adult lives ended up living 25 percent longer—about the same as if they had been calorically restricted. Mice are not people, of course, but rapamycin raised the possibility, at least, that *something* might slow aging and delay the onset of age-related diseases. "Rapamycin was the first robust hit, the first drug that everybody said that this

CELL BIOLOGY

Aging's Off-Switch

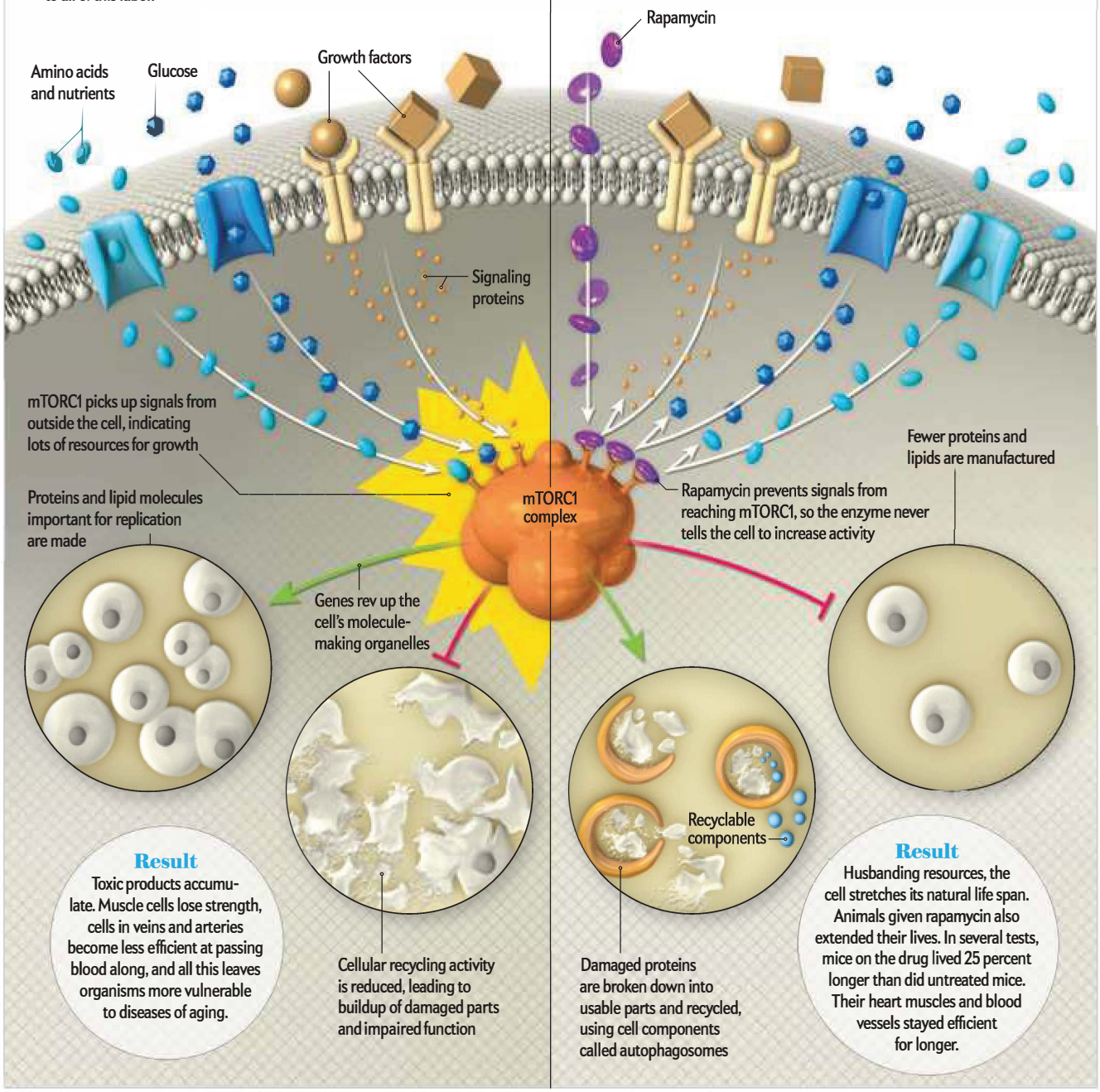
In the soil of Easter Island in the 1970s, researchers found a compound that stopped the growth of fungus cells. They called the substance rapamycin after Rapa Nui, the native name for the island. What the compound did, scientists eventually learned, was interfere with an enzyme within cells that is essential for such activities as growth and replication. Because these activities eventually degrade cell functions, blocking the enzyme stretched out the prime of cellular lives. The enzyme, dubbed mTOR for "mechanistic target of rapamycin," seems to be a switch to turn aging off and on in cells and to make animals live longer.

