

Some researchers now believe that certain diseases can be postponed simply by slowing down the aging process.

Could Expanding Longevity Delay Disease?

Live Long & Prosper

by Gene Held

While they don't rank up there with death and taxes, disease and disability are close seconds in the certainty department as people age beyond the conventional three score and 10 years.

Traditionally, it's been thought that finding cures for the diseases that prey on aging bodies—cancer, dementia, heart disease—was the way to improve human longevity. But new research is leading some experts in the field to suggest that the equation needs to be flipped: Modulate aging processes, and the diseases associated with them will recede as a result.

At the recent Living to 100 and Beyond symposium, held January 2008 in Lake Buena Vista, Fla., three prominent researchers elaborated on this idea.

Aging and Disease: Cause or Effect?

Luncheon speaker S. Jay Olshansky, a professor of epidemiology at the University of Illinois at Chicago's School of Public Health, is a biodemographer and biogerontologist who has focused his research on the upper limits of human longevity. Although there's currently no treatment for aging and he adamantly denounces the many ludicrous claims of the anti-aging industry, Olshansky believes evidence is growing to support the notion that genetic and dietary interventions can retard nearly all late-life diseases.

"Biogerontologists have progressed far beyond merely describing cellular aging, cell death, free radicals, and telomere shortening to actually manipulating molecular machinery and cell functions," Olshansky writes in a paper, co-authored with



CHRISTINE BALERAS, TOM GRILL / ISTOCK



Robert Butler, Richard Miller, and Daniel Perry, published in the March 2007 issue of *The Scientist*.

The paper points to findings that the genes that are responsible for slowing growth in early life typically postpone all the signs and symptoms of aging in parallel. Hormones similar to insulin and IGF-1 (insulin-like growth factor) are involved in aging, life span, and protection against injury in worms, flies, and mice, and they extend the life span in all of those animals.

“The hormones help individual cells buffer the toxic effects of free radicals, radiation damage, environmental toxins, and protein aggregates that contribute to various late-life malfunctions. An extension of disease-free life span of ap-

proximately 40 percent has already been achieved repeatedly in experiments with mice and rats,” Olshansky and his co-authors explain.

Experiments demonstrating that gene manipulation, reduction of caloric intake, changing the signaling pathways of specific physiological mechanisms, and other interventions extending the life spans of both invertebrates and mammals have human implications, Olshansky believes.

“Several lines of evidence in models ranging from simple eukaryotes to mammals suggest that our own bodies may well have ‘switches’ that influence how quickly we age,” he states. “These switches that influence aging are not set in stone. They are potentially adjustable.”

Lessons from the Lowly Worm

Symposium keynote speaker Cynthia Kenyon, director of the Hillblom Center for the Biology of Aging at the University of California, San Francisco, has done some of the scientific legwork on which Olshansky bases his assertion.

Kenyon, an internationally recognized molecular biologist known for her groundbreaking work exploring the genetics of aging, has focused much of her research on a tiny worm less than a millimeter long, the nematode *Caenorhabditis elegans*. Since different animals have varying life spans, Kenyon reasoned there must be genes that control the rate at which they age. Working with *C. elegans*, she discovered that mutations damaging a gene called *daf-2* double the worm's lifespan.

Following up on her research, other scientists have determined that *daf-2* encodes a protein on the cell surface that acts as a hormone receptor. Hormones provide a communication pathway for cells in one part of the body to tell cells in another part how to act. The DAF-2 hormone receptor is similar to the human hormone receptors for insulin and IGF-1. High levels of insulin and IGF-1 signal the body's cells to promote growth and food storage. Low levels of signaling promote cell maintenance. Since the evolutionary process often recycles the same genes in different species (known as biological conservation), the question is whether these genes influence aging in other animals, including humans.

During the process of determining how a reduction in DAF-2 extends life span, Kenyon's lab discovered that another gene, *daf-16*, is required for this longevity. The *daf-16* gene encodes a protein that regulates the activity of other genes. The normal, non-mutant form of *daf-2* initiates a chain of events inside the cell that prevents DAF-16 proteins from accumulating in the cell's nucleus, where the DNA resides. Deactivation of *daf-2* enables DAF-16 proteins to accumulate and affect a wide array of downstream genes. These genes are involved in antioxidant activity, antibacterial protection, protein-folding, and various metabolic activities, including carbon metabolism and fat transport.

In addition to enhancement resulting from a defective *daf-2* gene, *daf-16* can be activated by other proteins. High levels of these proteins (HSF-1, SIR-2, and JNK-1) promote cell maintenance, and it's known that this occurs in species other than just worms. Activation of another longevity process, in conjunction with *daf-2* inhibition, results in worms with life spans six times as long as normal.

