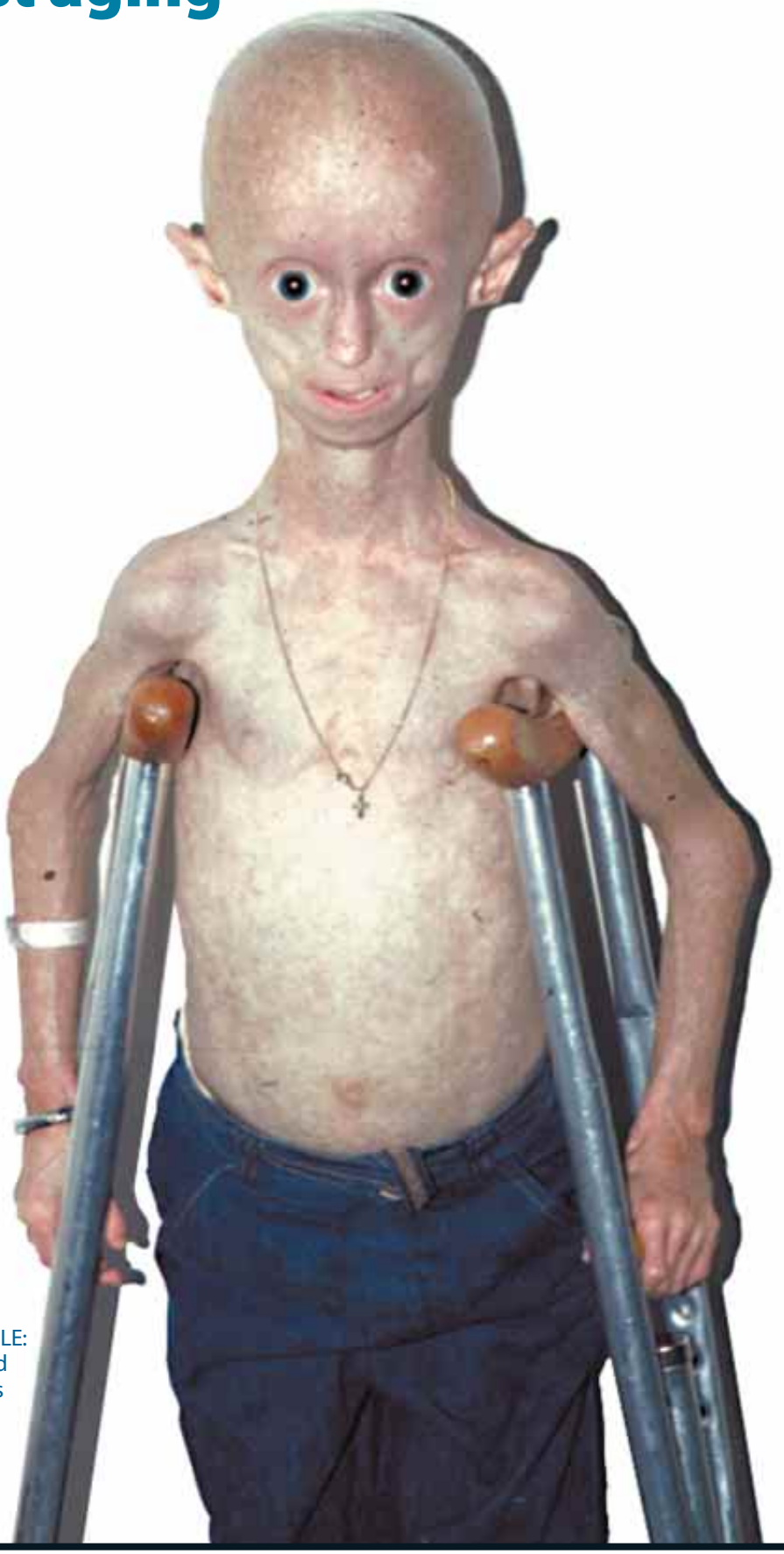
against aging



OLD YOUNG PEOPLE: Hutchinson-Gilford syndrome patients often die by their early teens from heart disease or stroke.

W. TED BROWN *Institute for Basic Research in Developmental Disabilities*

CHILDREN WITH DISEASES OF THE ELDERLY AND STUDIES OF GENES THAT EXTEND LIFE SPAN IN ANIMALS ARE OPENING A WINDOW ON HOW WE AGE

# of hyperaging and methuselah genes

BY EVELYN STRAUSS

Three-year-old Sam likes to feel starfish in his hands, and you can just forget about changing the subject when he's discussing planets. But Sam is not quite your average toddler. He's almost bald, his seven teeth don't align properly, and he is smaller than his peers. So far these are the only clues that he has Hutchinson-Gilford syndrome, a rare genetic disorder that mimics some aspects of aging.

