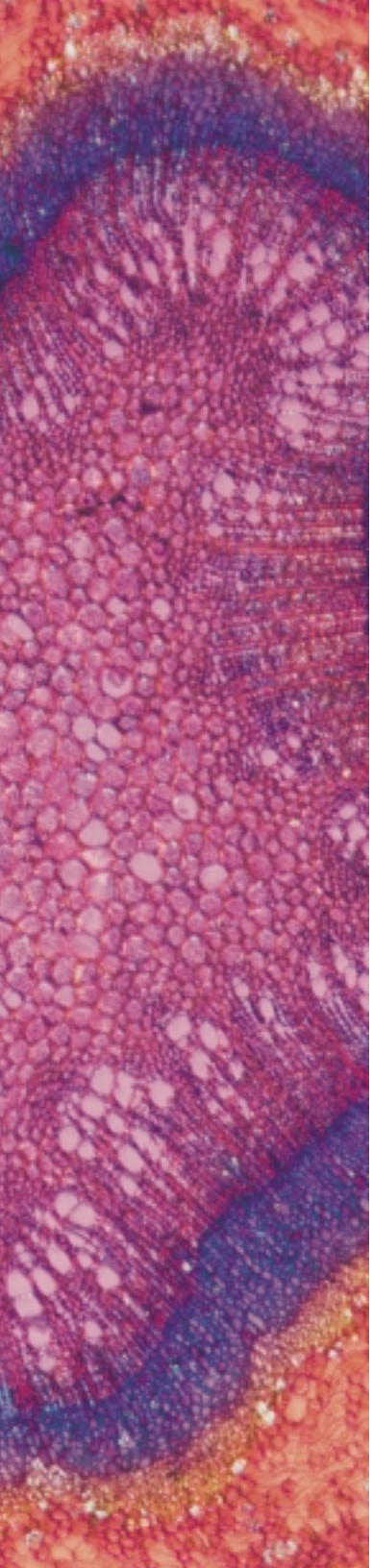

Aging Under the Microscope

A Biological Quest

NATIONAL INSTITUTE ON AGING ■ ✦ ✶ ✸ NATIONAL INSTITUTES OF HEALTH

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"One of two things happens after sixty,
when old age takes a fellow by the hand.
Either the rascal takes charge as general factotum,
and you are in his grip body and soul;
or you take him by the neck at the first encounter
and after a good shaking make him go your way."

—William Osler, 1913

Life is short, so enjoy every minute. Hang gliding, for me, lifts the spirit and recharges the old batteries. It is the greatest sport going, and lots of exercise too.

— Robert Byrd
hang glider, age 74

Introduction

The study of aging is not what it used to be. Gerontology was a young science when Congress created the National Institute on Aging (NIA) in 1974 as part of the National Institutes of Health (NIH). At that time, theories of aging abounded, but data was scant. Gerontology lacked, or was just in the early stages of developing, ways to explore the fundamentals of the aging process. Knowledge of aging clustered around specific diseases associated with advancing age; indeed the notion that aging equated with decline and illness was widespread.

Now, nearly 30 years later, the science base has grown in depth, breadth, and detail. And, with this growth have come new insights into the processes and experience of aging. Where gerontologists once looked for a single, all-encompassing theory to explain aging—a single gene, for instance, or the decline of the immune system—they are now finding multiple processes, combining and interacting on many levels. Cells, proteins, tissues, and organ systems are all involved, and gerontologists are now able to discern many more of the mechanisms by which these components cause or react to aging.

Much of this research has been supported or conducted by the NIA. In addition to research in its laboratories in Baltimore and Bethesda, Maryland, the Institute sponsors basic, clinical, epidemiological, and social research on aging at universities, medical centers, and other sites worldwide. As this work evolves and new knowledge accumulates, gerontologists hope to move closer to their ultimate goal of promoting health and independence throughout the lifespan.

Posing Questions, Finding Answers

In 1965, a lawyer made an unusual deal with one of his older clients, Jeanne Calment of Arles, France. In exchange for ownership of her apartment, he agreed to pay her a monthly pension for the rest of her life. Because Mme. Calment was 90 years old at the time, it seemed likely that the lawyer would only have to make a few payments before her demise. As it turned out, however, it was a much better bargain for Mme. Calment. During the next 32 years of her extraordinary life, she was paid three times the worth of the apartment.

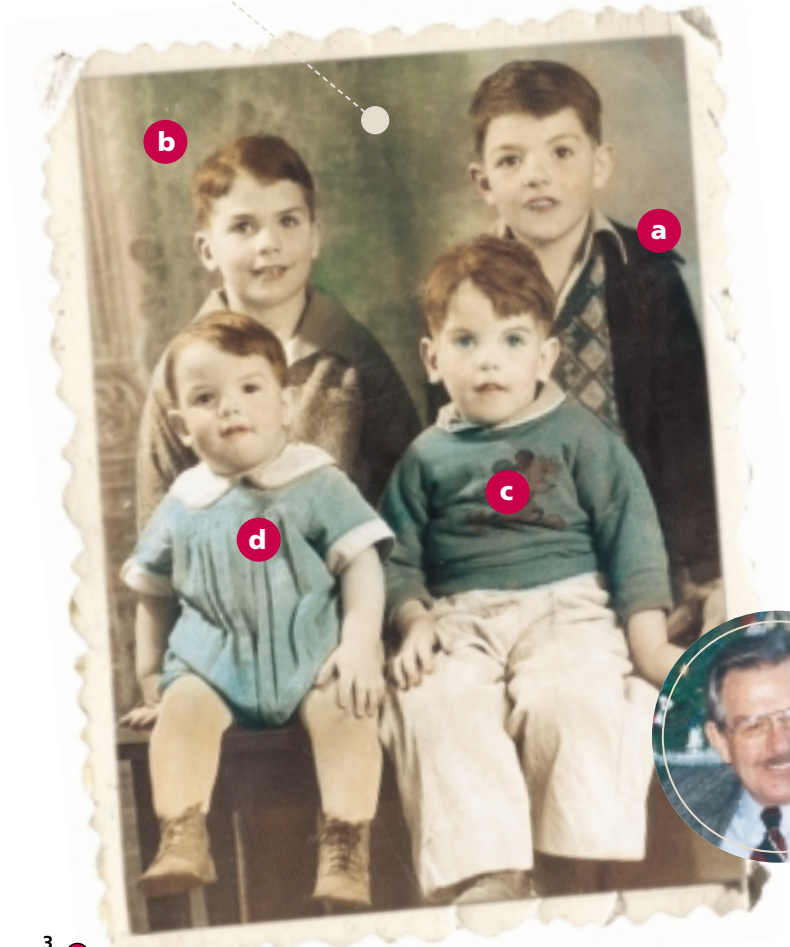
"We all make bad deals in life," Mme. Calment once joked to the astounded attorney. When her well-documented life ended on August 4, 1997 at age 122 years 5 months and 14 days, she is believed to have lived longer than any other person in recorded history. She outlived Shigechiyo Izumi of Japan, who had held the unverified longevity record of 120 years, 237 days. She outlived her husband, who died in 1942, four years before their 50th wedding anniversary. She outlived her daughter, who died in 1936. She outlived her only grandson, who died in 1963. And yes, she outlived her lawyer who died—at age 77—soon after Mme. Calment's 120th birthday.

Long lives like Mme. Calment's are a wonder. Of the planet's current 6 billion inhabitants, perhaps no more than 25 people are more than 110 years old. So these super centenarians, as they are known, are clearly humanity's ultimate marathoners. But why? What factors allowed Jeanne Calment, who was 14 when the Eiffel Tower was completed and who once sold painting supplies to Vincent Van Gogh, to live such a long life that she herself became part of history?

Is genetics the key factor? Mme. Calment's ancestors were legendary for their long lives. Is it where people live? As of 2001, ten of the world's oldest people were Japanese, six were American, three were French, and two were Italian. Is there something special about how these people live? Mme. Calment took up fencing lessons at 85, still rode a bicycle at age 100, smoked until she was 117, and ate a diet rich in olive oil all of her life. In truth, there probably is no single "secret" of aging. More than likely, all of these elements—heredity, environment, and lifestyle—have complex roles in determining whether an individual will have a long and healthy life, according to scientists who study aging.

At her 120th birthday party, a journalist hesitantly told Mme. Calment, "Well, I guess I'll see you next year." Instantly, she shot back, "I don't see why not. You look to be in pretty good health to me!"

Four brothers, below (a) 9 years old, (b) 7 years old, (c) 5 years old, and (d) 3 years old; at lower right, the brothers pictured 52 years later. Visible signs of aging can vary, even among family members, depending on a number of environmental and genetic factors.



These scientists, called gerontologists, ponder other fundamental questions. Why do we age? What happens as we age? Why do some people age faster or slower and in different ways than others? Is there a maximum human lifespan beyond which we cannot live no matter how optimal our environment or favorable our genes? And finally for all of us, the most important question: How can insights into longevity be used to fight the diseases and disabilities associated with old age to make sure this period of life is healthy, active, and independent?

Researchers at the National Institute on Aging (NIA), part of the National Institutes of Health, are seeking answers to these and other important questions. Established by the Federal Government in 1974, the NIA conducts and supports research on aging and educates the public about its findings.

Aging Under the Microscope: A Biological Quest describes what we know so far about the answers to these questions. It offers an overview of research on aging and longevity, describing the major puzzle pieces already in place and, to the extent possible, the shapes of those that are missing.

What Is Aging? What Is Senescence?

Aging is a complex natural process potentially involving every molecule, cell, and organ in the body. In its broadest sense, aging merely refers to changes that occur during the lifespan. However, this definition includes some changes that aren't necessarily problematic, and usually don't affect an individual's viability. Gray hair and wrinkles, for instance, certainly are manifestations of aging, but neither is harmful.

To differentiate these superficial changes from those that increase the risk of disease, disability, or death, gerontologists prefer to use a more precise term—senescence—to describe aging. Senescence is the progressive deterioration of many bodily functions over time. This loss of function is accompanied by decreased fertility and increased risk of mortality as an individual

gets older. The rate and progression of this process can vary greatly from person to person, but generally over time every major organ of the body is affected. As we age, for instance, lung tissue loses much of its elasticity, and the muscles of the rib cage shrink. As a result, maximum vital breathing capacity progressively diminishes in each decade of life, beginning at about age 20. With age, blood vessels accumulate fatty deposits and lose much of their flexibility, resulting in arteriosclerosis or "hardening of the arteries." In the gastrointestinal system, production of digestive enzymes diminishes, and as a result, tissues lose much of their ability to break down and absorb foods properly. In women, vaginal fluid production decreases and sexual tissues atrophy with increasing age. In men, sperm production decreases and the prostate enlarges.

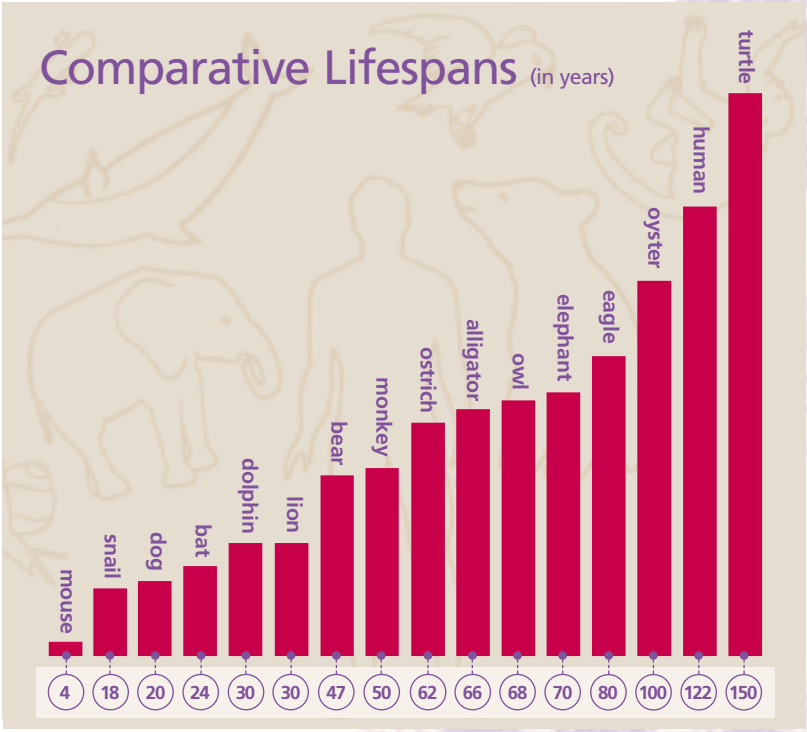
Why these and other changes occur with advancing age both intrigues and perplexes gerontologists. In fact, senescence is one of nature's least understood biological processes. Gerontologists, for instance, disagree about when senescence begins. Some argue it begins at birth. Others contend it sets in after the peak reproductive years. But clearly, senescence, whether it begins at birth or age 20, 30, or 40, leads to an accumulating loss of bodily functions, which ultimately increases the probability of death, as we get older.

What is the Difference Between Life Expectancy and Lifespan?

When George Washington celebrated his 60th birthday in 1792, he had outlived all of his male ancestors, dating back for several generations. He had outlived a typical Virginian of his era by about 15 years. To achieve this relative "old age," he had survived smallpox, mumps, pneumonia, dysentery, typhoid fever, a staphylococcal infection of the hip, four bouts of malaria, and two nearly fatal encounters with influenza.

When Jeanne Calment was born in 1875, the illnesses that plagued Washington's generation still took many lives, health care was still fairly primitive, and the life expectancy—the average number of years from birth that an individual can expect to live—was still less than 50 years worldwide.

Yet Mme. Calment, perhaps because she was born with a set of extraordinary genes or was simply fortunate enough to elude many of the illnesses that claim so many others, beat the odds and set



the benchmark for maximum human lifespan—the greatest age reached by any member of a species.