When TOR Is On

The enzyme has two complexes, and the one called mTORC1 acts like a sensor for the cell's environment. When nutrients are abundant and energy for growth is easy to find, mTORC1 kicks the cell into high gear. It helps the cell take up glucose for energy, growth factors that trigger replication, and amino acids that can be used to make proteins essential to all of this labor.

When TOR Is Off

The drug rapamycin shields mTORC1, keeping it from detecting glucose or growth signals or nutrients, even when they surround the cell. As a result, the cell behaves as if it is living through a time of scarcity and slows down to conserve its resources. Major cellular functions are ramped down, in particular growth and replication.



might be the real thing," says Brian Kennedy, CEO of the Buck Institute for Research on Aging in Novato, Calif.

Rapamycin is not without drawbacks, however. It can have unpleasant side effects, notably the appearance of mouth sores in some patients, and more frequent infections (because it suppresses immune response). In the mouse studies, the males appeared to suffer from testicular shrinkage. Those effects were acceptable for cancer and transplant patients, who were already quite sick, but they might disqualify it as an antiaging drug for otherwise healthy people. But what if you gave it to those healthy people in a different way or in lower doses? Could it, somehow, extend human life span as well?

To try and answer those questions, Kaeberlein and his colleague Daniel Promislow are starting an unusual clinical trial of low-dose rapamycin in middle-aged pet dogs. Our canine companions, they figure, are reasonable stand-ins for us: "They share our environment, and they get all the same diseases we get as they get older," Kaeberlein says. According to their preliminary data, dogs treated with rapamycin for just a few weeks displayed more youthful cardiac function, as measured by an echocardiogram. "We can clearly see that the heart is contracting better in the dogs that have gotten rapamycin than in the ones that haven't," Kaeberlein says. "In aging animals, poor blood flow is probably a factor in the decline of other body tissues."

One encouraging sign for the drug's potential as an antiaging agent, Kaeberlein says, is that in small amounts rapamycin may be working more as an immune modulator rather than a suppressor. It actually appears to *enhance* some kinds of immune function at these lower doses. A small human trial by Novartis, which markets a version of rapamycin as a cancer treatment called Afinitor, showed that older adults who took the drug actually responded better to a flu vaccine. This would indicate that it might enhance the immune response in some cases. One other interesting piece of evidence: a Dutch study found that healthy nonagenarians had lower levels of mTOR activity.

The next step, funds permitting, is to do a longer-term longitudinal study of rapamycin in older dogs, tracking their progress as they age. If the results reflect those achieved in mice—if the dogs live longer and healthier lives—they could justify a human clinical trial. "We could know, five years from now, to what extent it is actually working," Kaeberlein says.

STRETCHING LIVES

CONNECTING "HEALTHIER" to "longer" is key. Our life spans have been stretching out, but the latter part of our lives is prone to periods of disease and disability. As demographers James W. Vaupel and Jim Oeppen demonstrated in a 2002 *Science* paper, life expectancy for the longest-lived populations has been growing more or less linearly since the 1840s (currently Japanese females are at the top of the list). People have been living longer than ever before in human history.