No one can predict what course Sam's disease will take, but children with Hutchinson-Gilford syndrome typically develop arthritis and grow slowly. Their skin becomes thin, and age spots and prominent veins emerge. Most acquire severe atherosclerosis that can thwart blood flow to the brain and other organs. About 50 percent of afflicted children die of heart disease or stroke by their early teens.

When Sam's mother isn't talking to him about Neil Armstrong and Buzz Aldrin, she's in the laboratory, looking for the biochemical basis of her son's disease. Leslie B. Gordon's work on Hutchinson-Gilford syndrome—and research on other related disorders—may have implications far beyond finding a cure for a rare disease. It might also provide clues about the normal human aging process and yield insight into diseases common to old age, such as atherosclerosis, which could lead to new avenues of research for treatments that prolong life.

Hutchinson-Gilford syndrome is one of several human progerias; "progeria" means premature aging. Very little is known about the disease, and the condition is extremely rare—only about 100 cases have been documented since it was first described in 1886. Although the disease appears to be caused by a genetic defect, it doesn't run in families, suggesting that the mutation occurs randomly in egg or sperm cells or at some point after fertilization. Because researchers can't track the gene through relatives, this disorder doesn't lend itself to traditional gene-hunting approaches.

So Gordon, a research associate in the department of anatomy and cell biology at Tufts University School of Medicine, is taking a different tack. She's focusing on the one consistent difference between Hutchinson-Gilford patients and healthy children: sick kids have much higher levels of a particular compound—hyaluronic acid (HA)—in their urine. HA is necessary for life because it helps hold tissue together, but too much of it might be a bad thing, Gordon says. People with another form of progeria, called Werner syndrome, also have high levels of HA, and its concentrations creep up in elderly people, too.

A Trickle of Evidence

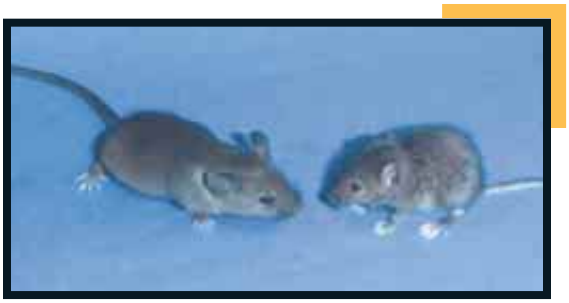
Plaques that build up in the blood vessels of people who die of heart disease are steeped in HA. "Whether it's cause or effect, no one really knows," Gordon says. "These kids have these same plaques throughout their bodies, and that's what plays a major role in causing heart attacks and strokes."

The idea that HA contributes to heart disease is not new, but work in this area has been fostered recently by new analytical tools. In this relatively unexplored area of research, Gordon is trying to follow the trickle of evidence to its source. She wants to find out whether the disease grows more severe as HA levels rise and to establish whether the chemical does indeed promote plaque formation. If such a connection were confirmed, it could lead to therapies that fight both Hutchinson-Gilford syndrome and cardiovascular disease by lowering HA levels. "Any treatments that help these children will

very likely help millions of people with cardiovascular disease and potentially other problems associated with aging," she says.

In another classical premature aging disease, Werner syndrome (WS), symptoms don't begin until adolescence or early adulthood. In this syndrome, hair thins and goes gray, skin wrinkles, and muscles atrophy. Individuals with this condition suffer from cataracts, diabetes, heart disease and other afflictions that don't typically strike until old age.

Although people with Hutchinson-Gilford and WS look old and share many ailments with geriatric patients, the physiological changes overlap only partially with how people usually age.



MAKOTO KURO-O University of Texas Southwestern Medical Center at Dallas

DODDERING RODENT: A *klotho* mutant mouse (*right*) has a small, bent back, unlike a normal mouse (*left*), and a range of age-related disorders, such as atherosclerosis and osteoporosis.

WS sufferers experience a high incidence of cancer, for example, but "they include rare, weird cancers that you don't see too often," says George M. Martin of the University of Washington.

Still, these disorders can provide some intriguing insights, says W. Ted Brown of the Institute for Basic Research in Developmental Disabilities in Staten Island, N.Y. "Mutations in one gene can produce a set of effects that dramatically resemble aging. That implies that relatively few genes could be controlling aging."