Life expectancy in the United States rose dramatically in the 20th century, from about 47 years in 1900 to about 73 years for males and 79 years for females in 1999. This increase is mostly due to improvements in environmental factors—sanitation, the discovery of antibiotics, and medical care. Now, as scientists make headway against chronic diseases like cancer and heart disease, some think life expectancy can be extended even further in the 21st century.

As part of this quest, gerontologists are studying a variety of life forms including yeast, fruit flies, nematodes, mice, and primates in search of clues applicable to human aging. As they explore the genes, cells, and organs involved in aging, they are uncovering more and more of the secrets of longevity. As a result, life extension may some day be more than the stuff of myth. In addition, as gerontologists apply their expanding knowledge to medicine, the prevention or retardation of the onset of some age-related diseases and disabilities may become realistic goals.

Why Do We Age?

Gerontologists have proposed many theories to explain the diversity of the aging process in nature. Pacific salmon, for instance, reproduce only once and die within hours of spawning, while at the other end of the spectrum, sea anemones, which reproduce asexually, show few, if any, outward signs of deterioration until the very end of their long lives. Most gerontologists now agree that no single theory can account for this wide spectrum. In fact, with the tools of biotechnology and an influx of new knowledge, all-encompassing theories of aging are giving way to a more diverse perspective.

Aging today is viewed as many processes, interactive and interdependent, that determine lifespan and health, and gerontologists are studying a multitude of factors that may be involved. The rest of this booklet describes what we know and don't know about many of these factors, and where we think scientists are likely to find answers to questions about aging and longevity.

Pacific salmon, above, live about 5 years and reproduce only once. They undergo rapid physical deterioration and die soon after breeding. In contrast, Rougheye rockfish, right, are estimated to live more than 200 years, yet show few outward signs of aging and are apparently capable of reproducing frequently, even in late life. These differences intrigue some gerontologists.

"Next to the miracle of life itself, aging and death are perhaps the greatest mysteries."

—Caleb Finch, Ph.D.
Gerontologist, University of Southern California

Theories of Aging

Theories of aging fall into two groups. The programmed theories hold that aging follows a biological timetable, perhaps a continuation of the one that regulates childhood growth and development. The damage or error theories emphasize environmental assaults to our systems that gradually cause things to go wrong. Many of the theories of aging are not mutually exclusive. Here is a brief and very simplified rundown of the major theories.

PROGRAMMED THEORIES

Programmed Longevity. Aging is the result of the sequential switching on and off of certain genes, with senescence being defined as the time when age-associated deficits are manifested.

Endocrine Theory. Biological clocks act through hormones to control the pace of aging.

Immunological Theory. A programmed decline in immune system functions leads to an increased vulnerability to infectious disease and thus aging and death.

ERROR THEORIES

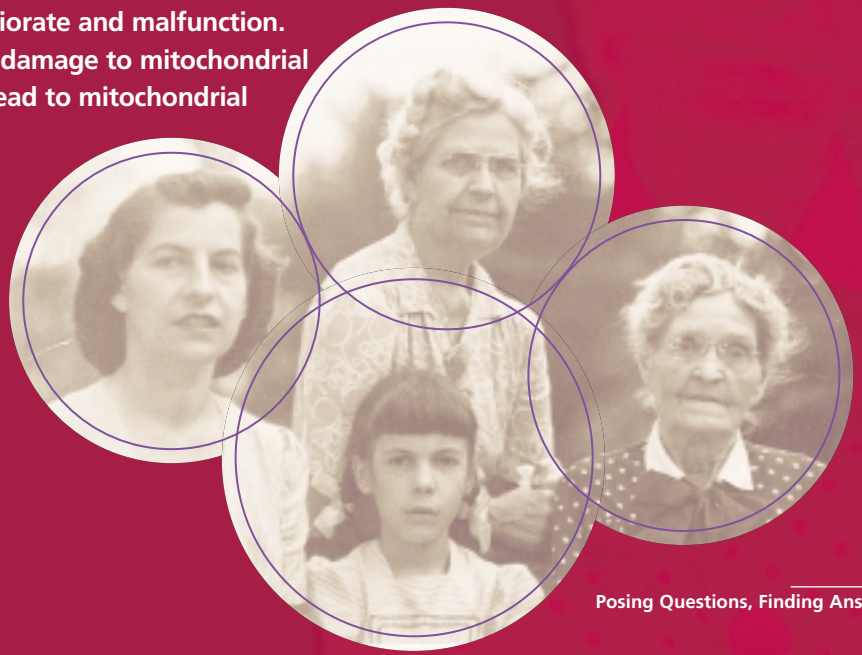
Wear and Tear. Cells and tissues have vital parts that wear out.

Rate of Living. The greater an organism's rate of oxygen basal metabolism, the shorter its life span.

Crosslinking. An accumulation of crosslinked proteins damages cells and tissues, slowing down bodily processes.

Free Radicals. Accumulated damage caused by oxygen radicals causes cells, and eventually organs, to stop functioning.

Somatic DNA Damage. Genetic mutations occur and accumulate with increasing age, causing cells to deteriorate and malfunction. In particular, damage to mitochondrial DNA might lead to mitochondrial dysfunction.



Four generations of a family. Although it is fairly easy to estimate the approximate ages of the women in this picture, gerontologists have not yet found any reliable way to measure these stark differences in human age under the microscope — either at the cellular or molecular level. Most gerontologists now believe no single theory fully explains the changes that occur in the aging body.

The Genetic Connection

Each year on her birthday, Jeanne Calment sent her lawyer a note, which read, “Excuse me if I’m still alive, but my parents didn’t raise shoddy goods.” Her brother, who died at age 97, apparently wasn’t too “shoddy” himself. When another super centenarian, Sarah Knauss of Allentown, Pennsylvania, died in 1999 at age 119, her daughter was 96.

Some families seem blessed with long lives. In fact, siblings of centenarians have a four times greater chance of living into their early nineties than most people, according to researchers at the New England Centenarian Study in Boston. A coincidence? Hardly. What likely helps set these hardy individuals apart are extraordinary sets of genes, the coded segments of DNA (deoxyribonucleic acid), which are strung like beads along the chromosomes of nearly every living cell. In humans, the nucleus of each cell holds 23 pairs of chromosomes, and together these chromosomes contain about 30,000 genes.

There is little doubt that genes have a tremendous impact on aging and longevity. Based on studies of identical twins, who share the exact same set of genes, scientists now suspect that lifespan is determined by both environmental and genetic factors, with genetics accounting for up to 35 percent of this complex interaction. Although different animal species vary up to 100 times in lifespan—humans live five times longer than cats, for instance—scientists are discovering some surprising similarities between our genes and those of other species. Even single-celled yeast, one of nature's simplest organisms, may provide scientists with important genetic clues about human aging and longevity **(See Tracking Down a Longevity Gene, page 9)**.

Longevity Genes

Researchers have found evidence of several genes that seem to be related to longevity determination. Longevity-related genes have been found in tiny roundworms called nematodes, in fruit flies, and even in mice. Like yeast, nematodes and fruit flies have attracted a lot of attention from gerontologists because their short lifespans and their well-characterized genetic composition make them relatively easy to study. Investigators, for instance, can perform nearly 2,000 roundworm studies in the time it would take them to do one human study.

Under normal conditions, some genes are thought to manufacture proteins that limit lifespan. But when these same genes are mutated, they either produce defective proteins or no proteins at all. The net effect is these mutations promote longevity.

"I don't think the trick is staying young. I think the trick is aging well."

— Thomas Perls, M.D.
Director, New England Centenarian Study

Mary Lavigne, age 102, shares a laugh in her home with Thomas Perls, M.D., founder and director of the New England Centenarian Study. Ms. Lavigne has lived in three centuries. Perls and his colleagues are studying centenarians and their siblings for signs of longevity genes and other genetic traits.

Tracking Down a Longevity Gene

Investigators are finding clues to aging and longevity in yeast, one-celled organisms that have some intriguing genetic similarities to human cells. In a laboratory at Louisiana State University Medical Center in New Orleans, Michal Jazwinski, Ph.D., has found genes that seem to promote longevity in these rapidly dividing, easy-to-study organisms.

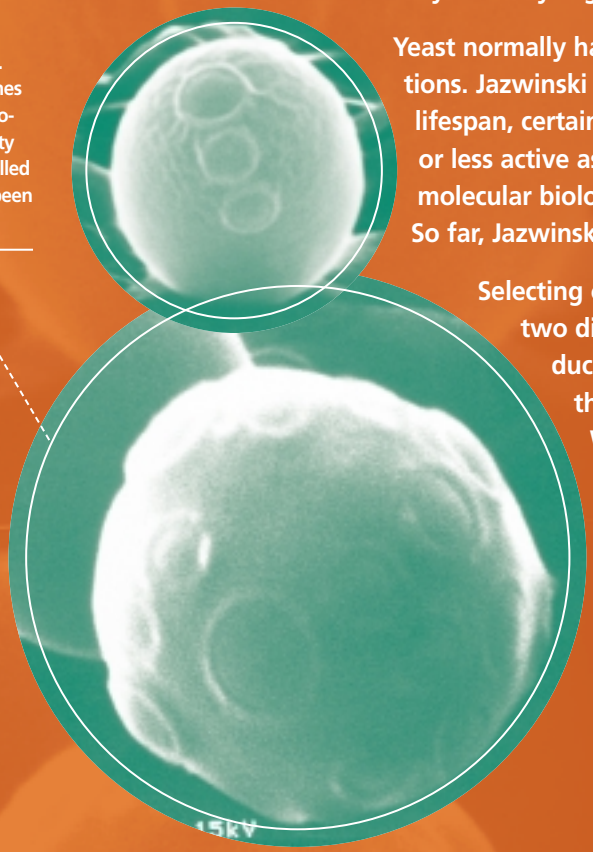
Yeast normally have about 21 cell divisions or generations. Jazwinski observed that over the course of that lifespan, certain genes in the yeast are more active or less active as the cells age; in the language of molecular biology, they are differentially expressed. So far, Jazwinski has found 14 such genes in yeast.

Selecting one of these genes, Jazwinski tried two different experiments. First, he introduced the gene into yeast cells in a form that allowed him to control its activity. When the gene was activated to a greater degree than normal, or overexpressed, some of the yeast cells went on dividing for 27 or 28 generations; their period of activity was extended by 30 percent.

In his second experiment, Jazwinski mutated the gene. When he introduced this non-working version into a group of yeast cells, they had only about 12 divisions.

The two experiments made it clear that the gene, now called LAG-1, influences the number of divisions in yeast or, according to some researchers' ways of thinking, its longevity. (LAG-1 is short for longevity assurance gene.) But how it works is still a mystery. One small clue lies in its sequence of DNA bases—its genetic code—which suggests that it produces a protein found in cell membranes. One next step is to study the function of that protein. Similar sequences have been found in human DNA, so a second investigative path is to clone the human gene and study its function. If there turns out to be a human LAG-1 counterpart, new insights into aging may be uncovered.

In another laboratory, Leonard Guarente, Ph.D., of the Massachusetts Institute of Technology found that mutation of a silencing gene—a gene that "turns off" other genes—delayed aging 30 percent in yeast. The gene, which is also found in *C. elegans* and other animals, produces an enzyme that alters the structure of DNA, which, in turn, alters patterns of gene expression.



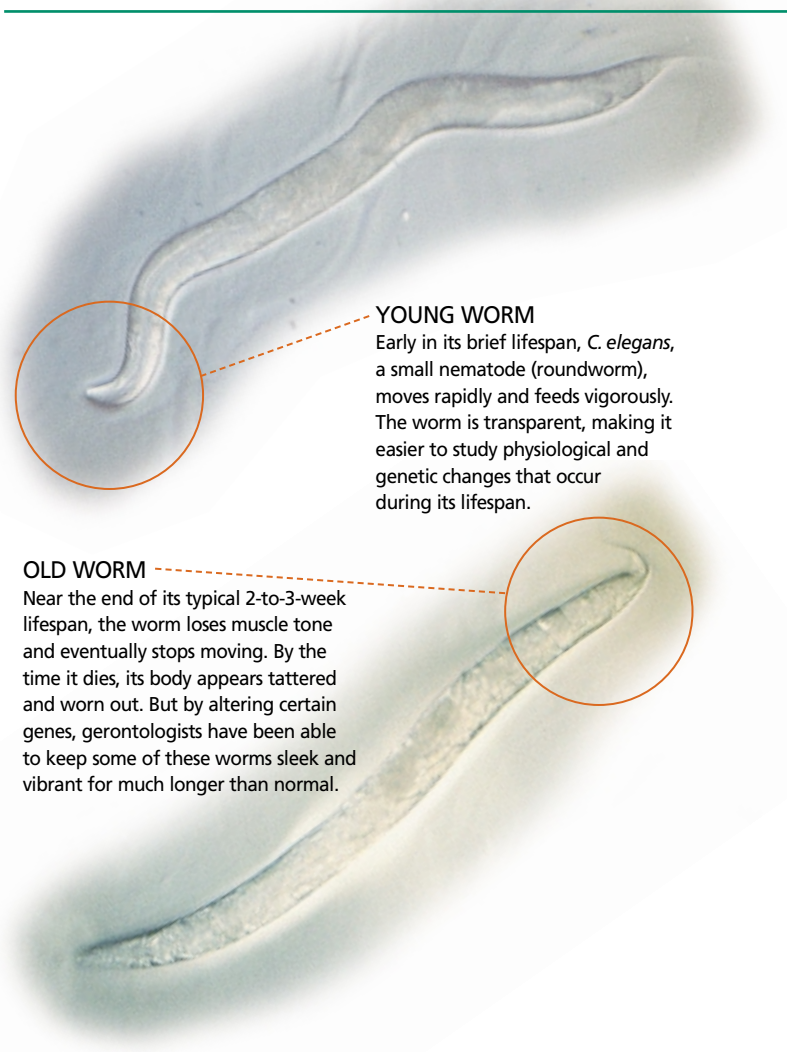
Yeast could help gerontologists understand the genetics of aging. More than 14 genes that appear to promote the longevity of these single-celled organisms have been discovered.

