



GETTING ON IN YEARS:

A multitude of maladies // and decades of decrepitude // or, with a pill or a tweak of the genes // a **painless, peaceful, dignified decline?**

Is Aging a Disease?

BY BRANDON KEIM // PHOTO ILLUSTRATIONS BY JULIEN PACAUD

When David Harrison began studying aging, he had yet to experience its effects. In his late twenties, he was fit, healthy and impervious to harsh New England winters; on all but the coldest days, he'd strap on cross-country skis and head for the Maine hills. Now, though, at age 67, he sees in himself the progressive decline he has long observed in the mice and other animals of his research. A decade ago, doctors removed a prostate tumor before the cancer spread to his bones, but other problems have accumulated. Some, such as high blood pressure and high cholesterol, are easily treated, but they're accompanied by elevated insulin levels and weight gain—a constellation of disorders called “metabolic syndrome,” which often precedes heart disease, diabetes and stroke. Dieting, exercise and drugs only slow its progression. And he now spends winters in North Carolina, where the milder climate seems to help him dodge another apparent symptom of his advancing years: chest colds that linger for weeks. “I feel the shadow of aging’s progression growing closer,” Harrison says.

He's careful to say “aging,” not “age,” a crucial distinction in his work as a gerontologist at the Jackson Laboratory in Bar Harbor, Maine. Some lucky people reach their nineties or beyond without being struck down by any of the diseases on a long list—heart failure, diabetes, stroke, Alzheimer's, Parkinson's, cancer—that become much more common after middle age and kill most Americans. And though those maladies are often grouped together as “diseases of aging,” that's usually just

a convenient catchall—they're what tends to happen when you get old. Each illness has its own phalanx of researchers striving to understand its unique causes and find ways to prevent or treat the damage it does. But some scientists take a more holistic view. They think aging itself is the issue, and that when you trace heart disease, cancer and Alzheimer's back to their roots, they all seem to stem from the same problems that span multiple body systems and lead them to ultimately malfunction.

To support this argument, researchers point to the fact that many diseases of aging seem to share networks of genes and molecular pathways. Harrison, like other longevity researchers, emphasizes that his work to decipher and improve those biological processes is not a quest for a fountain of youth—he doesn't think people can live indefinitely. Indeed, “longevity research” may be a misnomer. Though these scientists routinely produce lab animals with exceptionally long lives, their goal for humans is less to help them live longer than to fulfill their allotted span in good health. They're working to develop drugs that might delay the onset of multiple diseases of aging by acting on shared causes. That's preferable, they say, to standard practice today—fighting off diseases one at a time in a process that provides not health but prolonged decrepitude.

Despite their success in producing long-lived animals, however, scientists so far have only a fragmentary understanding of the extraordinarily complex mechanisms that appear to determine why some mice and other species, under certain circumstances, survive so much longer than others do. One method—caloric restriction—has been a particular focus because it has

seemed to be a surefire method for extending longevity and thus might reveal biological secrets that could help push back the age at which so many human diseases take hold. Yet the approach now appears to work only in some animals, further complicating research that was thought to be well understood. Meanwhile, other scientists are approaching this puzzle from a different angle, studying people who live long, healthy lives to find out what makes them special—an approach that advances in genomic analysis should make increasingly productive.

Modern longevity research traces its roots to the early 1930s, when a nutritionist at Cornell University, Clive McCay, set up an experiment. Reasoning that slowing an animal's growth could help extend its life—the candle that burns half as fast burns twice as long, so to speak—he fed rats roughly a third less than normal. They tended to live about 40% longer than their well-fed counterparts. What's more, the rats on normal diets became scruffy and weak with age, but McCay's calorie-restricted rats stayed sleek and healthy. Autopsies revealed little evidence of the heart disease, cancer and diabetes that kill rats as well as humans.

Subsequent generations of researchers picked up where McCay had left off, replicating his results up and down the animal chain. Whatever mechanisms had extended the life spans of his rats weren't unique to that species but rather appeared to be preserved through aeons of evolution—perhaps extending to primates, even humans. University of Wisconsin researchers announced in July 2009 that after 20 years of caloric restriction, 38 rhesus monkeys had markedly lower rates of heart disease, diabetes, cancer and brain disease than members of a control group. And the calorie-restricted animals were bushy-haired and bright-eyed at an age when physical decline is ordinarily as visible in monkeys as in humans.

Yet mice on strict diets seem vulnerable to infectious diseases and, despite their vigorous appearance, may have weaker muscles and frailer bones. Caloric restriction also decreases libido. “Even if we thought caloric restriction was generally beneficial, we'd want to create something that mimicked its most beneficial parts and left out the others,” says Steven Austad, a gerontologist at the University of Texas Health Science Center.

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led by James Nelson, a colleague of Austad's, tested caloric restriction on a genetically diverse array of 41 mouse strains. Though some of the mice on a restricted diet had extended life spans, others seemed to derive no benefit or to die earlier than normal. "The results raise the possibility that life extension by dietary restriction may not be universal," the two wrote in the journal *Aging Cell*.