That's not to say the same thing could be done in humans. However, what is known from the work of two other biologists, Nir Barzilai and Pinchas Cohen, is that IGF-1 levels can influence aging. Also, the same genes that Kenyon said influence aging in other animals, including flies, mice, and dogs, have been linked to humans, suggesting that this is an ancient system that will affect lifespan in humans as well. In fact, mutations in the IGF-1 receptor that reduce its activity have been found to be over-represented in human centenarians. In addition, the human *daf-16* gene (called *FOXO*) has been linked to increased longevity in a recent study of humans in Japan.

Telomeres and the Hayflick Limit

Kenyon's work (and the work of others) draws a clear link between aging and the diseases of old age (heart disease, cancer, etc.) via the hormone system. But the hormone system is only one of many biological systems being studied to determine the reason we age.

Early in his career, Leonard Hayflick, a professor of anatomy at the University of California, San Francisco, School of Medicine, discovered that normal human fetal cells are capable of no more than about 50 population doublings before becoming senescent. This finding overturned a scientific dogma that had held sway since the beginning of the 20th century.

Hayflick also discovered that normal cells must have a counting mechanism and are mortal while cancer cells are immortal. This work established his reputation as one of the premier research scientists in the field. Other researchers, building on his findings, discovered that the reason for the "Hayflick limit" lies with the telomere, a section of DNA at the ends of chromosomes. These telomeres act like the caplets on shoestrings, protecting them from

Because of the discovery of genes that influence the rate of aging, we may be witnessing a change in the way people view aging. Thomas Kuhn's classic *The Structure of Scientific Revolutions* describes the conditions that must exist and the processes that occur when science develops a new paradigm. It makes fascinating reading when juxtaposed with the scientific literature on aging. The progress of this field seems to be following in lockstep with the observations Kuhn made. Aging research has not yet attained its defining paradigm despite more than seven decades of effort, but all signs point toward the eventual development of such a model. Once the paradigm is achieved a snowball effect should ensue, because it is the paradigm that defines the questions that are even worth asking, thereby providing both direction and a quickening pace for research.



In addition to the resources mentioned at the end of this article, actuaries desiring further information on aging can turn to *Why We Age: What Science is Discovering about the Body's Journey Through Life*, by Steven Austad, a biologist at the University of Texas, Health Science Center in San Antonio. For those with a more scientific leaning, *The Handbook of the Biology of Aging* is an excellent series that's updated and rewritten in its entirety every few years.

Also, the Society of Actuaries has organized a number of international conferences on living to 100 and beyond (Hayflick, Kenyon, and Olshansky participated in the most recent one held in January 2008 in Lake Buena Vista, Fla.) and has published the proceedings of these meetings in the form of online monographs. Go to www.soa.org/livingto100monographs.

unraveling. Because of a quirk in the copying process, the telomeres shorten every time a normal cell divides, eventually reaching a point at which the cell is no longer capable of replicating.

Distinguishing aging from longevity and also from aged-related diseases, Hayflick told symposium attendees that the causes of aging are known: "Aging is the loss of molecular structure (hence function) caused by the intrinsic thermodynamic instability of complex biomolecules, or increasing entropy." Biological aging, Hayflick added, is a random "systemic loss of molecular fidelity that eventually exceeds repair or maintenance capacity."

"Age changes are not caused by genes," Hayflick said. "Age changes simply increase vulnerability to disease or pathology."

Longevity, on the other hand, is indirectly governed by the genome through cellular repair and maintenance mechanisms. Longevity is determined by how long those mechanisms can maintain the cell's molecules in a biologically active state. However, those mechanisms are themselves subject to the same destructive processes they seek to ameliorate and, as a result, the maintenance functions degrade over time.

"Longevity is governed by the enormous excess, or physiological reserve, reached at the time of reproductive maturation," Hayflick explained. "This is achieved through natural selection to better guarantee survival to the age of reproductive success." Thus, longevity is incidental to the main goal of reproduction.

Hayflick believes that the life span of humans and their predecessor species increased rapidly until about 100,000 years ago. This is supported by several lines of reasoning. The life spans of mammals have not only increased over evolutionary time, they also correlate well with the brain weight to body weight ratio. Humans have the greatest ratio of all mammals and are also the longest lived (although recent evidence suggests the humpback whale lives to 175 years and may violate this rule).