Worms, Genes, and Aging

For instance, a mutation of a gene whimsically named "I'm Not Dead Yet" or INDY, can double the lifespan of fruit flies. In studies supported by the NIA, these fruit flies not only lived longer, they thrived. By the time that 80 to 90 percent of normal flies were dead, many of the INDY flies were still vigorous and capable of reproduction. At least two other life-extending genetic mutations have been detected in the fruit fly genome.

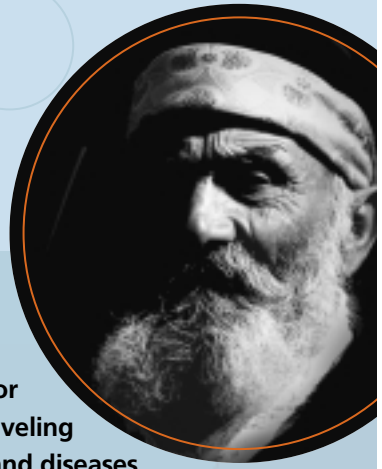
In *C. elegans*, a nematode (roundworm), researchers have found yet another treasure trove of genetic clues about the aging process. By altering certain genes, researchers can substantially extend the normal 2-to-3-week lifespan of these tiny worms. One of these genes, called *daf*-2, controls a special stage in the worm's development called dauer formation. A dauer forms, if, in the first few hours of its brief life, a worm finds food scarce. In this state, *C. elegans* grows a cuticle for protection and can go into hibernation for several months. When the food supply is ample again, the worm emerges from this metabolically slowed, non-aging state and continues its normal life cycle. The protein produced by the *daf*-2 gene drives the worm's development past or out of the dauer state. But Cynthia Kenyon, Ph.D., and her colleagues at the University of California, San Francisco, found that *daf*-2 does much more. It also can regulate the lifespan of normal, fertile adults. By altering this gene so that its activity is reduced, Kenyon's team found lifespan of well-fed worms, which did not form a dauer, could be doubled. Other investigators have detected mutations in similar *daf* genes that increase nematode lifespan three or even four-fold.

The genes isolated so far are only a few of what scientists think may be dozens, perhaps hundreds, of longevity- and aging-related genes. But tracking them down in organisms like nematodes and fruit flies is just the beginning. The next big question for many gerontologists is whether counterparts in people—human homologs—of the genes found in laboratory animals have similar effects. The *daf*-2 gene in *C. elegans*, for instance, is similar to a gene found in humans that functions in hormone control.



YOUNG WORM
Early in its brief lifespan, *C. elegans*, a small nematode (roundworm), moves rapidly and feeds vigorously. The worm is transparent, making it easier to study physiological and genetic changes that occur during its lifespan.

OLD WORM
Near the end of its typical 2-to-3-week lifespan, the worm loses muscle tone and eventually stops moving. By the time it dies, its body appears tattered and worn out. But by altering certain genes, gerontologists have been able to keep some of these worms sleek and vibrant for much longer than normal.



Age-related Traits Are All in the Family

Finding longevity genes is only one of many goals for gerontologists. An equally important mission is unraveling the genetic processes involved in age-related traits and diseases.

NIA and Italian investigators are focusing their attention on Sardinia, a secluded Mediterranean island. Since settlers first occupied the island thousands of years ago, the population has grown without much immigration from the outside world. Because they are more closely related than people living in other societies, Sardinians share much of the same genetic information, which makes it easier to track genetic effects through generations.

When a particular trait exists in a genetically isolated "founder" population such as Sardinia, it is likely that the same few genes are responsible for the trait in most or all affected individuals. Once the genes for a certain complex trait are identified within the founder population, researchers can use this information to isolate interacting genes and assess their importance in more genetically diverse cultures, like the United States. Other large founder populations exist in Finland, Iceland, and French-speaking Quebec.

In a study called the Progenia project, gerontologists are studying Sardinians for evidence of genetic influences on two traits: severe arterial stiffness and frequent positive emotions. Vascular stiffness may be an important predictor of heart disease mortality. Reports also suggest that joyfulness and other positive emotions can have profound impact on life satisfaction and health as we age. Gerontologists suspect these traits have strong genetic components. As the project progresses, investigators plan to conduct genetic analysis on individuals who share extreme values of these traits and will attempt to identify the underlying genes.

Ultimately, gerontologists hope founder population studies yield results that will help prevent certain age-related diseases.

In the worm, this gene makes a protein that looks much like the receptor for the hormone insulin. In humans, this hormone controls functions including food utilization pathways, glucose metabolism, and cell growth. These and other genetic linkages are under intense scrutiny, and ultimately could yield clues about how genes interact with environmental factors to influence longevity in humans and other species. Caloric restriction, for example, is the only known intervention shown to prolong life in species ranging from yeast to rodents. Scientists suspect this intervention works in yeast, worms, and other species, in part, because it triggers alterations of genetic activity. Caloric restriction also may work, partially, by altering metabolic pathways involved in energy utilization. **(See The Next Step: Caloric Restriction in Primates, page 36).**

Many investigators, however, interpret these findings cautiously because there are important differences between human genes and those of lower animals. In fact, the structural similarity is only about 30 percent, which means that comparing yeast genes to human genes, for instance, is like comparing a go-cart to a high-performance racing car. The basic machinery may be similar, but one is far less complex than the other. So while yeast, worms, and other simple organisms are helpful models of aging, they probably don't completely mimic the process that occurs in humans. For this reason,

Gerontologists study many different animals including zebrafish (left) and birds like budgerigars (background) for genetic clues about aging.

gerontologists study the genetics of mice, primates, and other mammals that are more closely related to us. Some researchers are also studying human cells for more precise clues about how genes regulate human longevity and aging.

Other unanswered questions concern the roles played by these genes. What exactly do they do? How and when are they activated? On one level, all genes function by transcribing their "codes"—actually DNA base sequences—into another nucleic acid called messenger ribonucleic acid or mRNA. Messenger RNA is then translated into proteins. Transcription and translation together constitute the process known as gene expression.

The proteins expressed by genes carry out a multitude of functions in each cell and tissue in the body, and some of these functions are related to aging. So, when we ask what longevity or aging-related genes do, we are actually asking what their protein products do at the cellular and tissue levels. Increasingly, gerontologists also are asking how alterations in the process of gene expression itself may affect aging. Technological advances, which allow researchers to observe the expression of thousands of genes at once, are speeding the investigation of this process. In time, this emerging technology could help clarify what changes are occurring simultaneously in diverse cells, as they get older. **(See Microarrays in Action, at right).**

Microarrays in Action

All cells have the same complement of genes. The form and function of any given cell is determined by which of these genes are turned on and off. As a cell grows, matures and ages, the pattern of genes turned on and off changes. Detecting these changes was once a tedious process that involved testing one gene at a time. No longer.

Gene expression microarray technology, a potent scientific tool, is helping gerontologists rapidly clarify what genetic changes occur in cells as they get older. Also known as "gene chips," microarrays allow researchers to survey the expression of thousands of genes at once. The match-box size glass chips contain DNA that has been exposed to messenger RNA (mRNA), a nucleic acid that translates information contained in DNA into proteins. Each kind of mRNA binds to its corresponding DNA probe, and the amount of mRNA that binds to each gene's DNA on the chip is an indicator of the activity level of that gene.

Investigators using this technology have found relatively few changes in gene expression occur in aging tissues. In some studies, comparing tissue taken from young animals versus older animals, fewer than two of every 100 genes have shown major changes in activity over time. But these limited changes may have significant impact on the ability of aging tissues and organs to function properly. In time, microarrays might help gerontologists to more precisely characterize the genes involved in the aging of specific tissues or organs, and accelerate our understanding of its underlying mechanisms.

In the Lab of the Long-Lived Fruit Flies

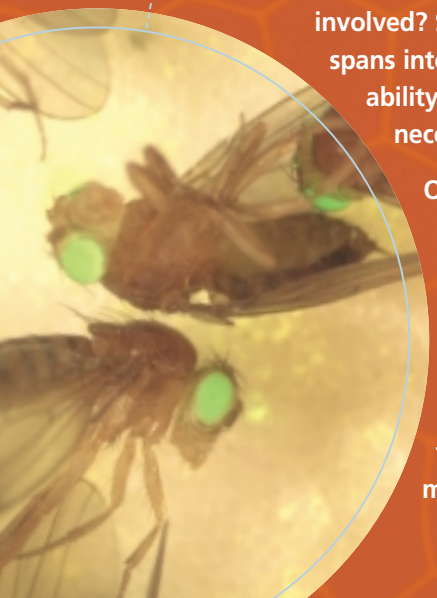
A laboratory at the University of California, Irvine, is the home of thousands of Drosophila melanogaster, or fruit flies, that routinely live for 70 or 80 days, nearly twice the average Drosophila lifespan. Here evolutionary biologist Michael Rose, Ph.D., has bred the long-lived stocks by selecting and mating flies late in life.

To begin the process of genetic selection, Rose first collected eggs laid by middle-age fruit flies and let them hatch in isolation. The progeny were then transferred to a communal plexiglass cage to eat, grow, and breed under conditions ideal for mating. Once they had reached advanced ages, the eggs laid by older females (and fertilized by older males) were again collected and removed to individual hatching vials. The cycle was repeated, but with succeeding generations, the day on which the eggs were collected was progressively postponed. After 2 years and 15 generations, the laboratory had stocks of Drosophila with longer lifespans.

The next question is what genes and what gene products are involved? Since the first experiments, Rose has bred longer life spans into fruit flies by selecting for other characteristics, such as ability to resist starvation, so the flies' long lifespans are not necessarily tied to their fertility late in life.

One possibility is that the antioxidant enzyme, superoxide dismutase (SOD), is involved. Two laboratory studies, including work by John Tower, Ph.D., at the University of Southern California, have shown that genetically altered fruit flies that produce greater amounts of SOD have extended lifespans. This finding has given a boost to the hypothesis that antioxidant enzymes like SOD are linked to aging or longevity. However, to date, similar experiments in other species have been inconclusive.

The eyes of these genetically altered fruit flies appear fluorescent under the microscope. By altering gene expression in fruit flies and other organisms, investigators are learning much about aging.



For now, investigators have found evidence that some proteins, such as antioxidant enzymes, prevent damage to cells, while others may repair damaged DNA, regulate glucose metabolism, or help cells respond to stress. Other gene products are thought to influence replicative senescence.

Cellular Senescence

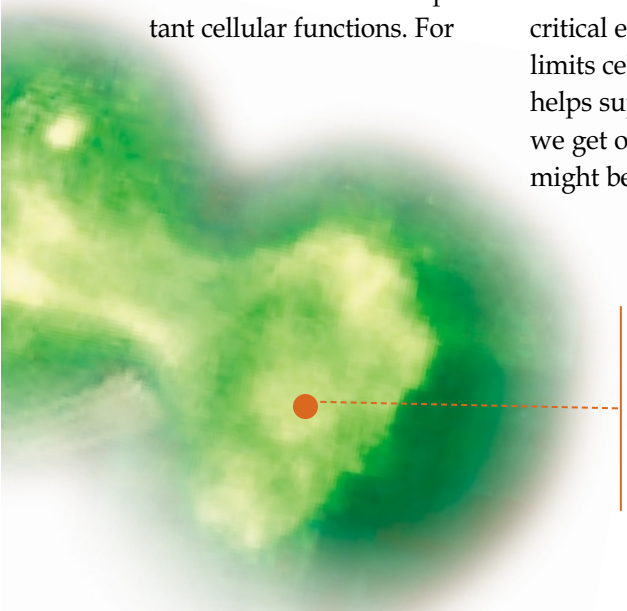
During the process of cell division or mitosis, a cell's nucleus dissolves, and its chromosomes condense into visible thread-like structures that replicate. The resulting 92 chromosomes separate, migrating to opposite sides of the cell where new nuclei—each with 46 chromosomes—are formed. Once this occurs, the original cell, following the chromosomes' lead, pulls apart and forms two identical daughter cells. It is this process that allows us to grow from a single cell into 100 trillion cells, composing the organ systems that make our bodies.

Early in life, nearly all of the body's cells can divide. But this process doesn't go on indefinitely. Researchers have learned that cells have finite proliferative lifespans, at least when studied in test tubes—*in vitro*. After a certain number of divisions, they enter a state in which they no longer proliferate and DNA synthesis is blocked. For example, young human fibroblasts—structural cells that hold skin and other tissues together—divide about 50 times and then stop. This phenomenon is known as the Hayflick limit, after Leonard Hayflick, who with Paul Moorhead described it in 1961 while at the Wistar Institute in Philadelphia. At least four genes involved in this

process have been identified. This special aspect of cellular senescence is known as replicative senescence.

However, we do not die because we run out of cells (even the oldest people have plenty of proliferating fibroblasts and other types of cells). In fact, most senescent cells are not dead or dying. They continue to respond to hormones and other outside stimuli, but can't proliferate. Evidence suggests they can continue to work at many levels for some time after they cease dividing. Senescence, however, can cause radical shifts in some important cellular functions. For instance, senescent cells are resistant to dying and, as a result, they occur more often in aging bodies. Cellular senescence also triggers important changes in gene expression. Normally, fibroblasts are responsible for creating an underlying structure, called the extracellular matrix, which controls the growth of other cells. But senescent fibroblasts secrete enzymes that actually degrade this matrix. Gerontologists suspect the breakdown of this structure may contribute to the increased risk of cancer as we age. So, cellular senescence may be critical early in life because it limits cell proliferation and helps suppress cancer. But as we get older, senescent cells might be harmful because changes in the genes they express might actually promote unregulated growth and tumor formation. This concept that genes, which have beneficial effects early in life, can also have detrimental effects later is known as antagonistic pleiotropy. Some gerontologists speculate that a better understanding of antagonistic pleiotropy might reveal much about what aging is, and how cellular senescence contributes to it.

