Mutations that cripple a molecular relay system similar to the mammalian insulin and insulin-like growth factor 1 signaling pathways enhance longevity in worms and flies. The pathways appear to influence mammalian life span as well, but that idea is far from proven. Now, rare genetic perturbations in those signals are opening a window onto how the pathways influence human aging. And new studies on rodents with similar genetic snafus might help scientists ink in the connections.

When it comes to research on aging, lab worms strut their stuff. But what everyone wants to know is whether the secrets worms divulge apply to people. Studies on humans with rare mutations might provide the answer. The idea is tantalizing, but investigating aging in people—especially small numbers of them—is arduous. Ongoing work on mainstay lab mammals might help bolster the enterprise.

Research during the past decade has revealed a signaling pathway that influences aging in several organisms. Mutations that cripple this pathway can extend the longevity of nematodes and fruit flies twofold or more. The single invertebrate pathway resembles two overlapping pathways in mammals, one controlled by insulin and the other by insulin-like growth factor 1 (IGF-1) (see “Growing Old Together”). Because the machinery is similar, researchers have hoped that, as in worms and flies, tweaking one or both pathways could extend human longevity or improve health in the elderly. Worm and fly biologists have elucidated many details of how aging is influenced by these signals, which control growth and metabolism by turning genes on and off. But a key problem is proving that the same mechanisms operate in people. The answer could be obtainable: Humans with rare mutations that disrupt IGF-1 signaling are the genetic counterparts to certain lines of long-lived rodents. Discerning whether these individuals also show exceptional longevity is a daunting task, especially because quantifying human aging is difficult (see Miller Perspective and “Magic Markers”). But where studies of these humans lose steam, continuing work on rodents might help fill in links from worms and flies to people.

A Human Angle
Certain dwarf rodents provided the first hints that the worm and fly signals modulate aging in mammals. These diminutive animals—such as the Ames dwarf and Snell dwarf mice—outlive normal creatures by about 50%. The rodents lack proteins important for pituitary development; normally, the pituitary gland disperses growth hormone (GH) into the bloodstream and tissues crank out IGF-1 in response. Because these dwarfs don’t produce GH, they carry abnormally small IGF-1 concentrations, connecting a dearth of IGF-1 with slowed aging (see Bartke Viewpoint). Technological obstacles and ethical concerns preclude genetic manipulations to test the hypothesis in people. But nature might provide a viable avenue by which to explore the question: These dwarf rodents already have human counterparts. For instance, several human populations carry mutations in Prop1, the same gene that falters in Ames dwarf mice. These individuals could help researchers decipher how insulin and IGF-1 signaling affect aging in people. The prospects are tremendous, but bringing the idea to fruition will be laborious: Because these mutations are extremely rare—individuals with any given mutation typically number far less than 100—researchers can’t get the volume of data necessary to the People
Experimental animals have taken center stage as researchers have connected insulin-related signaling to aging—and continuing studies should fill in the links. People with glitches in the mammalian versions of these pathways might also help researchers understand how the signals influence human aging.

R. John Davenport
(Published 17 December 2003)
to make accurate assessments of longevity, says endocrinologist John Parks of Emory University School of Medicine in Atlanta, Georgia. Still, the promise these groups provide is too great to ignore. “It’s imperative to look at the evidence for and against effects on life span in these humans,” says Parks.

One group of humans with inherited pituitary flaws lives on the island of Krk, off the coast of Croatia. Records provide ages of death for four individuals in this group, who lived to 68, 77, 83, and 91 years. “It’s clear that they were older than average,” says Parks—but if these folks are typical, the Krk inhabitants aren’t as hardy as their rodent cousins are. “These were not people who were living to 120.” Why humans might show life span changes that are different from those of similarly modified rodents is unknown. Detrimental effects of hormone deprivation, which stunts growth, might be more pronounced in an organism that lives nearly 100—instead of about 2—years, or they might be minimized in the sheltered environment in which lab animals exist (see “Get Wild”). Researchers need to gather statistics on the 20 other known, affected individuals, but even with those numbers, getting robust longevity data will be difficult, says Parks: “The bottom line is, we’re not sure exactly what’s going on in these people [in terms of longevity].” Complicating matters further, many individuals with these pituitary defects now receive hormone therapy; the therapy helps patients mature more normally, but “it kills the experiment,” says physiologist Andrzej Bartke of Southern Illinois University School of Medicine in Springfield.