At the same time, however, health span—defined as the length of healthy life—has not been growing quite as fast. This means that the period of disease and disability at the end of life, the dreaded decline of old age, has actually been getting longer. The only thing that changes, as we live longer and longer, is that we fall victim to different ailments. As mortality rates from heart disease and cancer drop, more of us become vulnerable to Alzheimer's disease. One in nine Americans older than 65 is affected by Alzheimer's or other forms of cognitive decline, with risk rising drastically after age 80.

"The rise of Alzheimer's disease has been astonishing, but it's exactly what you would expect if you push people into age windows where this disease is common, the late 70s and 80s," says S. Jay Olshansky, a demographer at the University of Illinois at Chicago. "If we continue on this path, I think that it will get worse. The alternative is to slow aging and compress morbidity and mortality into a shorter time period."

Olshansky has not met Kristal, but the Guinness record holder seems to be the kind of old person he has in mind. At 113, Kristal is still sharp mentally and a witty conversationalist. He has managed to resist the deadly illnesses of aging—not only cancer and heart disease but also Alzheimer's and diabetes, which together account for about half of deaths in the developed world. In centenarians like him, researchers find, the period of sickness at the end of life is often much shorter than for people who die in their 70s. A successful antiaging drug would need to mimic the same effect, rather than merely prolong life at the expense of health and well-being, Olshansky says.

But until very recently, investigators have faced a formidable stumbling block to developing that kind of drug: the U.S. Food and Drug Administration has not considered aging to be a disease. Therefore, it would not approve any drug that targeted the aging process itself. From the agency's point of view, this policy made sense: There is no objective way to "measure" aging—no blood test, for example, that can determine whether a person is aging more quickly or slowly than normal. So how would we know if an antiaging drug was working? That official stance eliminated any incentive for a drug company to invest in research into aging and drugs that might slow it down. There was simply no path to approval and to market.

The path began to clear in 2015, however, when the agency gave approval to a clinical trial meant to assess the antiaging properties of metformin. Approved for type 2 diabetes (the most common form) in the U.K. in the 1950s, metformin passed FDA review in the U.S. in 1994. It has since been prescribed to millions of patients as a first-line treatment. Now available as a cheap generic, it is one of the world's most common prescriptions, so much so that the World Health Organization has declared it an "essential" medication. It increases cells' sensitivity to insulin, the hormone that signals them to take in sugar (glucose) from the blood.

Because so many people take the drug, researchers have been able to detect intriguing patterns among patients. In particular, epidemiological studies have found that those on metformin seem to have a lower incidence of cancer. Other studies have suggested that metformin may have beneficial cardiovascular effects. Moreover, whereas diabetics generally lose several years of life expectancy, a 2014 analysis of British patient data found that older diabetics who were taking metformin were actually living 18 percent *longer* than matched nondiabetic controls. They also lived longer than diabetics using another common class of medications, the sulfonylureas, indicating that it was the metformin itself, and not just control of diabetes, that conferred a longevity advantage.

How exactly that works is not entirely clear. The mechanism of action of metformin, which is derived from an ancient herbal remedy called French lilac or goat's rue, has been debated among scientists for decades. One thing it is known to do is activate the AMPK pathway and its favorable metabolic changes. It also

seems to affect insulin through other paths and even to inhibit mTOR somewhat.

The possibility that metformin might enhance longevity caught the attention of Albert Einstein's Barzilai, among others. As head of a major study of Ashkenazi Jewish centenarians, Barzilai knew that long-lived people rarely have problems with high blood glucose or diabetes; ultraefficient processing of blood glucose in fact is a marker for longevity. Metformin, he thinks, might alter our metabolism to more closely resemble that of a centenarian. "A lot of its antidiabetic activity is also antiaging, just improving cellular function and insulin sensitivity," Barzilai says. He actually takes the drug himself as a preventive because his parents both had diabetes. He stops just short of saying that everyone older than 50 should think about getting a prescription (he is 60). "It looks like a superdrug," Barzilai says. "It looks like it's involved in many things related to aging."

"There are 60 years of data in humans showing that it targets a whole lot of conditions that, in aggregate, would have you believe that it's targeting fundamental aging processes," agrees James L. Kirkland, director of the Robert and Arlene Kogod Center for Aging Research at the Mayo Clinic and a collaborator on the metformin studies.