Nelson speculates that some mouse strains, already predisposed to long life—just as people in some families routinely live into their nineties and beyond—may naturally experience the biochemical changes that low-caloric intake induces. He thinks being put on an extreme diet may push those changes too far, canceling out the beneficial impact, just as increasing the dose of a drug too high can make it toxic. Regardless, the study's results don't invalidate earlier research, and Austad considers them a boon for longevity research. "How do you slow aging? What are the cellular mechanisms? Now we're in a better position to investigate, because we can compare mice in which restricting calories works with those mice in which it doesn't," he says.

Answering such questions is really the point of this research: to provide a window on the aging process at a molecular level. Originally researchers used caloric reduction to catalogue gene and protein changes in single-cell organisms. Then they looked at what happened when they tweaked just one factor—say, switching a particular gene on or off. "In the 1990s, the forefront of this field was in the discovery of longevity genes in simple organisms," says David Sinclair, a Harvard University gerontologist. Most of the next decade, he says, was spent asking whether those genes are also in mammals and whether they play a similar role in prolonging life by delaying aging's normal diseases. Now that we know they do have that effect, the next research phase is to find out how these genes, identified in piecemeal fashion, fit together.

After decades of studying caloric restriction, researchers have a general idea how it works. Low nutrient levels prompt cells to conserve energy and improve self-repair mechanisms, enabling the cells to live longer and function more effectively. Hundreds of genes, proteins and enzymes are involved, and though most roles are not yet known, some genes seem more important than others. Sinclair's specialty is SIRT1, one of seven sirtuin genes that produce enzymes active in metabolism-related cell functions. It has been in the news partly because it's activated by resveratrol, a compound that occurs naturally in grape skins and red wine (though a human dose of resveratrol comparable to what's used in mouse studies would require consumption of about 750 bottles of wine a day).

Like many genes implicated in longevity, SIRT1 has multiple functions. It appears to accelerate the conversion of fat into energy, in part by revving up mitochondria—the cell's molecular power plants—in muscle. SIRT1 increases production of insulin in pancreas cells and of bone-rebuilding cells in marrow. More broadly, SIRT1 enzymes seem to be beacons for proteins that repair damaged DNA.

One major source of DNA damage that can contribute to aging is the oxygen free radical. By-products of mitochondrial activity, free radicals bind quickly and corrosively to other molecules; they also damage mitochondria, which have their own DNA. High levels of mitochondrial malfunction have been found in diseased heart and brain tissue, and some researchers think it may be a cause rather than an effect of such diseases as type 2 diabetes, Parkinson's and heart disease.

In 2004, Sinclair co-founded Sirtris Pharmaceuticals, which has developed a series of compounds that activate SIRT1. In tests of obese mice, the compounds have prevented diabetes. In thinner mice, the drugs have slowed aging, leaving the mice with thicker bones, cataract-free eyes and stronger hearts. One study produced an iconic image: a resveratrol-dosed mouse

The Time of Your Life //

61 Percentage of Americans who die of heart disease, cancer, stroke, diabetes or Alzheimer's, five of the most common diseases of aging—a group whose ailments might one day be treated by drugs that target an as-yet-unknown common underlying cause

1,826 Number of twins in a recent Danish study that found the greater the difference between how old each one looked to subjective assessors, the more likely the older-looking twin died first

24 Number of studies that have examined the association between low grip strength and premature mortality

3 Times by which one's chance of dying or suffering a significant disability within six years increases if one cannot walk a quarter-mile

43 Percentage of people 100 and older who have had a history of significant age-related disease after age 80

3 Percentage of people 110 and older who have had such disease after age 80—suggesting that these people might share an underlying biological similarity that those who don't live that long do not

running effortlessly on a treadmill, with an untreated mouse beside it keeping up only when its tail was shocked.

“So far, in mice, these molecules work in staving off many diseases of aging,” Sinclair says. GlaxoSmithKline bought Sirtris in 2008, and the company is now doing human trials of a SIRT1 activator for diabetes and heart disease. It also plans to test the drugs on the skin disease psoriasis and on a neurodegenerative disease such as Alzheimer's. In both diseases, inflammation causes tissue damage that is reduced in animals taking SIRT1 activators. While that research seems promising, some longevity researchers, including Austad, are skeptical. They contend that Sirtris's mouse studies were run on a few select strains rather than on genetically diverse varieties. Further clouding the picture, a different group of researchers reported that Sirtris's molecules may not directly activate SIRT1 but do activate other genes that seem linked to SIRT1 function.

Austad, however, has been impressed by the potential of another drug, rapamycin, already approved as an immunosuppressant for people receiving organ transplants. As a potent inhibitor of cell growth, it caught the attention of longevity researchers, who found that rapamycin produced caloric-restriction-like changes in lower-model organisms.