Several years ago scientists tracked down the gene responsible for WS. In its healthy form the gene encodes a protein that unwinds DNA, presumably so other proteins that manipulate DNA can wriggle between the strands to do their work. No one yet knows exactly how a defective version of this gene, which would give rise to a faulty protein, could lead to WS. But many ideas are floating around.

In test-tube experiments, WS cells are much more susceptible than normal to harm from a compound that is toxic to DNA. These results suggest that the abnormal WS protein might fail to repair damaged DNA.

And that's just one thought. Studies on a yeast protein that resembles the WS protein have suggested that it undermines DNA integrity in other ways. A mutation in a yeast gene that encodes this protein shortens life span. In cells carrying the altered gene, DNA is cut after it loops into circles, and the ends stick together. The resulting DNA circles contribute to the cell's eventual demise. No one has detected similar DNA rings in cells of people with WS or from old individuals. Some researchers have conjectured, however, that the normal WS protein quashes formation of aberrant DNA structures in humans, a process that might go awry when the gene suffers a mutation.

Already studies on WS have spurred investigators to think about new ways of looking at common disorders of human aging. Perhaps DNA damage from subtle but common variations in the WS gene may predispose people to vascular disease, cataracts and diabetes, even if they don't suffer from a full-blown form of the disease.

The big limitation of studying humans, of course, is that you can't manipulate people as you can laboratory animals. Enter a mutant mouse strain that is afflicted at a young age with many of the diseases common to older humans. The defect in the responsible mouse gene—called *klotho*, after the goddess in Greek mythology who spins the thread of life—accelerates the onset of disorders such as atherosclerosis and osteoporosis.

Researchers have isolated the *klotho* gene from both mice and humans. The human *klotho* lies in a region of the chromosome with no known genetic disorders. Because mice with defective *klotho* exhibit some aspects of premature aging, the gene may be analogous to progeria genes, such as those responsible for Hutchinson-Gilford and Werner syndromes. It's even possible that *klotho* is the yet to be revealed gene that underlies Hutchinson-Gilford. "It would be interesting to see if Hutchinson-Gilford patients have a mutation in the *klotho* gene," says Makoto Kuro-o of the University of Texas Southwestern Medical Center at Dallas.

Antiaging Hormone

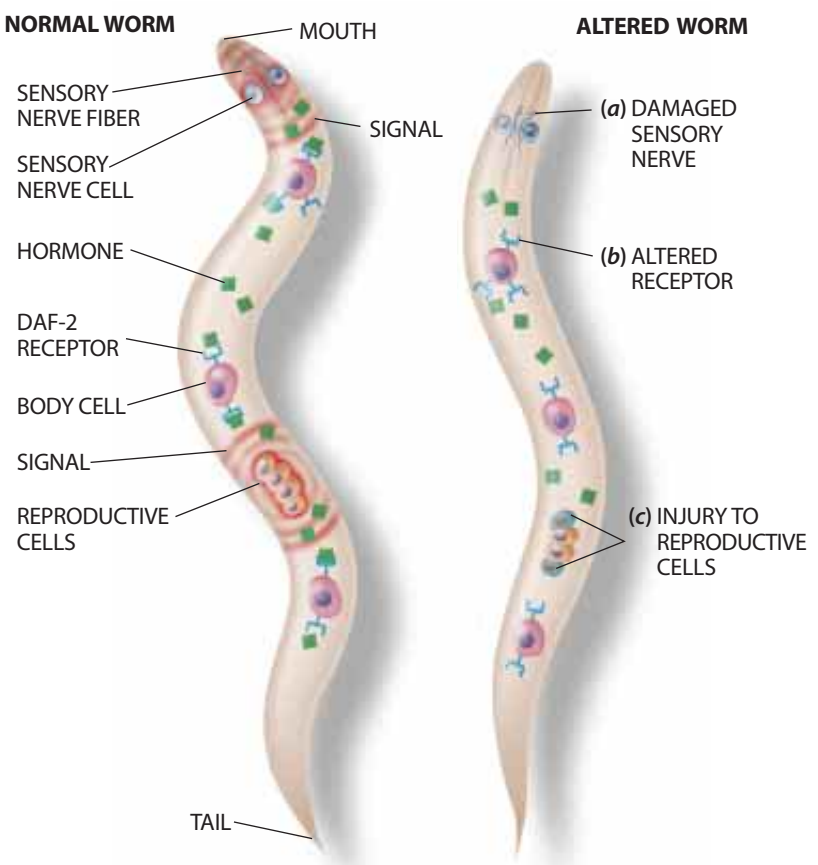
Based on an analysis of *klotho*'s DNA and the symptoms exhibited by the mice, Kuro-o hypothesizes that the mutated gene encodes an aberrant protein that circulates in the blood and triggers age-related processes in different tissues—perhaps a buildup of plaque in blood vessels. If so, the normal version of the protein might do the opposite—serving as what Kuro-o calls an "antiaging hormone." The idea of such a blood-borne factor that might keep at least some tissues healthy is a new concept for mammalian aging, Kuro-o says. He is trying to identify the molecules with which the klotho protein interacts in tissues and to figure out how cells with defective *klotho* behave differently from normal cells.

