The Fountain of Health

Antiaging research could provide a powerful approach to treating the many diseases of old age.

By David Rotman

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For the better part of two decades, Richard Weindruch, a professor of medicine at the University of Wisconsin-Madison, has fed half of a colony of 78 rhesus monkeys a diet adequate in nutrition but severely limited in calories -- 30 percent fewer calories than are fed to the control group. Scientists have known for nearly 70 years that such calorie restriction extends the life span of rodents, and Weindruch is determined to find out whether it can extend the life span of one of man's closest relatives, too.

It's too early to know the answer for certain. The monkeys in Weindruch's lab are only now growing elderly. And with 80 percent of them still alive, "there are too few deaths" to indicate whether the animals on the restricted diet will live longer, says Weindruch. But one thing is already clear: the monkeys on the restricted diet are healthier. Roughly twice as many of the monkeys in the control group have died from age-related diseases, and perhaps most dramatically, none of the animals on the restricted diet have developed diabetes, a leading cause of death in rhesus monkeys.

These encouraging, albeit preliminary, results are sure to cheer those few who have adopted severe calorie-restricted diets in hopes of living longer. But their real significance is the further evidence they provide that calorie restriction affects the molecular and genetic events that govern aging and the diseases of aging. Indeed, while calorie restriction remains impractical for all but the most determined dieters, it is providing an invaluable window on the molecular and cellular biology of disease resistance and the aging process.

Up until a decade or so ago, most biologists believed that the aging process was not only immensely complex but also inevitable. People aged, they assumed, much the way an old car does: eventually, everything just falls apart. Then in the early 1990s, Cynthia Kenyon, a young molecular biologist at the University of California, San Francisco, found that mutating a single gene, called *daf-2*, in worms doubled their life spans. Before the discovery, says Kenyon, "everyone thought aging just happened. To control aging, you had to fix everything, so it was impossible." Kenyon's research suggested a compelling alternative: that a relatively simple genetic network controlled the rate of aging.

The race to find the genetic fountain of youth was on. Within a few years, Leonard Guarente, a biologist at MIT, found that in yeast, another gene produced a similar dramatic increase in life span. Soon after, Guarente and his MIT coworkers made another startling discovery: the yeast antiaging gene, called *sir2*, required for its activity a

common molecule that is involved in numerous metabolic reactions. Guarente, it seemed, had found a possible connection between an antiaging gene and diet. The gene, Guarente thought, might be responsible for the health benefits of calorie restriction; and indeed, the lab soon confirmed that calorie restriction in yeast had life-extending effects only when *sir2* was present.

Since the discovery of these and other antiaging genes in lower organisms, the scientific search for live-longer genes in people has, not surprisingly, garnered much publicity. Often lost in the excitement about the prospect of triple-digit birthdays, however, is a far more realistic and immediate implication of the research. While learning how to extend the life span of humans could take many decades, if it's even possible, researchers are already using insights gained from studies of aging and the effects of calorie restriction to search for new drugs to treat the numerous diseases tied to getting old.

The incidences of many illnesses, including cardiovascular disease, Alzheimer's, and cancer, rise nearly exponentially with age. And while we still don't know exactly why, we *do* know that calorie restriction -- at least in test animals -- delays the onset of a broad swath of these age-related diseases. "It's something people are surprised to hear, because it really begs the question, how is that possible? There must be some common metabolic component. But no one really knows how all those diseases can be tied together," says Guarente. Nevertheless, some biologists hope that a drug that mimics the molecular effects of calorie restriction might also delay the onset of some or all of these diseases.

At least one company, Sirtris, a small but heavily funded startup in Cambridge, MA, believes it is close to finding such drugs. The company, which boasts an impressive group of prominent molecular biologists and geneticists on its scientific board, was cofounded by David Sinclair, a former postdoctoral researcher in Guarente's lab and now an associate professor at Harvard Medical School. Sirtris has come up with hundreds of molecules that activate the SIRT1 enzyme, which is produced by the mammalian homologue of *sir2*. (Seven different *SIRT* genes have been found in humans; these and their homologues in other species are collectively known as sirtuins.) If the company is on the right track -- and Sirtris says potential drug candidates for treating diabetes and neurodegenerative diseases are expected to begin preliminary human tests over the next several years -- the molecules could mimic the genetic effects of calorie restriction, offering its apparent health benefits without its drawbacks.