Despite a paucity of longevity data, these populations are hinting at how altering hormone concentrations with the goal of extending life might impact health. Investigations of other humans with malfunctioning pituitaries suggest that even if such changes confer long life, they come with a downside. For instance, members of a family in the Dominican Republic with mutations in the Prop1 gene are shorter than average and, even in their 20s, appear adolescent and don’t show signs of puberty—so even if such individuals lived long, they’d be saddled with unusually small stature and fertility problems. They nevertheless exhibit characteristics of aging, such as wrinkled skin. Other individuals acquire age-related diseases unusually early. Members of the Hutterite Brethren in North America—who also carry a Prop1 mutation—develop osteoporosis while still young, for example.

In a Brazilian population with a genetic variation analogous to that carried by another long-lived dwarf rodent, the Little mouse,[9] several people are in their 60s and 70s, establishing that they have at least normal longevity. However, many of them have increased blood pressure, cholesterol concentrations, and fat deposits. In addition, people in an Ecuadorian clan with Laron[10] syndrome—caused by mutations in the gene that encodes the GH receptor protein—have relatively normal mortality. However, like the Brazilian population, they display risk factors for cardiovascular disease. Why these people have apparently normal life spans isn’t clear. Such findings at first might disappoint those interested in manipulating hormone signaling to improve health—but these apparent contradictions resemble those seen in the long-lived rodents, bolstering the notion that the animals will yield insights into human physiology.

Despite a paucity of longevity data, these populations are hinting at how altering hormone concentrations with the goal of extending life might impact health. Investigations of other humans with malfunctioning pituitaries suggest that even if such changes confer long life, they come with a downside. For instance, members of a family in the Dominican Republic with mutations in the Prop1 gene are shorter than average and, even in their 20s, appear adolescent and don’t show signs of puberty—so even if such individuals lived long, they’d be saddled with unusually small stature and fertility problems. They nevertheless exhibit characteristics of aging, such as wrinkled skin. Other individuals acquire age-related diseases unusually early. Members of the Hutterite Brethren in North America—who also carry a Prop1 mutation—develop osteoporosis while still young, for example.

In a Brazilian population with a genetic variation analogous to that carried by another long-lived dwarf rodent, the Little mouse,[9] several people are in their 60s and 70s, establishing that they have at least normal longevity. However, many of them have increased blood pressure, cholesterol concentrations, and fat deposits. In addition, people in an Ecuadorian clan with Laron[10] syndrome—caused by mutations in the gene that encodes the GH receptor protein—have relatively normal mortality. However, like the Brazilian population, they display risk factors for cardiovascular disease. Why these people have apparently normal life spans isn’t clear. Such findings at first might disappoint those interested in manipulating hormone signaling to improve health—but these apparent contradictions resemble those seen in the long-lived rodents, bolstering the notion that the animals will yield insights into human physiology.

Despite the difficulties in distilling sound numbers from human populations, Parks thinks that these groups harbor important information. He wants to identify physiological parameters that provide an indicator of aging and measure them in these populations. Such studies could provide a more practical method of gauging longevity than life-span records. They could also reveal how quickly different tissues deteriorate, despite normal life span. He’d like to use “a battery of tests to give an inference of how far along these people are in the aging process.” No such study is in the works as of yet, and no one has uncovered a reliable biomarker for aging, but Parks says, “I need a really good aging associate: someone who knows all of the ins and outs of human aging and the limitations of the assays.”

Data from humans with other problems might help bolster the endeavor. Cancer stems pituitary function far more frequently than mutations do, Parks notes. Individuals with pituitary cancer have shortened life spans, but scientists don’t know whether the
hormone deficiency or the cancer is the fatal flaw. Parks says that if researchers engineer a mouse model of this so-called acquired hypopituitarism—triggered in some way other than cancer—it could help reveal whether leaving pituitary function intact during early life but negating it later could allow animals to develop normally yet live extra-long. Perhaps the animals would also provide insight into whether extended life span is separable from small body size, an ongoing controversy (see below).