But for now, many major questions about cellular senescence remain unanswered. Investigators, for example, are uncertain whether senescent cells accumulate in all tissues and organs with increasing age, thus contributing to the gradual loss of the body's capacity to heal wounds, maintain strong bones, and fend off infections. Accumulation of senescent cells, if it



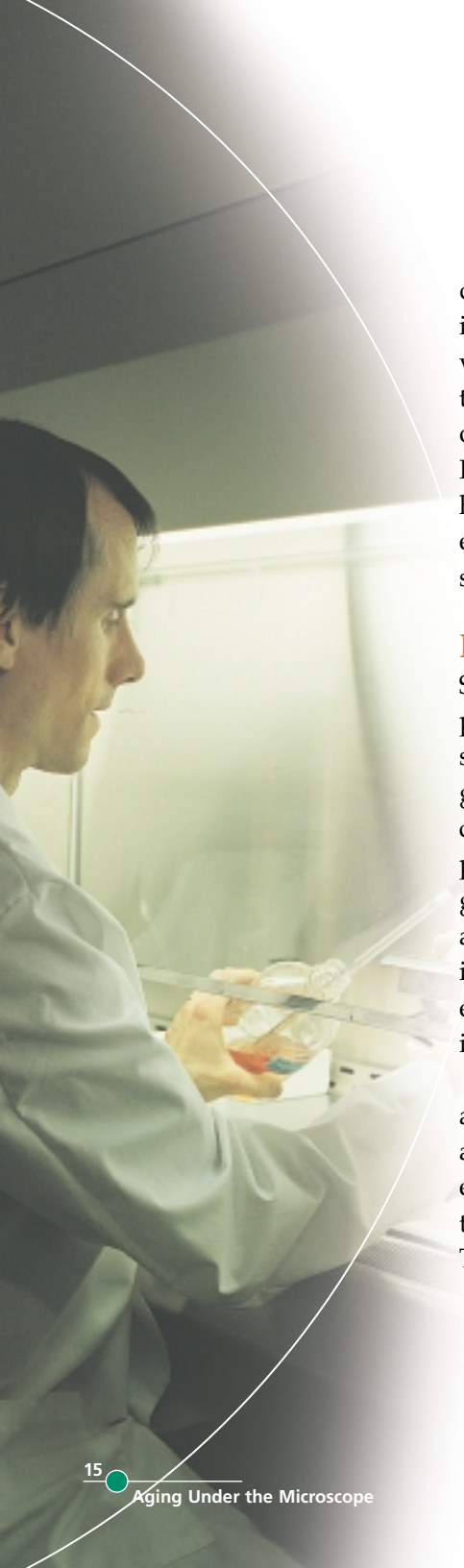
CELL DIVISION
Daughter cells divide during mitosis. Early in life, nearly all cells can divide. But over time, this capacity diminishes. Cellular senescence is one of many biological processes that gerontologists study.

Limits To Growth

For decades, researchers believed normal plant and animal cells could be propagated forever in test tubes (*in vitro*). But in 1961, Leonard Hayflick, Ph.D., (below) disproved this idea in experiments with skin and lung fibroblast cells. Hayflick is a professor of anatomy at the University of California, San Francisco.

YOUNG FIBROBLASTS
These human lung fibroblasts, shown after about the 10th *in vitro* population doubling, grow vigorously and complete the replication process more rapidly than older cells.

OLD FIBROBLASTS
Nearing senescence, these lung fibroblasts are noticeably larger and tend to divide more slowly than their younger counterparts. After about 50 *in vitro* population doublings, these cells stop dividing. This phenomenon is known as the Hayflick limit.



does occur, could, in turn, indirectly increase an individual's vulnerability to the diseases and disabilities often associated with aging. However, no feature of aging has yet been unequivocally explained by *in vitro* cellular senescence.

Proliferative Genes

Searching for explanations of proliferation and senescence, scientists have found certain genes that appear to trigger cell proliferation. One example of such a proliferative gene is *c-fos*, which encodes a short-lived protein that is thought to regulate the expression of other genes important in cell division.

Proliferative genes, such as *c-fos* and others of its kind, are countered by anti-proliferative genes, which seem to interfere with division. The first evidence of an anti-proliferative gene came from an eye tumor called retinoblastoma. When one of the genes from retinoblastoma cells—later called the RB gene—became inactive, the cells went on dividing indefinitely and produced a tumor. But when the RB gene product was activated, the cells stopped dividing. This gene's product, in other words, appeared to suppress proliferation. Another well-characterized gene of this type is the *p53* gene, which produces a protein that also limits cell proliferation. These genes are called tumor suppressor genes.

Limited proliferation is the norm in the world of human cells. In some cases, however, a cell somehow escapes this control mechanism and goes on dividing, becoming, in the terms of cell biology, immortal. And because immortal cells eventually form tumors, this is one area in which aging research and cancer research intersect. When tumor suppressor genes are inactivated, investigators theorize it turns on a complex process that leads to development of a tumor. So replicative senescence apparently has been retained through evolution as a defense against cancer.

Scientists are unraveling how the products of these genes promote and suppress cell proliferation. There are indications that a multi-layer control system is at work, involving a host of intricate mechanisms that interact to maintain a balance between the two kinds of genes. Some genes, for instance, appear to suppress or silence other genes. Mutations in these silencing genes have been shown to affect the lifespan of *C. elegans* and yeast. Many gerontologists are studying how silencing and other mechanisms such as telomere shortening influence replicative senescence.

Telomeres

Every chromosome has tails at its ends that get shorter as a cell divides. These tails, called telomeres, all have the same short sequence of DNA bases (TTAGGG in humans and other vertebrates) repeated thousands of times. These repetitive snippets do not contain any vital genetic information, but acting much like the hard, plastic covering on the ends of shoestrings, they help keep chromosomes intact.

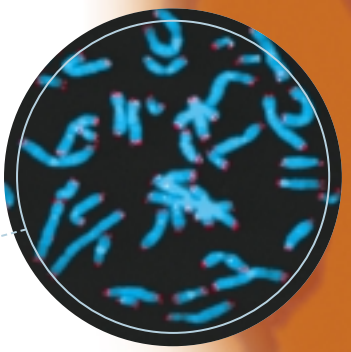
During mitosis, the molecular machinery that replicates DNA can't completely copy the extreme ends of chromosomes. So each time a cell divides, the telomeres get shorter. Over time, scientists theorize,

telomeres become so short that their function is disrupted, and this, in turn, leads the cell to stop proliferating. Average telomere length, therefore, gives some indication of how many divisions the cell has already undergone and how many remain before it can no longer replicate.

This apparent counting mechanism, almost like an abacus keeping track of the cell's age, has led to speculation that telomeres serve as molecular meters of cell division. But some scientists suspect telomere length is just one aspect of a complex mechanism. Elizabeth Blackburn, Ph.D., of the University of California, San Francisco, for instance, has accumulated evidence that some cells with extremely short, but structurally sound telomeres continue to proliferate, while others with long, but "frayed" telomeres undergo senescence. Telomere researchers also are exploring other possible ways in which these chromosome ends regulate cellular lifespan, and believe that proteins associated with telomeres play a role.

Telomere research is another territory where cancer and aging research merge. In immortal cancer cells, telomeres act abnormally—they no longer shrink with each cell division. In the search for clues to this phenomenon, researchers have discovered an enzyme called telomerase. This enzyme, which is not active in most adult cells (egg and sperm cells are among the exceptions), seems to swing into action in advanced cancers, enabling cells to replace lost telomeric sequences and divide indefinitely. This finding has led to speculation that if a drug could be developed to block telomerase activity, it might aid in cancer treatment.

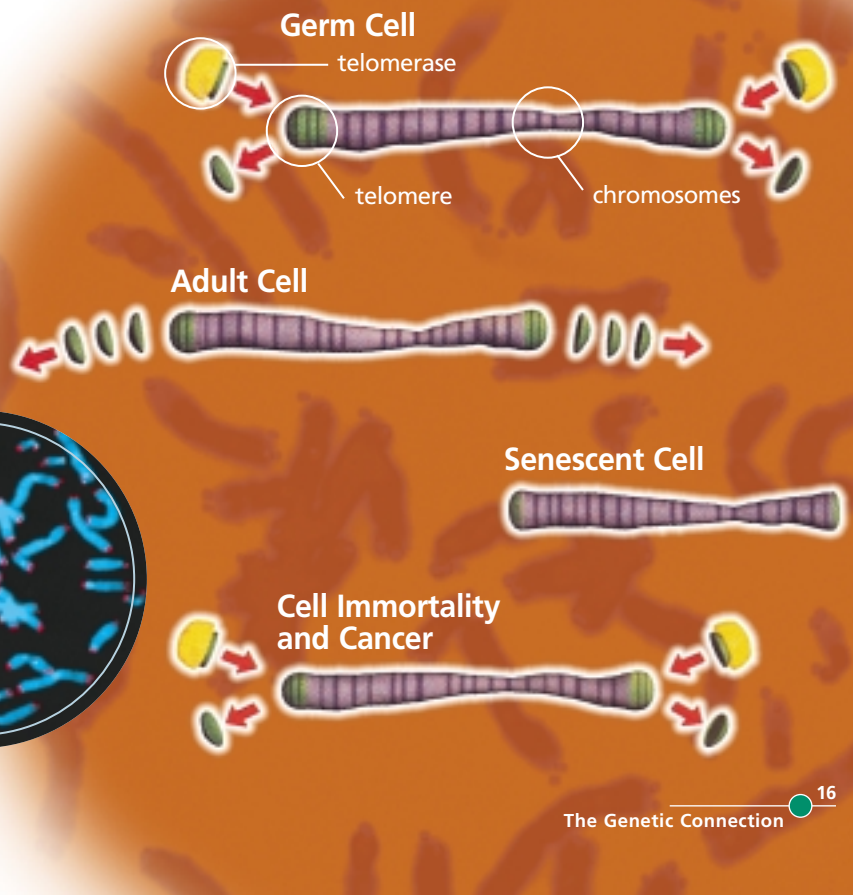
Whether cell senescence is explained by abnormal gene products, telomere shortening, or other factors, the question of what senescence has to do with the aging of organisms continues to be the focus of rigorous study.



TELOMERES
At each end of every chromosome (blue) are telomeres (red), repetitive DNA sequences that appear to help regulate cellular replication. Gerontologists are working to learn more about telomere structure and function.

TELOMERES: The Cancer Connection

Certain cells, such as egg and sperm cells, use telomerase, an enzyme, to restore telomeres to the ends of their chromosomes, insuring that they can continue to reproduce and promote survival of the species. But most adult cells lack this capacity, and when telomeres reach a critical length, these cells stop proliferating. In immortal cancer cells, telomeres act abnormally—they cease shortening with each cell division. Investigators suspect telomerase is somehow activated in cancer cells.



Biochemistry and Aging

As important as genes are, they do not act in a vacuum. Everyday metabolic activities—even breathing—expose cells to biochemical substances that can promote random DNA damage and other cellular breakdowns. Of these factors, oxygen radicals and crosslinking of proteins have become focal points of scientific exploration. Gerontologists also are studying other important proteins—heat shock proteins, hormones, and growth factors—that may play a role in aging and longevity. In short, the biochemistry of aging is a rich territory with an expanding frontier.

Oxygen Radicals

Oxygen sustains us. Every cell in the body needs it to survive. Yet, paradoxically, oxygen also wreaks havoc in the body and may be a primary catalyst for much of the damage we associate with aging. This damage occurs as a direct result of how cells metabolize it.

Oxygen is processed within a cell by tiny ogan-elles called mitochondria. Mitochondria convert oxy-gen and food into adenosine triphosphate (ATP), an energy-releasing molecule that powers most cellular processes. In essence, mito-chondria are furnaces, and like all furnaces, they pro-duce potentially harmful by-products. In cells, these by-products are called oxy-gen free radicals, also known as reactive oxygen species.

A free radical can be produced from almost any molecule when it loses an electron from one or more of its atoms. In cells, they are commonly created when mitochondria combine oxy-gen with hydrogen to form water. This transformation releases energy into the cell, but it also can shred electrons from oxygen. When this happens it leaves the oxygen atom—now an unstable oxygen free radical—with one unpaired electron. Because electrons are most stable when they are paired, oxygen free radicals steal mates for their lone electrons from other molecules. These molecules, in turn, become unstable and combine readily with other molecules.

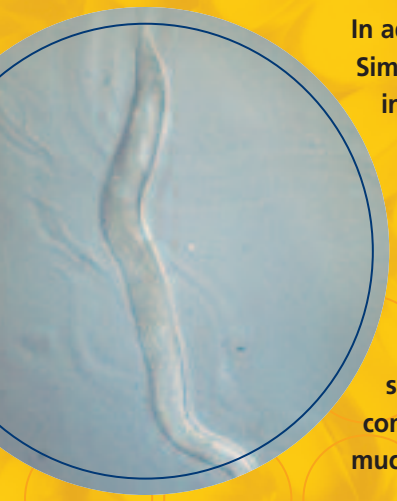
This process, called oxidation, can spark a chain reaction resulting in a series of products, some of which are actually beneficial. The immune system, for instance, uses free radicals to destroy bacteria and other patho-gens. Another oxidizing molecule, called nitric oxide, helps nerve cells in the brain communicate with each other.

Free radicals, however, also can be vandals that cause extensive damage to proteins, membranes, and DNA. Mitochondria are particularly prone to free radical damage. The major source of free radical

This mitochondrion is a cellular power-house, continuously generating ATP, an energy-releasing molecule, as well as potentially harmful by-products such as oxygen free radicals. Hundreds of mito-chondria exist in every cell. With age, increasing oxidative damage to these organelles may decrease their efficiency.

Antioxidants and Aging Nematodes

A worm barely the size of a comma printed on this page may change how investigators think about oxygen radicals, antioxidants, and aging. *C. elegans* nematodes immersed in a liquid containing a potent antioxidant drug lived 44 percent longer than worms not treated with this substance. It was the first time that any drug had extended the lifespan of any multi-cellular organism. The finding lends credence to the hypothesis that oxygen radicals have a significant role in the aging process.