Human life spans may still be increasing, Hayflick says, but imperceptibly so. In his book, *How and Why We Age*, Hayflick states that while past natural increases are evidence that life spans are plastic and may have the potential to increase in the future, he doubts that human intervention in the process is possible. The complexity is just too great. Human life span may be increasing naturally but at such a slow rate that we do not yet have methods to detect it. At the same time, Hayflick admits that most researchers probably wouldn't agree with him on this point and suggests that most would say it's not a matter of "if" but "when," and would maintain that "when" may be "soon."

"The ability for humans to manipulate the aging process has always been 50 years in the future," Hayflick adds.

Research Priorities

In Hayflick's view, there are a number of areas that need attention in order to further research. In a post-symposium interview, Hayflick noted that some animals don't appear to age at all, yet studies to determine why this is so haven't been done. He also took aim at what he calls the physician's mantra: "If the greatest risk factor for age-associated disease is age, then why isn't the aging process being studied rather than the diseases that result from it? Just as studying the diseases of childhood doesn't tell

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Language on the Biology of Aging from the 2008 Senate Appropriations Bill

you anything about the developmental process, studying the diseases of old age won't tell you anything about aging."

Hayflick believes that the National Institute on Aging (NIA) is approaching the issue from the wrong direction because the diseases of old age are a result of the aging process; that is, of the body's reduced capacity to fend them off. Less than 5 percent of the NIA's budget is directed toward true aging research, Hayflick said, and 45 percent of the NIA funds for biological research are spent on age-associated diseases (cancer, heart disease, and stroke), even though the National Institutes of Health contains specific institutes that are dedicated to research on those diseases. The NIA spends 50 percent of its budget on Alzheimer's disease, Hayflick said, the resolution of which will add 19 days onto human longevity.

Olshansky echoes Hayflick's frustration with the NIA's distribution of research funds, questioning why the agency devotes such a large portion of resources to studying Alzheimer's disease rather than to the study of aging itself, which is the biggest risk factor not only for Alzheimer's but for many other diseases as well.

The issue of funding is so vexing in fact that in 2005, Daniel Perry, executive director of the Alliance for Aging Research, arranged a congressional briefing on aging research. In 2007, Sen. Tom Harkin (D-Iowa) asked Perry, Olshansky, and others to provide language for the Senate Appropriations Committee urging an increase in research funding on the biological basis of aging. The language was included in the committee's report on the 2008 appropriations bill that passed in the Senate last year and became part of the 2008 appropriations bill. (See above.)

Longevity Dividend

In recent writings, Olshansky has focused on what he calls the longevity dividend. Pointing to studies with animals, Olshansky suggests that delays in aging could have a double payoff in both longer, healthier lives and in reduced periods of compromised health with its burdensome costs. Olshansky and others have delineated what they say is a modest and realistically achievable goal of a "deceleration in the rate of aging sufficient to delay all aging-related diseases and disorders by about seven years." Such a delay, they argue, would yield health and longevity benefits greater than what would be achieved from the elimination of all cancer and heart disease deaths. Furthermore, it could be achieved for generations living today.

Countering this rosy outlook, Olshansky told symposium attendees, are expanding levels of obesity, particularly among the young, which bode poorly for the future. This is especially true for health care where, according to one study that Olshan-

The Committee commends the NIA for work it has done to improve understanding of the biological factors that regulate the processes of aging.

These new discoveries have led many scientists to believe that it may become possible to postpone the onset of a wide range of fatal and disabling diseases, in a coordinated fashion, by retardation of the aging process. It is widely understood that chronic illness is a powerful driver of medical costs, which in the United States are expected to reach \$16,000,000,000,000 annually by 2030. To alleviate this financial burden and to develop interventions that can extend health and longevity, the Committee urges the NIA to increase dramatically its annual investment in the biological basis of aging."

sky cited, "the net result of these phenomena may be a population that is, paradoxically, more obese, diabetic, arthritic, disabled, and medicated but with a lower overall CVD [cardiovascular disease] risk."

"Some subgroups of the population will experience an accelerated increase in life expectancy," Olshansky said, "other subgroups of the population an actual decline in life expectancy."

Olshansky, Kenyon, and Hayflick may have differing views as to what is achievable

within a given time frame, but even their disagreements are productive since science isn't a collection of facts but an ongoing series of arguments as to the nature of the world around us. And there is much about which they agree, including the need to direct additional funds to basic research, as opposed to the diseases of old age.

A proposed initiative to survey the aging research community is currently under review by the Society of Actuaries. The objective would be to provide scientific input adequate for actuarial modeling, with the goal of determining whether an increase in funding specifically targeted at aging research would provide an understanding of aging sufficient to result in significantly reduced health care costs.

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