Rapamycin's mechanisms aren't fully understood, but like SIRT1, they appear to involve cell breakdown and mitochondrial function. The drug acts on mTOR, one of several genes in a network that regulates cell growth and metabolism. (One of the other genes is insulin-like growth factor 1, or IGF-1. Valter Longo, a University of Southern California gerontologist, has used IGF-1 inhibition to engineer yeast that lived for 10 weeks—10 times its normal life span.) In an experiment published last July, Jackson Laboratory's Harrison led one of three teams that independently studied rapamycin's effect on a selection of genetically diverse mice. They were 20 months old when they received the drug, roughly comparable to 60-year-old people. Rapamycin extended the normal life span for males by 28% and for females by 38%. Austad now plans to study rapamycin's effects on marmosets, which are small primates.

But rapamycin isn't on a fast track to approval as a human longevity drug. Its side effects—including immune system suppression and cancer—are known to be dangerous. Yet because the drug is used in people for other purposes, it may be possible to analyze whether it also slows aging. Such studies would be extremely difficult—people taking rapamycin by definition have serious health problems, which would complicate any analysis—but signs of effects on age-related diseases might be detected among thousands of patients getting the drug.

All of this longevity research follows a bottom-up approach, looking for life-lengthening effects in simpler species and then ultimately experimenting with humans. Thomas Perls, in contrast, works from the top down. He's the director of the New England Centenarian Study of 2,200 people born more than a century ago.

Most people who live to be 100 are surprisingly healthy; they've somehow avoided many of the debilitating diseases that claim the vast majority of humans. By looking for patterns in their genetic makeup, lifestyles and histories, Perls and others hope to shed light on what makes the difference. (The Long Life Family Study, an offshoot of the New England Centenarian Study, has enrolled 250 long-lived families; and the LonGenity study at New York City's Albert Einstein College of Medicine has recruited 500 Ashkenazic Jewish centenarians.) They're aided by ongoing advances in genomic analysis that provide powerful tools to map the genes of long-lived humans and compare those configurations both with those of other centenarians and with the genomes of people less resistant to diseases of aging.

That broad approach, just beginning in these human studies, may eventually corroborate, expand or disprove some of what



Eating lots of vegetables and little red meat, not smoking, exercising the body and mind, and learning to manage stress are all important. Still, there's undoubtedly a genetic component, as well as a role for therapies that can compensate for the usual process of systemic breakdown. And Perls doesn't doubt that many of the maladies that show up late in life have a common biological root. "It's absolutely true," he says. "That's what makes age-related diseases related to aging."

According to a Robert Wood Johnson Foundation estimate, some three-quarters of the \$2.3 trillion the United States spends on health care each year goes to treat chronic diseases—most of which are diseases of aging. If scientists identify drugs that could push back the onset of several of those diseases, there could be an enormous economic benefit. But most people aren't as frightened by aging's economic burdens as they are by the prospect of lingering for years as mind and body fail. Avoiding that is the most tantalizing promise of longevity research, and in animals, at least, it seems possible. Describing an especially long-lived strain of mice, Washington University calorie restriction researcher Luigi Fontana says that as many as half die with no obvious cause of death. "There are no major pathological lesions," he says, comparing the manner of their passing with that of many human centenarians: They're healthy until almost the very end.

Death itself is still inevitable and—in these seemingly symptom-free cases—a fascinating scientific puzzle. "Maybe it's a systemic failure, where you can't maintain homeostasis," Sierra says. But the puzzle of those deaths is perhaps less important than their nature. "The fact that we can't ascertain the cause of death might be a good thing," he says. "We all want to die in our sleep, in perfect health. That's the ideal." ■

longevity work in animals has shown. There's an intuitive appeal in going at the puzzle from this direction, and even the researchers doing the animal studies acknowledge that their painstaking protein-by-protein tracing of genes and pathways can seem limited when the consensus is that aging almost certainly involves hundreds or thousands of genes operating in concert.

Yet Felipe Sierra, who directs the National Institute of Aging's Division of Aging Biology, thinks the piece-by-piece approach has been necessary and continues to be crucial. He notes that the top-down research is new, whereas scientists have been scrutinizing the genes and molecular pathways activated by caloric restriction for many years. "We're not ready to put everything under one big tent yet," Sierra says.

So far, Perls says, studies of centenarians suggest that commonsense behavioral factors play a major role in longevity.

→ DOSSIER

1. "Prolonging the Life Span," by C.M. McCay and Mary F. Crowell, *The Scientific Monthly*, November 1934. An account of the discovery that a calorie-restricted diet extends the lives of laboratory rats, sparking decades of research that eventually led to investigations of longevity's molecular mechanisms.
2. "Rapamycin Fed Late in Life Extends Lifespan in Genetically Heterogeneous Mice," by David E. Harrison et al., *Nature*, July 9, 2009. The authors describe findings that were later independently replicated in three research centers, working with mouse populations as genetically diverse as those of humans.
3. "New Model of Health Promotion and Disease Prevention for the 21st Century," by Robert N. Butler et al., *British Medical Journal*, July 8, 2008. The authors argue that slowing aging could yield greater benefits than treatments for individual diseases.