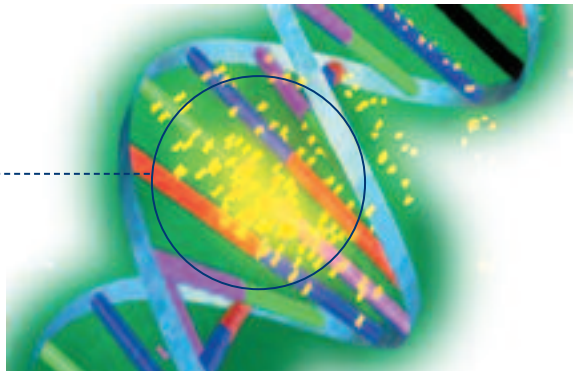
In addition, the international team of investigators, led by Simon Melov, Ph.D., of the Buck Center for Research in Aging in California, restored a normal lifespan to mutant worms that had a mitochondrial defect, which caused increased oxygen radical production and accelerated aging. The worms showed no apparent ill effects from the treatment.

EUK-134, the drug used in the experiment, was a synthetic form of superoxide dismutase (SOD) and catalase, two enzymes that counteract the effects of oxidative stress. Like other antioxidants, such as vitamin E, these compounds convert oxygen radicals to water. But they are much more potent.

While it is only one study, and its results have not been confirmed in other species, this investigation supports the concept that antioxidant defenses may be critical during aging. It also suggests that one day it may be possible to use similar interventions to treat age-related conditions in humans.

production in the body, they are also one of its prime targets. As the damage mounts, mitochondria become less efficient, progressively generating less ATP and more free radicals. Over time, according to the free radical theory, oxidative damage accumulates in our cells and tissues, triggering many of the bodily changes that occur as we age. Free radicals have been implicated not only in aging but also in degenerative disorders, including cancer, atherosclerosis, cataracts, and neurodegeneration.

But free radicals, which also can be produced by tobacco smoke, sun exposure, and other environmental factors, do not go unchecked. Cells utilize substances called antioxidants to counteract them. These substances including nutrients—the familiar vitamins C and E—as well as enzymes produced in the cell, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, prevent most oxidative damage. Nonetheless, some free radicals manage to circumvent these defenses and do harm. As a result, cellular repair mechanisms eventually falter and some internal breakdowns are inevitable. These breakdowns can lead to cellular senescence, and eventually may trigger apoptosis, a form of programmed cell death.



Oxygen free radicals, the bright yellow spots in this illustration, can attack and damage DNA, leading to mutations.

Support for the free radical theory, first proposed in 1956 by chemist Denham Harman, M.D., Ph.D., comes from studies of antioxidants, particularly SOD. SOD converts an oxygen radical known as superoxide anion into hydrogen peroxide, which can be degraded by an enzyme, called catalase, into oxygen and water. Studies have shown that inserting extra copies of the SOD gene into fruit flies extends their average lifespan by as much as 30 percent.

Other experimental evidence lends support to the free radical hypothesis. For example, higher levels of SOD and catalase have been found in long-lived nematodes. In one compelling study, giving nematodes synthetic forms of these antioxidants significantly extended their normal lifespan. **(See Antioxidants and Aging Nematodes, page 19)**.

The discovery of antioxidants raised hopes that people could retard aging simply by adding them to the diet. So far, studies of antioxidant-laden foods and supplements in humans have yielded little support for this premise. Further research, including large-scale epidemiological studies, might clarify whether dietary antioxidants can help people live longer, healthier lives. For now, however, the effectiveness of dietary antioxidant supplementation remains controversial. In the meantime, gerontologists are investigating other intriguing biochemical processes affected by free radicals, including protein crosslinking.

Protein Crosslinking

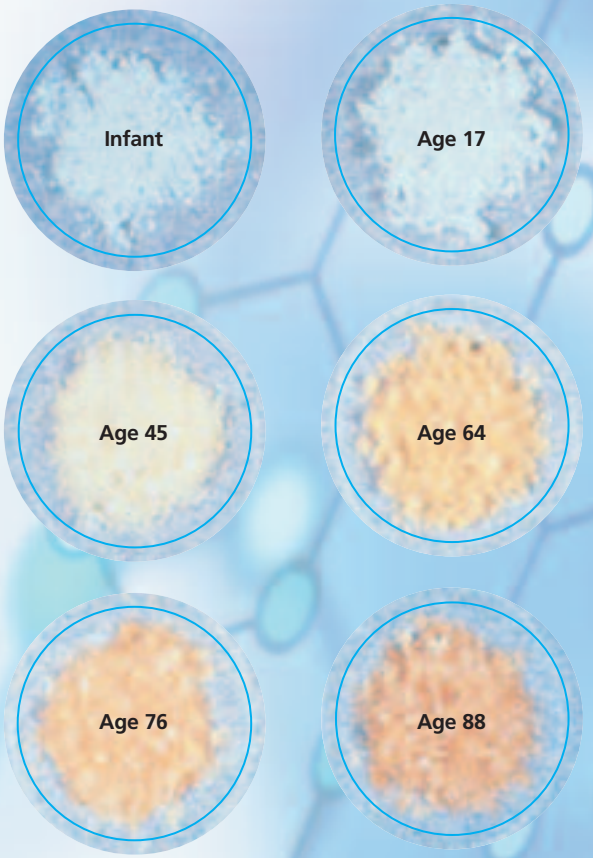
Blood sugar—glucose—is another suspect in cellular deterioration. In a process called non-enzymatic glycosylation or glycation, glucose molecules attach themselves to proteins, setting in motion a chain of chemical reactions that ends in the proteins binding together or crosslinking, thus altering their biological and structural roles. The process is slow and complex, but crosslinked proteins accumulate with time and eventually disrupt cellular function.

Investigators suspect that glycation and oxidation are interdependent processes since free radicals and crosslinks seem to accelerate the formation of one another.

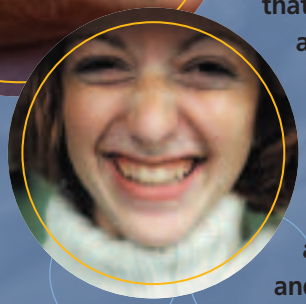
SOD

Protein Crosslinking

Human rib cartilage shows the effects of protein crosslinks, which slowly accumulate through complex pathways and eventually disrupt cellular function. With age, as glucose binds to its proteins, the cartilage turns brown and becomes less supple. This process, called the Maillard reaction, is similar to what happens when bread is toasted.



Research on Sunlight May Help Explain What Happens to Skin as We Age



As anyone who reads beauty magazines knows, sunlight damages skin in ways that seem similar to aging. It's well-established that long-term, sunlight-induced damage causes wrinkles. And in both normal aging and photoaging—the process initiated by sunlight—the skin becomes drier and loses elasticity. Although gerontologists think that the normal or intrinsic aging process is probably not the same as photoaging, there are enough similarities to make this a tantalizing field of study.

The process of photoaging may hold clues to normal aging because many of the same cells are affected. Photoaging, for example, damages collagen and elastin, the two proteins that give skin its elasticity. These proteins decline as we age, along with the fibroblast cells that manufacture them. In addition, the enzymes that break down collagen and elastin increase.

Other changes occur in keratinocytes, upper-layer skin cells that are shed and renewed regularly. In the normal aging process the turnover of keratinocytes slows down and in photoaging they are damaged. Still other skin cells, called melanocytes, are also affected by both processes: they decline with normal aging and are killed in photoaging. (Stopped in their tracks by sunlight, these normally migratory cells show up as freckles in light skin.)

What we don't know yet is exactly how photoaging damages cells. Ultraviolet light can damage DNA and could be the culprit. Free radicals could be involved in some way. Researchers continue to explore these and other factors in the effort to understand photoaging.

Crosslinks, also known as advanced glycation end products (AGEs), seem to "stiffen" tissues and may cause some of the deterioration associated with aging. Collagen, for instance, the most common protein molecule in our bodies, forms the connective tissue that provides structure and support for organs and joints. When glucose binds with collagen—as it tends to do as we age—this normally supple protein loses much of its flexibility. As a result, lungs, arteries, tendons, and other tissues stiffen and become less efficient. In the circulatory system, AGEs may help trap LDL (the so-called "bad") cholesterol in artery walls, and thus contribute to the development of atherosclerosis. They also have been linked to clouded lenses (cataracts), reduced kidney function (nephropathy), and age-related neurological disorders including Alzheimer's disease.

These conditions appear at younger ages in people with diabetes, who have high glucose levels (hyperglycemia). Glycosylated hemoglobin in red blood cells, for instance, is an important marker doctors use to measure hyperglycemia. While the physiological effects of glycosylated hemoglobin are unclear, the disease it helps doctors detect—diabetes—is sometimes considered an accelerated model of aging. Not only do the complications of diabetes mimic the physiologic changes that can accompany old age, but people with this condition have shorter-than-average life expectancies. As a result, much research on cross-linking has focused on its relationship to diabetes as well as aging.

an AGEs

tioxidants

Just as the body has antioxidants to fight free-radical damage, it has other guardians, immune cells called macrophages, which combat glycation. Macrophages with special receptors for AGEs seek out and engulf them. Once AGEs are broken down, they are ejected into the blood stream where they are filtered out by the kidneys and eliminated in urine.

The only apparent drawback to this defense system is that it is not complete and levels of AGEs increase steadily with age. One reason is that kidney function tends to decline with advancing age. Another is that macrophages, like certain other components of the immune system, become less active. Why this happens is not known, but immunologists are beginning to learn more about how the immune system affects, and is affected by aging (**See The Immune System, page 31**). And in the meantime, diabetes researchers are investigating drugs that could supplement the body's natural defenses by blocking AGEs formation.

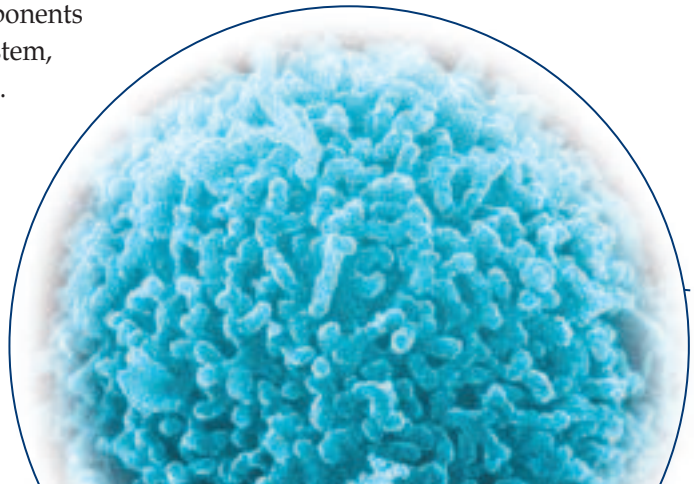
Crosslinking interests gerontologists for several reasons. It is associated with disorders that are common among older people, such as diabetes and heart disease; it progresses with age; and AGEs are potential targets for drugs. In addition, crosslinking may play a role in damage to DNA, which is another important focus for research on aging.

DNA Repair and Synthesis

In the normal wear and tear of cellular life, DNA undergoes continual damage. Attacked by oxygen radicals, ultraviolet light, and other toxic agents, it suffers damage in the form of deletions, or deleted sections, and mutations, or changes in the sequence of DNA bases that make up the genetic code. In addition, sometimes the DNA replication machinery makes an error.

Biologists theorize that this DNA damage, which gradually accumulates, leads to malfunctioning genes, proteins, cells, and, as the years go by, deteriorating tissues and organs.

Not surprisingly, numerous enzyme systems in the cell have evolved to detect and repair damaged DNA. For repair, transcription, and replication to occur, the double-helical structure that makes up DNA must be partially unwound. Enzymes called helicases do the unwinding. Investigators have found that people who have Werner's syndrome (WS), a rare disease with several features of premature aging, have a defect in one of their helicases. George Martin, M.D., of the University of Washington and other investigators are exploring the mechanisms involved in DNA repair in WS and



Macrophages, such as the one shown here, recognize foreign bodies such as bacteria, or altered molecules such as crosslinked proteins, and remove them from circulation.

Werner's Syndrome

WS patient age 14

WS patient age 48

Genetic defects are believed to be responsible for Werner's syndrome (WS), a disease in which people at a young chronological age develop some characteristics associated with aging, such as gray hair, wrinkled skin, diabetes, heart disease, and cancer. Because of the apparent acceleration of aging in WS, gerontologists are delving into its causes, hoping to shed light on the disease and the degenerative processes that occur with normal aging.

"The remarkable increase in our life span during the 20th Century has been due, in large part to the contributions of basic biomedical research…In the 21st Century, the advances in these basic sciences should lead to effective treatments of diseases of our aging population."

–Julius Axelrod, Ph.D.
1970 Nobel Laureate in Medicine

similar disorders, collectively known as progeroid syndromes. This research could help explain why DNA repair becomes less efficient during normal human aging.

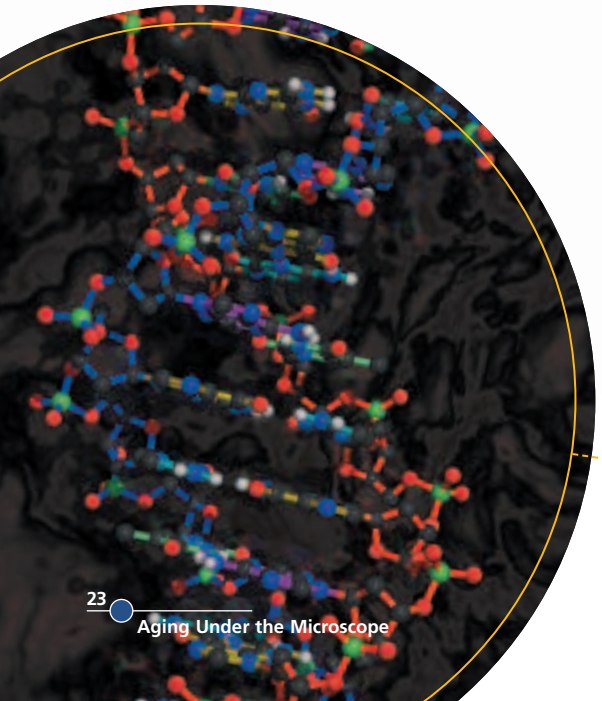
The repair process interests gerontologists for many reasons. It is known that an animal's ability to repair certain types of DNA damage is directly related to the lifespan of its species. Humans repair DNA, for example, more quickly and efficiently than mice or other animals with shorter lifespans. This suggests that DNA damage and repair are in some way part of the aging puzzle.