Yet to test suspected antiaging drugs in people, researchers have to deal with another obstacle: time. A conventional life span study would require decades to complete—literally, a lifetime. The trial approved in 2015, called TAME, for Targeting Aging with Metformin, takes a different approach. Rather than simply comparing longevity in healthy subjects who get the drug with those who do not, the scientists will instead look at the progression of aging-related diseases in each subject.

One of the hallmarks of aging is the way that older people often develop more than one chronic condition, such as high blood pressure and diabetes or heart disease and cognitive impairment. These so-called comorbidities, one disease on top of another, are a major cause of misery in the elderly (not to mention a driver of increased health care spending). In the TAME trial, scientists plan to give metformin to elderly patients who already have one aging-related condition, such as diabetes or high blood pressure. The subjects will be monitored for five to seven years and compared against a control group that has agreed not to take the drug to see whether or not they go on to acquire other age-related diseases at a faster or slower rate. If metformin is really slowing the aging process, then it should be able to stave off the progression of comorbidities.

The TAME trial, then, will really be measuring metformin's effect on health span—evaluating it as, in essence, preventive medicine. "The same kind of process occurred with, for example, giving antihypertensives to people who haven't had a heart attack," Kirkland says.

If the TAME study is successful, and the drug agency shows an openness to test new medications that target aging, Barzilai thinks, pharmaceutical companies will begin to move into the space—and not just traditional pharma but ventures such as the Google-backed Calico project, where none other than Kenyon, who discovered the *DAF-2* aging gene two decades ago, is vice president of aging research. Calico, some reports have speculated, may be investing more than $1 billion in a search for drugs that will extend health span, an amount close to the entire budget of the National Institute on Aging.

"If longevity is a side effect" of extending health span, Barzilai says half-jokingly, "we'll apologize for that."

PILLS FOR THE AGES

THE PIPELINE of potential antiaging medications is already beginning to fill. Acarbose, another antidiabetic agent, has extended life span significantly in male mice, for example. Like metformin, it is already approved for human use, so it, too, could be a candidate for a clinical trial against aging. Still another drug, alpha-estradiol, has also had good results in the same kind of trials that revealed rapamycin's antiaging effect.

A newer and perhaps even more promising group of antiaging drug candidates does not work on metabolic pathways but by clearing out so-called senescent cells, which have stopped dividing but have not actually died. Like cellular zombies, they sit there and secrete small proteins known as cytokines that can damage the cells around them. Kirkland believes that their true function is as a cancer defense mechanism—a way for the body to kill neighboring cells that may be malignant. Senescent cells also play a role in wound healing because the cytokines they secrete help to marshal the immune system. Unfortunately, their toxic effects reach far beyond the immediate neighborhood, contributing to the low-grade inflammation that characterizes aging bodies—and, paradoxically, increasing cancer risk in surrounding tissues. Kirkland and others see them as a key driver of the aging process.

Even worse, the older we get, the more senescent cells we harbor. What if we could get rid of them? Kirkland and his colleagues, including biologist Jan van Deursen of the Mayo Clinic, have shown that eliminating senescent cells from genetically modified mice seems to increase their health span. The problem is that those cells are very hard to isolate—they are dispersed among healthy cells—and even harder to kill. "They're very resistant to dying," Kirkland says. "They're hardy as all get-out."

A team of researchers at Mayo, the Scripps Research Institute and other institutions looked for drugs that could kill senescent cells by inducing apoptosis, or cell suicide. In 2015 they reported that they had found three. After a short treatment with the drugs, researchers saw a dramatic effect in mice that had high numbers of senescent cells. "That gives us reassurance that it's actually clearing senescent cells. And once they're dead, they're dead."

They have to die, perhaps, so that we might live. SA

Bill Gifford is author of *Spring Chicken: Stay Young Forever (Or Die Trying)* (Grand Central, 2015), a book about the science of aging.

MORE TO EXPLORE

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