"It's known that calorie restriction greatly enhances the body's natural ability to fight diseases," says Sinclair. The vital questions, he says, are what controls that process and whether we can develop drugs to target it. "We don't assume we know everything about it, but we do strongly believe that sirtuins are a major component in what could be a master regulatory system for human health."

Old Yeast

The identification of the life-extending effects of *sir2* in yeasts was no accident: Lenny

Guarente had been searching for the causes of yeast aging for almost a decade when he and his MIT graduate students methodically zeroed in on the gene in 1999. It was an important finding, but its real significance became more apparent over the next year and a half.

First, Guarente and his students found the *sir2* gene in round worms. Since yeast and worms diverged evolutionarily billions of years ago, the presence of the same gene in both organisms suggested that it might be shared by other animals, including humans. Then came the bombshell. The expression of the *sir2* gene required the presence of another molecule, called NAD; as any biologist knew, NAD is involved in numerous metabolic reactions in many organisms. "This finding that *sir2* was NAD dependent meant to us that *sir2* could connect aging to metabolism and therefore to diet," says Guarente. "Once you see this activity, a child could point out, Maybe this would connect to caloric restriction."

Perhaps not most children, but other molecular biologists certainly saw the connection, and labs around the world soon began to puzzle out the effects of *sir2*. Scientists knew that calorie restriction could have an impact on disease. And now there was evidence of a strong link between *sir2* and calorie restriction. "If you put those together," says Guarente, "you can formulate a hypothesis that *sir2* genes will impact diseases of aging."

Amidst this flurry of research, however, it was a 2003 paper in the journal *Nature* by Sinclair and his collaborators that really caught the attention of those hoping to turn the science of sirtuins into drugs. Sinclair identified a class of common chemicals, called polyphenols, that activate sirtuins. The findings suggested it might be possible to develop small-molecule drugs that could interact with sirtuins and turn on their apparent beneficial effects.

Six months after the *Nature* paper, Sinclair cofounded Sirtris with Christoph Westphal, then a partner at Polaris Venture Partners, a Waltham, MA-based venture capital firm. [Disclosure: Polaris general partner Robert Metcalfe is on *Technology Review's* board of directors.] Less than two years later, the startup has $45 million in venture financing and a series of drug candidates that activate *SIRT1* and other sirtuins in mammals. Within a few years, says Westphal, now Sirtris's CEO, the company hopes to begin testing the safety of the sirtuin activators in humans. "We're aiming to mimic calorie restriction with small molecules," says Westphal. "The great break for us was to find those small molecules."

Meanwhile, members of Sinclair's Harvard lab are busy conducting experiments on thousands of mice to prove the benefits of sirtuins in treating disease and aging. The mice are stacked in endless rows of small, clean cages packed into a series of locked rooms. Some of the mice, partly bald and stiff jointed, have been genetically engineered to age prematurely. Other cages hold animals genetically destined to get colon or prostate cancers, while yet other mice will develop neurological impairments of a kind associated with Alzheimer's disease. The researchers crossbreed these mice with animals genetically engineered to overexpress one of the sirtuin genes, then monitor how the offspring fare --

whether the sirtuins fight off the diseases or prevent premature aging. Taken together, it is a massive effort to understand the role of sirtuins in mammals, with thousands of mice providing different pieces of the puzzle.

Given that the mice experiments are just a year old, and mice typically live for around three years, results are still preliminary. There is not yet any conclusive evidence, for one thing, that activating or overexpressing sirtuins increases the life span of the mice. But Sinclair says that the studies completed so far all show "that the diseases in the mice have been ameliorated."

Look Up

Elixir Pharmaceuticals and Sirtris have much in common. Both firms were founded to discover drugs for age-related diseases, using core technology built around antiaging genes. Both feature rosters of star antiaging researchers, with Elixir counting Guarente and Kenyon among its founders. Just a few miles apart, Elixir is at the edge of MIT's campus, while Sirtris is next to Harvard University.

But despite their similarities, the two companies seem to have radically different outlooks. At Elixir, which was founded in 1999, there is no evidence of the kind of youthful bravado that characterizes Sirtris. On the whiteboard in his small office, Peter DiStefano, Elixir's chief scientific officer, patiently and meticulously diagrams some of the metabolic pathways that the company is investigating. Some directly involve *SIRT1*; some don't. Arrows overlap in a complicated mesh; some arrows just wander off, pointing to unknown territory. DiStefano's point is clear: these molecular mechanisms are immensely complicated and still not completely understood.