In addition, researchers have found defects in DNA repair in people with a genetic or familial susceptibility to cancer. If DNA repair processes decline with age while damage accumulates as scientists hypothesize, it could help explain why cancer is more common among older people.

Gerontologists who study DNA damage and repair have begun to uncover numerous complexities. Even within a single organism, repair rates can vary among cells, with the most efficient repair going on in germ (sperm and egg) cells. Moreover, certain genes are repaired more quickly than others, including those that regulate cell proliferation.

Especially intriguing is repair to a kind of DNA that resides not in the cell's nucleus but in its mitochondria. These small organelles are the principal sites of metabolism and energy production, and cells have hundreds of them. Investigators suspect mitochondrial DNA is injured at a much greater rate than nuclear DNA, possibly because the mitochondria produce a stream of damaging oxygen radicals during metabolism. Adding to its vulnerability, mitochondrial DNA is unprotected by the protein coat that helps shield DNA in the nucleus from damage.

Research has shown that mitochondrial DNA damage increases exponentially with age, and as a result, energy production in cells diminishes over time. These changes may cause declines in physiological performance, and may play a role in the development



DNA, the double helix cellular molecule that contains thousands of genes necessary for life, is constantly being damaged and repaired. Gerontologists suspect DNA repair mechanisms become less efficient with age. Accumulating DNA damage, including breaks in its structure or changes in its nucleotide sequences, can lead to some of the physical changes we associate with aging.

of age-related diseases. Investigators are examining how much mitochondrial DNA damage occurs in specific parts of the body such as the brain, what causes the damage, and whether it can be prevented.

Heat Shock Proteins

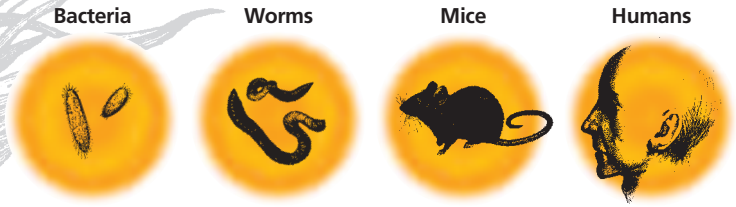
In the early 1960s, investigators noticed fruit flies did something unusual. When these insects were exposed to a burst of heat, they produced proteins that helped their cells survive the temperature change. Intrigued, researchers looked for these proteins in other animals, and found them in virtually every living thing including plants, bacteria, worms, mice, and yes, humans. Today, the role of these substances, known as heat shock proteins, in the aging process is under scrutiny.

Despite their name, heat shock proteins (HSPs) are produced when cells are exposed to various stresses, not only heat. Their expression can be triggered by exposure to toxic substances such as heavy metals and chemicals and even by behavioral and psychological stress.

What attracts aging researchers to HSPs is the finding that the levels at which they are produced depend on age. Old animals placed under stress—short-term, physical restraint, for example—have lower levels of a heat shock protein designated HSP-70 than young animals under similar stress. Moreover, in laboratory cultures of cells, researchers have found a striking decline in HSP-70 production as cells approach senescence.

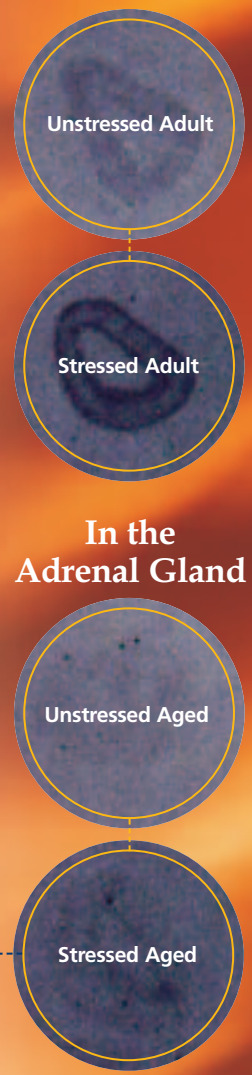
Exactly what role HSPs play in the aging process is not yet clear. They are known to help cells dismantle and dispose of damaged proteins. They also facilitate the making and transport of new proteins. But what proteins are involved and how they relate to aging is still the subject of speculation and study.

While at the NIA, Nikki Holbrook, Ph.D., and other researchers investigated the action of HSP-70 in specific sites, such as the adrenal cortex (the outer layer of the adrenal gland). In this gland as well as in blood vessels and possibly other sites, the expression of HSP-70 appears closely related to hormones released in response to stress, such as the glucocorticoids and catecholamines. Eventually, answers to the puzzle of HSPs may throw light on some parts of the neuroendocrine system, whose hormones and growth factors might have an important influence on the aging process.

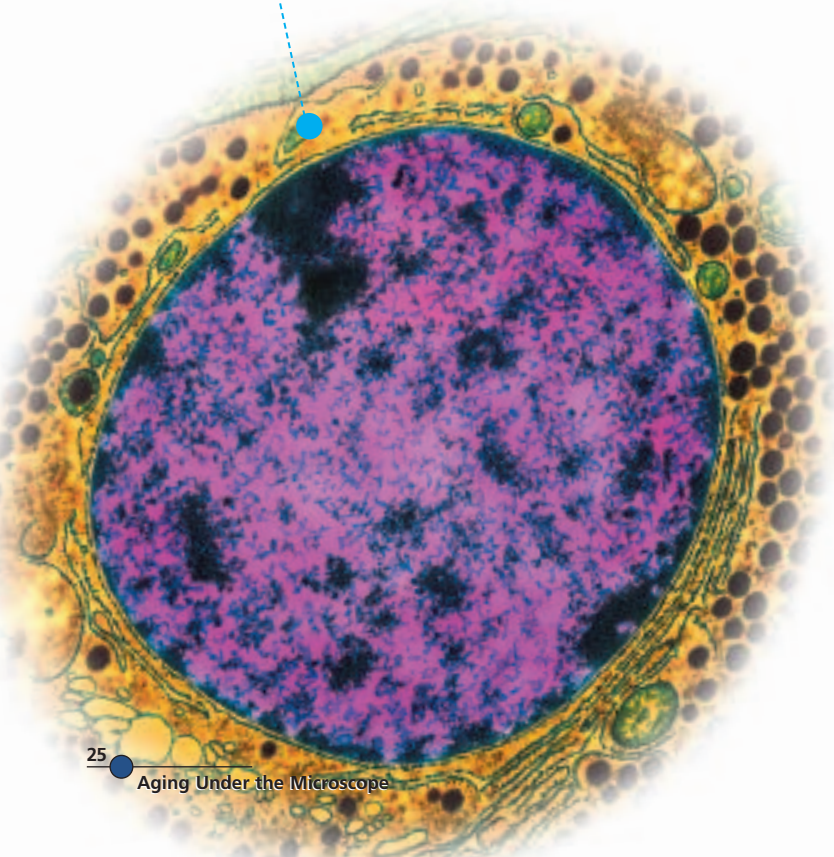


Since they were first discovered in fruit flies, heat shock proteins have been found in virtually every living thing.

Heat Shock Proteins



In certain circumstances, plants and animals produce heat shock proteins (HSPs). These proteins are believed to have an important role in helping cells respond to stress. The dark areas in these illustrations show increased expression of HSPs in short term, physically restrained rats. With age, genetic expression of these proteins diminishes.



In this colored transmission electron micrograph, growth hormone granules (brown) are visible in the cytoplasm (yellow) of a growth-hormone secreting endocrine cell from the pituitary gland. Visible cell organelles include mitochondria (round, green) and the nucleus (purple, center).

Hormones

Hormones are powerful chemicals that help keep our bodies working normally. Made by specialized groups of cells called glands, hormones stimulate, regulate, and control the function of various tissues and organs. They are involved in virtually every biological process including sexual reproduction, growth, metabolism, and immune function. These glands, including the pituitary, thyroid, adrenal, ovaries, and testes, release various hormones into the body as needed.

As we age, production of certain hormones, such as testosterone and estrogen, tends to decrease. Hormones with less familiar names, like melatonin and dehydroepiandrosterone (DHEA) are also not as abundant in older people as in younger adults. But what influence, if any, these natural hormonal declines have on the aging process is unclear.

Hormone Replacement

In the late 1980s, at Veterans Administration hospitals in Milwaukee and Chicago, 12 men age 60 and older began receiving injections three times a week that dramatically reversed some signs of aging. The injections increased their lean body (and presumably muscle) mass, reduced excess fat, and thickened skin. When the injections stopped, these changes reversed, and the signs of aging returned. What the men were taking was recombinant human growth hormone (hGH), a synthetic version of the hormone that is produced in the pituitary gland and plays a critical part in normal childhood growth and development. At the same time, evidence was accumulating that menopausal hormone therapy with estrogen (alone or in combination with a progestin in women with a uterus) could benefit postmenopausal women by reducing cardiovascular disease, colon cancer, and other diseases of aging. Further studies have indicated that, although estrogen remains an effective way to control hot flashes, long-term use of these hormones may increase risk for several major age-related diseases in some women, especially when treatment is started years after menopause. The finding that levels of testosterone in men decreased with aging raised the question of whether they too might benefit from sex hormone treatment.

As a result of these preliminary observational findings, the NIA launched a series of research initiatives to clarify what influence hormone replacement therapy might have on the aging process. So far, most of these studies have been inconclusive, but have led many investigators to question whether the risks of hormone replacement may outweigh

Hormones and Research on Aging

Produced by glands, organs, and tissues, hormones are the body's chemical messengers, flowing through the blood stream and searching out cells fitted with special receptors. Each receptor, like a lock, can be opened by the specific hormone that fits it and also, to a lesser extent, by closely related hormones. Here are some of the hormones and other growth factors of special interest to gerontologists.

ESTROGEN > Although it is primarily associated with women, men also produce small amounts of this sex hormone. Among its many roles, estrogen slows the bone thinning that accompanies aging. In premenopausal women the ovaries are the main manufacturers of estrogen (**image above**). After menopause, fat tissue is the major source of smaller amounts and weaker forms of estrogen than that produced by the ovaries. While many women with menopausal symptoms are helped by hormone therapy during and after menopause, some are placed at higher risk for certain diseases if they take it. The results of the WHI are prompting further studies about the usefulness and safety of this therapy when used by younger menopausal and postmenopausal women to control symptoms, such as hot flashes, and to prevent chronic diseases.

GROWTH HORMONE > This product of the pituitary gland appears to play a role in body composition and muscle and bone strength. It is released through the action of another trophic factor called growth hormone releasing hormone, which is produced in the brain. It works, in part, by stimulating the production of insulin-like growth factor, which comes mainly from the liver. All three hormones are being studied for their potential to strengthen muscle and bones and prevent frailty among older people. For now, however, there is no convincing evidence that taking growth hormone will improve the health of those who do not suffer a profound deficiency of this hormone.

MELATONIN > Contrary to some claims, secretion of this hormone, made by the pineal gland, does not necessarily diminish with age. Instead, a number of factors, including light, can affect production of this hormone, which seems to regulate various seasonal changes in the body. Current research does indicate that melatonin in low dosages may help some older individuals with their sleep. However, it is recommended that a physician knowledgeable in sleep medicine be consulted before self-medication. Claims that melatonin can slow or reverse aging are far from proven.

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Hormones and Research

TESTOSTERONE > **In men, testosterone (image below) is produced in the testes (women also produce small amounts of this hormone). Production peaks in early adulthood. However, the range of normal testosterone production is vast. So while there are some declines in testosterone production with age, most older men stay well within normal limits. The NIA is investigating the role of testosterone supplementation in delaying or preventing frailty. Preliminary results have been inconclusive, and it remains unclear if supplementation of this hormone can sharpen memory or help men maintain stout muscles, sturdy bones, and robust sexual activity. Investigators are also looking at its side effects, which may include an increased risk of certain cancers, particularly prostate cancer. A small percentage of men with profound deficiencies may be helped by prescription testosterone supplements.**

DHEA > **Short for dehydroepiandrosterone, DHEA is produced in the adrenal glands. It is a precursor to some other hormones, including testosterone and estrogen. Production peaks in the mid-20s, and gradually declines with age. What this drop means or how it affects the aging process, if at all, is unclear. Investigators are working to find more definite answers about DHEA's effects on aging, muscles, and the immune system. DHEA supplements, even when taken briefly, may cause liver damage and have other detrimental effects on the body.**

any benefit. Supplements of hGH, for instance, can promote diabetes, joint pain, carpal tunnel syndrome, and pooling of fluid in the skin and other tissues, which may lead to high blood pressure and heart failure. Studies in mice have raised other concerns about the hormone. Investigators have found that mice deficient in growth hormone production live substantially longer than normal mice, while mice overproducing growth hormone live shorter than average lives. This finding suggests that even if hGH replacement therapy is initially beneficial, ultimately it may be harmful and actually might curtail longevity.

Similarly, there is scant evidence that testosterone supplementation has any positive impact in healthy older men. In fact, some studies suggest supplementation might trigger excessive red blood cell production in some men. This can increase a man's risk of stroke.