Mousing for Longevity
Researchers will continue to strive for the ultimate prize: discerning how insulin-related signaling influences human life span. But scientists won’t be able to uncover all the details they want from humans, so future work on rodents—dwarf and otherwise—will continue to contribute. Previous studies on the Ames and Snell animals suggested a connection between decreased IGF-1 amounts and longevity, but the mice also harbor reduced amounts of thyroid-stimulating hormone and prolactin, creating uncertainty about which alteration is responsible for life-span extension. Other dwarf mice indicate IGF-1 more directly, because they carry mutations that dampen only GH signaling. But GH can exert its influence on cells and tissues by routes other than those that involve IGF-1, so researchers have begun tweaking the IGF-1 system, rather than manipulating it through GH. For instance, scientists have removed the mouse gene that encodes the IGF-1 receptor (IGF-1R), a cell surface protein that gloms onto IGF-1. Animals that lack IGF-1R die soon after birth, but mice with a half-dose of IGF-1R survive—and live about 25% longer than normal mice do, according to work published in January 2003 in Nature (see “One for All”).

To pinpoint how the hormone signals brake aging, future studies should tweak the pathway in more subtle ways, says neuroendocrinologist William Sonntag of Wake Forest University School of Medicine in Winston-Salem, North Carolina. For instance, previous work revealed that curtailing insulin-related signaling in worms during adulthood, but not during early life development, extends life span (see Sonntag and Ramsey Perspective). To find out whether the same holds true in mammals, “what we need are animal models where we can precisely control IGF-1 activity in adults or during development,” he says. Bartke agrees: “We need to be more selective. We need to turn [IGF-1] off during different stages of life or turn it down or eliminate it in different types of cells.”

Researchers are already beginning to conduct such studies. For instance, work published last year in Aging Cell by physiologist Richard Miller of the University of Michigan, Ann Arbor, and colleagues suggests that in mice, reduced IGF-1 concentrations early in life—rather than late, as in worms—is a key to longevity (see “The Shrimps Shall Inherit the Earth”). That finding doesn’t mesh with the way hormone therapy is administered. “The [U.S. Food and Drug Administration] recently made it possible to administer IGF-1 and GH deliberately to children who have no medical complaint other than they are short,” says Miller. “That’s remarkably shortsighted. All the evidence [supporting the notion that reducing IGF-1 extends life span] suggests that [this treatment] may be robbing children of life.”

Division of labor. IGF-1 and insulin utilize similar machinery to control separate cellular events. Insulin regulates primarily glucose uptake and storage, whereas IGF-1 spurs cellular reproduction and growth. How each of the pathways contributes to aging in mammals remains unclear, but rare human mutations and engineered rodents might help clarify the issue.

Insulin Insights
Other studies hint that combinations of signals might dial longevity up and down in mammals. In these creatures, the single worm and fly insulin-like pathway splits in two; insulin sparks one signal, and IGF-1 ignites the other. Insulin regulates metabolism, controlling glucose uptake from the blood into cells, whereas IGF-1 spurs cell growth and prods animals to develop into adults. Each pathway operates in many different tissues, and some tissues carry both systems. Moreover, both pathways harness many of the same components, and insulin and IGF-1 can each, when presenting high concentrations, activate
Although lab results suggest that limiting IGF-1 and GH extends longevity, consumers shell out untold dollars on GH-boosting injections, supplements, and sprays. Thanks to crafty sales pitches based on shaky claims, some adults believe that a burst of hormone—rather than a dearth of it—will counteract aging’s toll, keeping them wrinkle-free and virile. A limited number of scientifically sound studies suggest that GH makes bodies leaner and more muscular but could also increase the risk of cancer and diabetes (see “Lean, Yes—but Mean?”***).

Most researchers who study basic science say that the data aren’t convincing enough to justify the risks of GH therapy—despite its allure. But arguing this point in the face of flashy sales pitches and inspiring testimonials is difficult. “Some people in clinical medicine think that this is a very effective therapy [against some of the effects of aging],” says Bartke. “Against this background, the burden of proof that IGF-1 actually accelerates aging is very heavy.” But future studies on rodents and unusual human populations might solidify the idea that shutting down IGF-1 is the path for people who want to worm their way out of aging.

---

R. John Davenport is an associate editor of SAGE KE. He appreciates finding new pathways—especially in the mountains.

References
3. K. T. Coschigano et al., Deletion, but not antagonism, of the mouse growth hormone receptor results in severely decreased body weights, insulin and IGF-I levels and increased lifespan. Endocrinology 144, 3799-3810 (2003).