"It's hard to say when we will get to a drug development candidate [based on sirtuins]. It's a little early," he says. He points to a small sign above his door, positioned so that it's the last thing you see as you leave the office. It reads, "The animal is always right." The challenge, says DiStefano, is translating the knowledge of mechanisms at the cellular level into an understanding of effects on the whole organism. "You have to look at the entire animal. You can do a lot of cell-based experiments and see a lot of effects in cells, and those are absolutely important starting points, but you really need to glue it all together and figure out what happens at the organismal level."

Indeed, many questions about sirtuins remain unanswered. The genetic and molecular pathways involved in aging are complex, and their details remain much in dispute. Whether sirtuins are central to them is still, in fact, controversial: other labs are studying different genetic candidates for such a master role in the aging process. "It is still a very young field, and it suffers from lack of consensus," says Stephen Helfand, a professor of biology at Brown Medical School and discoverer of an aging gene called *indy* (for "I'm not dead yet") in fruit flies. "People don't agree on many things."

Even strong believers in sirtuins point out that scientists are just beginning to understand the genes' biology and their metabolic role. In particular, it's uncertain whether sirtuins act in mammals the same way they do in lower organisms. The experiments in which adding extra copies of *SIRT1* to mice failed to extend the life span of the animals are particularly troubling to some. Labs studying mice are also struggling to prove that the beneficial effects of calorie restriction require the activity of sirtuins -- something that Guarente showed for yeast and Helfand for fruit flies but that hasn't been demonstrated in mammals.

Risk Factor

At Elixir and Sirtris, there is little talk about slowing down the aging process. Rather, both companies are intensely focused on the discovery and development of drugs for various age-related diseases, such as type 2 diabetes. Sirtris's Westphal puts it bluntly: "I was never interested in a company that would try to prolong life. I was interested in a company that was going to use genes involved in diseases of aging and in finding an FDA-approved path to get those drugs approved for important disorders like diabetes and neurological disorders."

Nevertheless, antiaging research and drug discovery efforts like Sirtris's and Elixir's are closely linked and share a common premise; a few master genes are thought to regulate both the body's ability to fight off diseases associated with aging *and* the extension of life span. Though it is still a controversial hypothesis, Sinclair and Guarente believe that in times of adversity or stress -- when food is scarce, for instance -- sirtuins somehow marshal an organism's natural defenses. They argue that, among other things, activated *SIRT1* triggers changes in cells that mobilize repair mechanisms and increase energy production. It is, perhaps, these enhanced natural defense mechanisms that explain why animals on a calorie-restricted diet live longer and are healthier.

The idea that the genetic and molecular causes of aging and of many diseases are connected could provide a powerful new way of thinking about medicine, suggests Toren Finkel, a cardiologist at the National Heart, Lung, and Blood Institute in Bethesda, MD. Walk down the corridors of any hospital, he says, and you can't help but notice that many of the patients are elderly. "As cardiologists, we target what we view as causes of diseases -- clearly involved risk factors like hypertension." While that approach is effective, he says, it has largely ignored the most obvious factor in many diseases: age.

"It is obvious....We get sicker as we get older," says Finkel. He says he's not sure whether that observation "is so obvious it is stupid, or so obvious it is profound." But either way, he says, new research explaining the genetic and molecular events behind the aging process is, for the first time, raising the possibility of treating a broad range of diseases by intervening in that process. "No one had really thought about controlling aging as a practical way to control these diseases," says Finkel. "But it could be a powerful way of treating patients."

Our understanding of why people grow old is still primitive, but researchers say the drug discovery effort can push ahead regardless. "We don't understand a damn thing about

aging," admits Helfand. But he's quick to add that the health benefits of calorie restriction are well documented in many organisms. And that, he says, "is very exciting from a drug discovery perspective."

The goal is clear: the discovery of drugs that will delay the onset of many of our most devastating diseases, the kind of illnesses that frequently turn the golden years into years of chronic ill health. "Everybody associates caloric restriction with longevity and life span, but the effects on diseases are much more immediate and important," says Guarente. "If only we understood how [calorie restriction] works, such knowledge would guide us in drug development. We would have a drug that would favorably impact many of the common diseases."

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