Estrogen is perhaps the most well studied of all hormones. Yet results from the Women's Health Initiative (WHI), the first major placebo-controlled, randomized clinical trial of estrogen therapy with or without progestin to prevent some chronic diseases of aging, surprised the medical community. There were more cases of stroke, blood clots, heart disease, and breast cancer in postmenopausal women using estrogen and progestin in the study, and more cases of possible dementia in women over age 65, than in those using the placebo. But, there were also fewer bone fractures and cases of colon cancer. In postmenopausal women using estrogen alone, there were more cases of stroke

and fewer bone fractures than in those women on placebo. Other studies indicate that menopausal hormone therapy is effective in controlling moderate-to-severe menopausal symptoms, so research is ongoing to evaluate benefits and risks in menopausal and younger postmenopausal women.

As research continues, the pros and cons of hormone replacement may become more precisely defined. These hormonal supplements appear to increase risk and provide few clear-cut benefits for healthy individuals and do not seem to slow the aging process.

Growth Factors

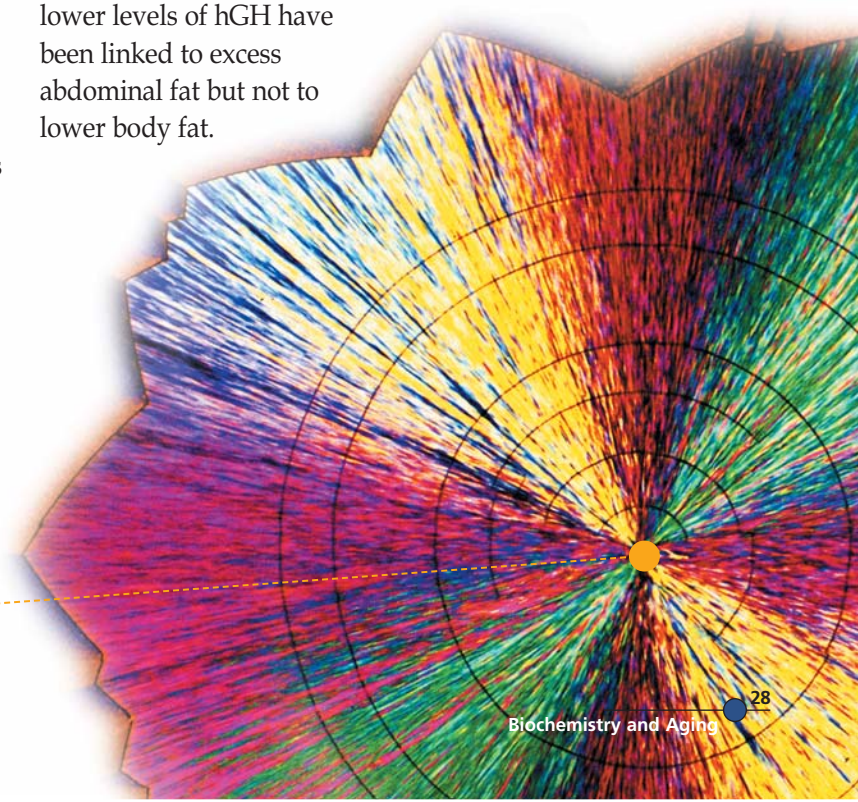
Some types of hormones can be referred to as growth or trophic factors. These factors include substances such as insulin-like growth factor (IGF-I), which mediates many of the actions of hGH. Another trophic factor of interest to gerontologists is growth hormone releasing hormone, which stimulates the release of hGH. Growth factors might have an important role in longevity determination. In nematodes, for instance, mutations in at least two genes in the IGF-I pathway result in extended lifespan.

The mechanisms—how hormones and growth factors produce their effects—are still a matter of intense speculation and study. Scientists know that these chemical messengers selectively stimulate cell activities, which in turn affect critical events, such as the size and functioning of skeletal muscle. However, the pathway from hormone to muscle is complex and still unclear.

Consider growth hormone. It begins by stimulating production of IGF-I. Produced primarily in the liver, IGF-I enters and flows through the blood stream, seeking out special IGF-I receptors on the surface of various cells, including muscle cells. Through these receptors it signals the muscle cells to increase in size and number, perhaps by stimulating their genes to produce more of special, muscle-specific proteins. Also involved at some point in this process are one or more of the six known proteins that specifically bind with IGF-I; their regulatory roles are still a mystery.

As if the cellular complexities weren't enough, the action of growth hormone also may be intertwined with a cluster of other factors—exercise, for example, which stimulates a certain amount of hGH secretion on its own, and obesity, which depresses production of hGH. Even the way fat is distributed in the body may make a difference; lower levels of hGH have been linked to excess abdominal fat but not to lower body fat.

> "Friends…drinking lots of good water, no alcohol, staying positive, and lots of singing will keep you alive for a long time."
>
> *—Chris Mortensen (1882-1998), America's oldest man, on his 115th birthday.*



Like many hormones, blood levels of progesterone, a reproductive hormone, (right) diminish with age. But what influence, if any, the natural decline in progesterone and other hormones has on the aging process in middle and late life is unclear.

Physiologic Clues

We don't know very much about the few men and women who have lived to 115 years of age or more, but we can assume that they eluded the diseases that kill many people in their 70s and 80s. At 122, Jeanne Calment, for instance, had lived a relatively disease-free life. In fact, escape from infectious disease is the most common reason that all of us can now expect to live longer than our grandparents.

Chronic diseases and disability were once thought inseparable from old age. This view is changing rapidly as one disease after another joins the ranks of those that can be prevented or at least controlled, often through changes in lifestyle.

We now know, for example, that most people can avoid lung disease by not smoking. And heart disease and stroke rates have fallen at the same time that Americans have lowered their fat consumption, begun to exercise more, and quit smoking.

So if chronic disease is not intrinsic to the aging process, as many gerontologists now believe, then what is? Are there universal or "normal" aging processes?

Normal Aging

Unlike most of us, Satchel Paige was never quite sure of his birth year. "My birth certificate was in our (family) Bible, and the goat ate the Bible," he said. But even had he known his chronological age, it may not have shed much light on how old he was physiologically. In fact, gerontologists are discovering that age in years doesn't necessarily correlate with physiological age.

For decades, investigators at the NIA have compiled data on heart function, lung capacity, and numerous other bodily functions in hopes that this information may one day be used to establish definitive measures of physiological aging. In theory, these biomarkers would be more precise indicators of aging than chronological age itself. Once established, these biomarkers could make it easier to study normal aging, diseases, and possible interventions. So far, however, no such biomarkers have been identified in humans.

"How old would you be if you didn't know how old you were?"

– Leroy "Satchel" Paige
Member, Baseball Hall of Fame. The oldest person to pitch in the major leagues – he was in his late 50s.

In the Baltimore Longitudinal Study of Aging (BLSA), volunteers, age 20 to 90, are screened every 2 years for physiological and psychological changes. They undergo a complete physical exam and a series of tests including muscle strength (shown), bone density, aerobic capacity, and glucose tolerance. Each assessment adds detail and focus to the BLSA's slowly growing picture of how we age.

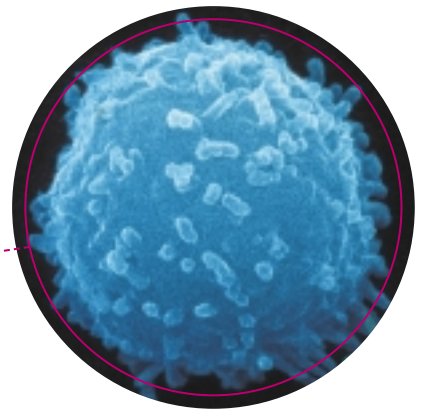
In fact, normal physiological aging is quite variable, according to investigators involved in the Baltimore Longitudinal Study of Aging, a long-term NIA study begun in 1958 that has tracked the lives of more than 1,000 people from age 20 to 90 and beyond. Not only do individuals age overall at vastly different rates, it is quite likely that age-related changes in various cells, tissues, and organs differ as well. For instance, kidney function may decline more rapidly in some individuals. In others, bone strength may diminish faster. The organs that age fastest in one person may not age as rapidly in another. This suggests that genes, lifestyle, and disease can all affect the rate of aging and that several distinct processes are involved.

Although this diversity lessens the likelihood of finding biomarkers of aging in humans, the quest for these indicators has yielded many insights into the physiology of two organ systems that may have important roles in the aging process. One of these is the endocrine system (**See Hormones and Research on Aging, page 26**). The other is the immune system.

The Immune System

When Shigechiyo Izumi of Japan contracted pneumonia and died in 1986 at the reputed age of 120, it was his immune system that failed. One of the many bacteria or viruses that cause pneumonia broke through the elaborate, natural defenses that protect humans from infection. Scientists have long known that these defenses decline with age; now, some of the underlying mechanisms are coming to light.

A multiplicity of cells, substances, and organs make up the immune system. The thymus, spleen, tonsils, bone marrow, and lymphatic system, for example, produce, store, and transport a host of cells and substances—B-lymphocytes and T-lymphocytes, antibodies, interleukins, and interferon, to name a few. Several are of special interest to gerontologists. These include the class of white blood cells called lymphocytes, which fight invading bacteria and other foreign cells.



The organs of the immune system are located throughout the body. White blood cells—lymphocytes—are key operatives of this system. With age, these cells become less active, making the body more vulnerable to bacteria, viruses and other pathogens.

What is Normal Aging?

Individuals age at extremely different rates. In fact even within one person, organs and organ systems show different rates of decline. However, some generalities can be made, based on data from the Baltimore Longitudinal Study of Aging.

HEART > Heart muscle thickens with age. Maximal oxygen consumption during exercise declines in men by about 10 percent with each decade of adult life and in women by about 7.5 percent. This decline occurs because the heart's maximum pumping rate and the body's ability to extract oxygen from blood both diminish with age.

ARTERIES > Arteries tend to stiffen with age. The older heart, in turn, needs to supply more force to propel the blood forward through the less elastic arteries.

LUNGS > Maximum breathing (vital) capacity may decline by about 40 percent between the ages of 20 and 70.

BRAIN > With age, the brain loses some of the structures (axons) that connect nerve cells (neurons) to each other, although the actual number of neurons seems to be less affected. The ability of individual neurons to function may diminish with age. Recent studies indicate that the adult nervous system is capable of producing new neurons, but the exact conditions that are critical for this have yet to be determined.

KIDNEYS > Kidneys gradually become less efficient at extracting wastes from the blood.

BLADDER > Bladder capacity declines. Urinary incontinence, which may occur after tissues atrophy, particularly in women, can often be managed through exercise and behavioral techniques.

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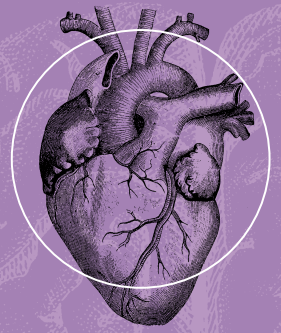
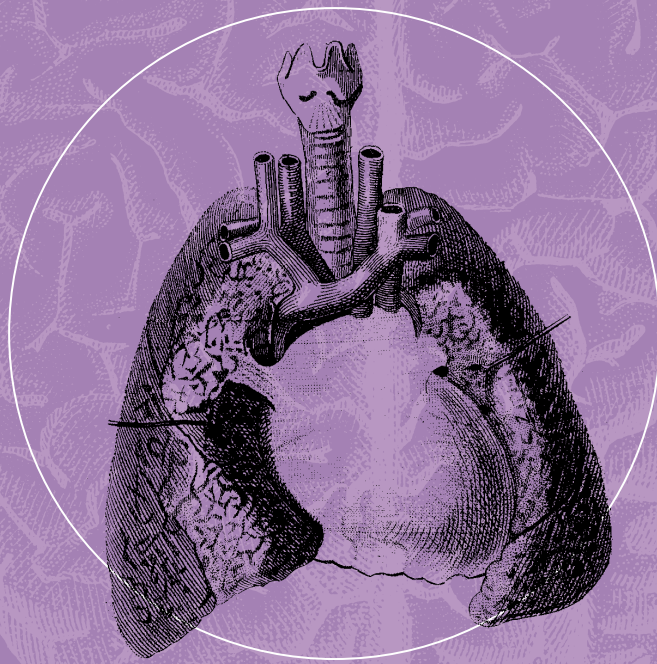
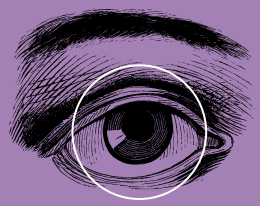
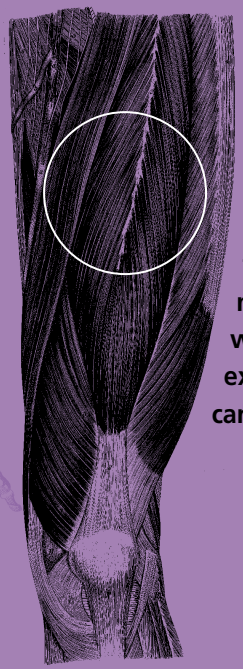




What is Normal Aging?



BODY FAT > Typically, body fat gradually increases in adulthood until individuals reach middle age. Then it usually stabilizes until late life, when body weight tends to decline. As weight falls, older individuals tend to lose both muscle and body fat. With age, fat is redistributed in the body, shifting from just beneath the skin to deeper organs. Women typically have a higher percentage of body fat than men. However, because of differences in how this fat is distributed—on the hips and thighs in women and on the abdomen in men—women may be less susceptible to certain conditions including heart disease.



MUSCLES > Without exercise, estimated muscle mass declines 22 percent for women and 23 percent for men between the ages of 30 and 70. Exercise can slow this rate of loss.

BONES > Bone mineral is lost and replaced throughout life; loss begins to outstrip replacement around age 35. This loss accelerates in women at menopause. Regular weight bearing exercise—walking, running, strength training—can slow bone loss.