When healthy versions of genes such as *klotho* or the one underlying WS go haywire, they expedite an organism's demise. Studying these mutations and disorders may well yield insight into particular illnesses and conditions of old age. But they will probably not shed much light on one of the most important questions surrounding aging research—that is, how scientists might move beyond simply fighting diseases of old age to finding ways of extending life span beyond the current maximum limit of about 120 years.

To go further, investigators have begun to examine how overproducing some proteins prolongs the lives of microbes, flies and mammals. In yeast, extra servings of a protein called Sir2 lengthen lifetime, increasing the number of times the organism can duplicate. In contrast, yeast harboring a defect in Sir2 has a curtailed life span.

Yeast Sir2 keeps large stretches of genes turned off. Perhaps, as organisms age, they lose their ability to silence genes effectively, suggests Leonard P. Guarente

long live the worms



CELL TWEAKING: The reproductive and sensory systems of the worm *Caenorhabditis elegans* send signals affecting activity of hormones that stimulate the daf-2 receptor on certain cells (*left*). Experiments suggest that those hormones influence longevity. Manipulated worms (*right*) live longer than normal when their sensory nerves are cut (*a*), the hormone receptor is genetically inactivated (*b*) or particular reproductive cells are injured (*c*).

JOHN W. KARAPELOU

of the Massachusetts Institute of Technology. In this scenario, activation of particular genes would spur changes in physiology that lead to aging. Mammals, too, carry a Sir2-like protein, and it may function in a manner similar to that of the one in yeast. Adding to the evidence, results in mice suggest that loss of silencing may promote mouse aging, says Bruce M. Howard of the National Institutes of Health. Other genes increase life span when overproduced as well. In flies, extra copies of enzymes that neutralize oxidants, harmful oxygen-containing molecules, extend the insects' lifetimes.

If natural aging results from general deterioration of various bodily functions, it might seem surprising that single mutations could dramatically lengthen life. Last year, though, researchers reported a strain of mouse that can live almost a third longer than normal because of a mutation in one gene.

It's now known that single gene mutations in other organisms can lengthen life span. Several long-lived worms carry mutations in a gene involved in a process that appears to use chemical signals to trigger activities inside cells. The gene resembles one in humans that encodes a protein that receives messages from hormones such as insulin and growth factors. Researchers believe genetic alterations in the worms that render this protein insensitive to such hormones increase their life span. No one knows exactly how this works, but the mutant worms—known as daf-2 mutants—increase production of enzymes that protect cells from oxidants [*see illustration at left*].

Studying worms suggests a general strategy for antiaging therapies. "If aging is regulated by a hormone, it can probably be slowed by a hormone," says Gary B. Ruvkun of Harvard Medical School. A drug that regulates such a hormone, however, may be a mixed blessing. Some but not all mutations predicted to decrease hormone signaling in worms also slow metabolism. As for possible antiaging treatments, what's the point of being alive if your metabolism is so slow that you're essentially asleep? Still, it's possible that scientists could find a hormone that affects longevity but not metabolism. Drugs that target such a hormone might prolong life without making people sluggish. Furthermore, many daf-2 mutants remain healthy and vigorous for much longer than their normal counterparts do, suggesting that extending life without slowing anyone down might be relatively easy, says Cynthia J. Kenyon of the University of California at San Francisco.

Every organism has its idiosyncrasies, but many basic truths of nature apply across the boundaries of species. The discovery of hormones that apparently control life span, or some aspect of age-related diseases in worms and mice, hints at a general biological mechanism for health and longevity that extends beyond any single organism. In the future, we may be able to apply lessons learned from our simpler cohabitants to stay younger and healthier ourselves.

Evelyn Strauss *is a science writer based in Santa Cruz, Calif.*

Further Information

Basic information about progeria can be found at the **Progeria Research Foundation** site at http://progeriaresearch.org on the World Wide Web.