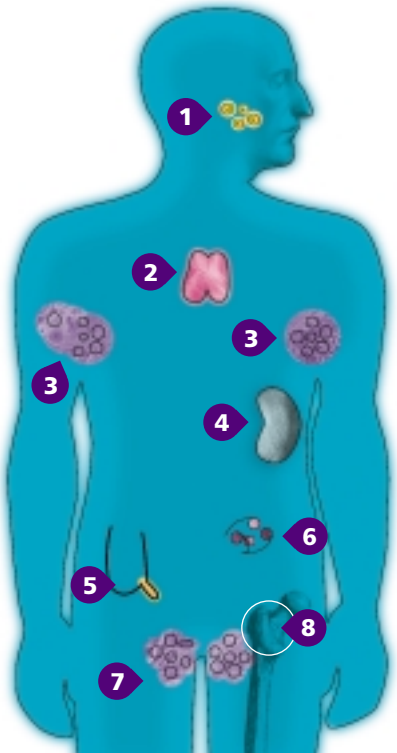
SIGHT > Difficulty focusing close up may begin in the 40s; the ability to distinguish fine details may begin to decline in the 70s. From 50 on, there is increased susceptibility to glare, greater difficulty in seeing at low levels of illumination, and more difficulty in detecting moving objects.

HEARING > It becomes more difficult to hear higher frequencies with age. Even older individuals who have good hearing thresholds may experience difficulty in understanding speech, especially in situations where there is background noise. Hearing declines more quickly in men than in women.

PERSONALITY > Personality is extraordinarily stable throughout adulthood. Generally, it does not change radically, even in the face of major events in life such as retirement, job loss, or death of loved ones. However, there are exceptions. Certain individuals facing these and other life-altering circumstances can and do show signs of personality change during the final years of life. An easy-going individual who loses a job after many years, for instance, may become disillusioned and develop a sullen disposition. But these out-of-character reversals of personality are relatively rare.

Lymphocytes fall into two major classes: B-cells and T-cells. B-cells mature in the bone marrow, and one of their functions is to secrete antibodies in response to infectious agents or antigens. T-cells develop in the thymus, which shrinks in size as people age; they are divided into cytotoxic T-cells and helper T-cells. Cytotoxic T-cells attack infected or damaged cells directly. Helper T-cells produce powerful chemicals, called lymphokines, that mobilize other immune system substances and cells.

T-cells and their lymphokine products have intrigued gerontologists ever since it was learned that T-cells—or more precisely the functioning population of T-cells—declines with age. While the number of T-cells remains about the same, the proportion of them that proliferate and function declines. Studies have also shown that in older people, T-cells destroyed by stresses such as irradiation or cancer chemotherapy take longer to renew than they do in younger people.



The Immune System

1. Tonsils and Adenoids
2. Thymus
3. Lymph Nodes
4. Spleen
5. Appendix
6. Peyer's Patches
7. Lymphatic Vessels
8. Bone Marrow

Most research on the aging immune system now centers on these cells. One group of T-cell products, interleukins, is found at different levels as people age. The interleukins—there are more than 20 identified so far—serve as messengers, relaying signals that regulate the immune response. Some, like interleukin-6, rise with age, and it is speculated that they interfere in some way with the immune response. Others, like interleukin-2, which stimulates T-cell proliferation, tend to fall with age. Gerontologists study the interleukins, not only for clues to the mechanisms of aging, but also for their potential in the detection and treatment of immune problems.

Meanwhile, compelling evidence suggests one intervention—caloric restriction—may counteract some of the natural declines in the immune system as well as in other physiological systems of aging animals.

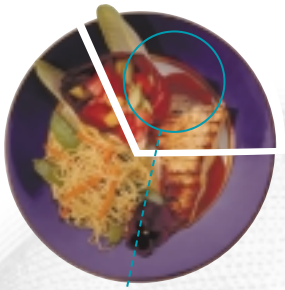
"To lengthen thy life, lessen thy meals."

– Benjamin Franklin, (1706-1790)

Caloric Restriction

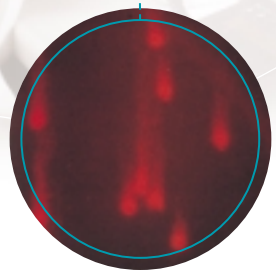
An inventor, statesman, diplomat, and scientist, Benjamin Franklin was a true Renaissance man renowned for his sage advice. Among his many pearls of wisdom: "To lengthen thy life, lessen thy meals." Nearly 275 years later, gerontologists are finding those words may turn out to be amazingly prophetic.

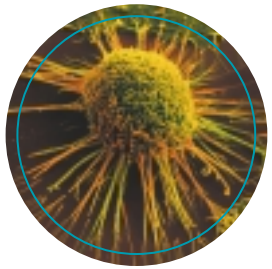
Since the 1930s, investigators have consistently found that laboratory rats and mice live up to 40 percent longer than usual when fed a diet that has at least 30 percent fewer calories than they would normally consume. The animals that eat this nutritionally balanced diet, which provides healthful

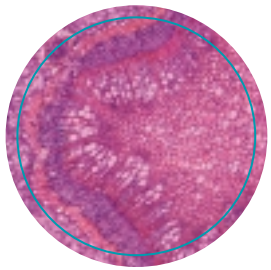


Feeding animals 30 to 40 percent fewer calories than normal appears to delay age-related degeneration of nearly every physiological system. But it remains uncertain whether caloric restriction could have the same effect in humans.

Data from animal studies suggests caloric restriction may help neurons resist dysfunction and death (top). Caloric restriction also might help the body fend off cancer (center), and other age-related cellular changes (bottom).







amounts of protein, fat, and vitamins and minerals, also appear to be more resistant to age-related diseases. In fact, caloric restriction appears to delay normal age-related degeneration of almost all physiological systems. And so far, caloric restriction has increased the lifespans of nearly every animal species studied including protozoa, fruit flies, mice, and other laboratory animals. Now investigators are exploring whether and how caloric restriction will affect aging in monkeys and other non-human primates, our closest relatives in the animal kingdom.

Why calorically restricted animals live far beyond their normal lifespans remains unclear. Because cutting down on calories slows metabolism, and free radicals are by-products of metabolism, caloric restriction may reduce oxidative damage to cells. Calorie restricted animals also have less glucose circulating in their blood than their freely feeding counterparts. This may lessen the potential for protein crosslinking, a biochemical process implicated in cellular aging. And because caloric restriction lowers body temperature slightly, cells may sustain less genetic damage than at normal body temperature. In addition, scientists speculate that caloric restriction preserves the capacity of cells to proliferate, and that it keeps the immune system functioning at youthful levels. Caloric restriction also may work through other mechanisms. It may, for instance, influence hormonal balance, cell senescence, or gene expression. Or, it might work through a combination of all of these mechanisms, plus other factors.

Many gerontologists are particularly intrigued by findings suggesting that animals on calorie restricted diets have reduced rates of disease. In one of the largest studies to date, Roderick Bronson, D.V.M., at Tufts University found that caloric restriction not only extended lifespan in mice, but also prevented or slowed down development of every disease and all types of tumors. Other rodent studies have found that caloric restriction may increase resistance of neurons in the brain to dysfunction and death. These results, described as "stunning" by gerontologists, have raised hope that further study of caloric restriction will help uncover the mechanisms responsible for disease in old age.

However, whether caloric restriction might have the same effect in primates remains a major question. In studies underway at NIA, rhesus and squirrel monkeys are growing up on a calorically restricted diet. Similar studies are also ongoing at the University of Wisconsin and the University of Maryland. Preliminary results from these studies show some promising early signs of improved health—including greater resistance to diabetes and heart disease—in these primates as they age. (**See The Next Step: Caloric Restriction in Primates, page 36**).

In the 1930s, investigators discovered that rats and mice fed fewer calories lived longer than rodents allowed to eat as much as they liked. Since then, caloric restriction has increased the lifespan of nearly every animal species studied.

The Next Step: Caloric Restriction in Primates

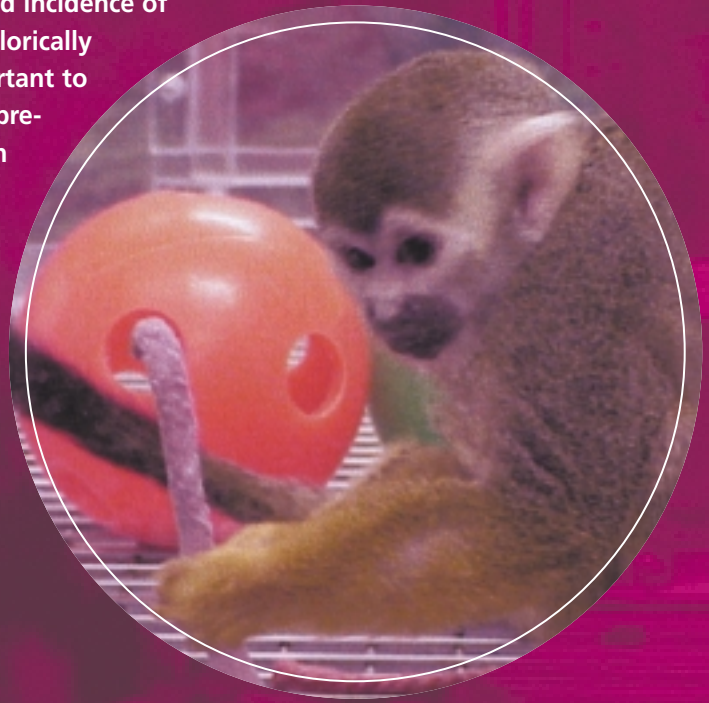
At the NIH Animal Center in Poolesville, Maryland, about 75 rhesus and squirrel monkeys are on diets; they eat 30 percent less than they would normally but get all the necessary nutrients. Another 75 monkeys, the control group, are eating as much as they want. The differences between the two groups, as they age, are beginning to provide insights into how caloric restriction influences lifespan.

The monkeys that arrived at the Poolesville laboratory in 1987 have responded to caloric restriction as expected; their maturation, measured by factors such as skeletal development and onset of puberty, has been delayed by about a year or year and a half. This is comparable to the delays in maturation seen in calorically restricted rodents.

As the monkeys continue to grow into middle age and beyond, Donald Ingram, Ph.D., and his colleagues at the NIA's Gerontology Research Center in Baltimore, where the project is coordinated, are monitoring dozens of signs of aging, ranging from immune response to activity level to antioxidant levels to fingernail growth. The measurements are being compared with those of the monkeys in the control group and should provide leads to some of the mechanisms at work in caloric restriction.

The monkeys on the restricted diet are smaller and weigh about 20 percent less than monkeys in the control group. However, the calorically restricted monkeys are no less physically active than animals allowed to eat at will.

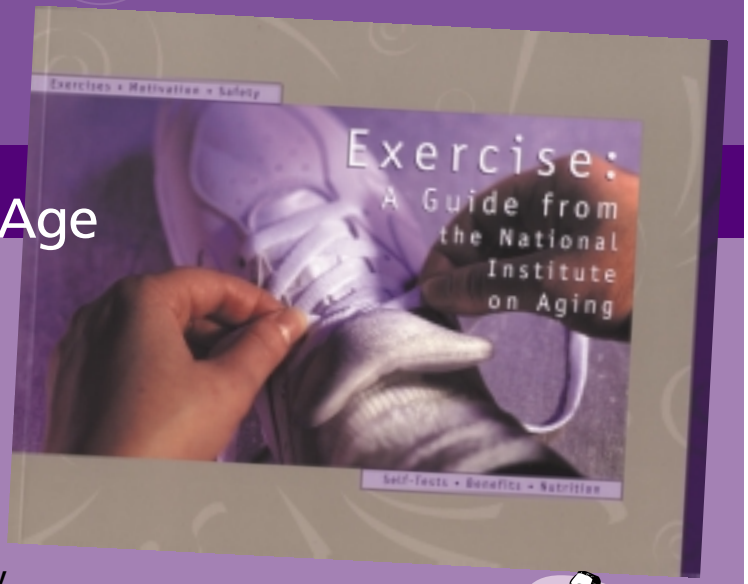
So far, some positive trends have been detected, including the possibility of reduced incidence of heart disease and cancer in the calorically restricted monkeys. But it is important to keep in mind that these data are preliminary, and investigators caution that it may be many more years before it can be determined if caloric restriction does indeed improve the health and extend the lifespan of aging primates.



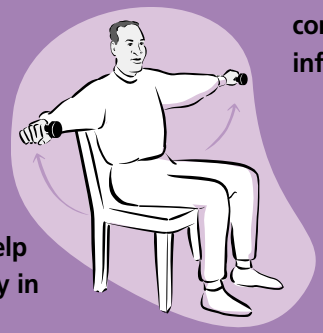
Exercise: It Works at Any Age

Regular physical activity may be the most important thing an older person can do to stay healthy and self-reliant. In fact, the more exercise you can do in later life, the better off you'll be.

Studies suggest regular, sustained exercise can help prevent or delay some diseases and disabilities as people grow older. And, in some cases, it can actually improve some of these conditions in older people who already have them. In a study conducted at Tufts University in Boston, for instance, some people age 80 and older were able to progress from using walkers to using canes after doing simple muscle-building exercises for just 10 weeks. In addition, physical activity can improve your mood, lessen your risk of developing adult-onset diabetes, slow bone loss, and reduce your risk of heart attack and stroke.



Endurance exercises such as brisk walking increase your stamina and improve the health of your heart, lungs and circulatory system. Strength exercises build muscles and reduce your risk of osteoporosis. Balance exercises help prevent a major cause of disability in older adults: falls. Flexibility or stretching exercises help keep your body limber. As part of a daily routine, these exercises and other physical activities you enjoy can make a difference in your life as you get older.



For a nominal fee, an exercise book and a 48-minute companion video are available from NIA. For more information about the book and video contact:

NIA Information Center
P.O. Box 8057
Gaithersburg, MD
1-(800)-222-2225
1-(800)-222-4225 TTY

Yet even if caloric restriction is successful in primates, it is unlikely that most people could maintain a diet of 30 percent fewer calories without drastic and, in all probability, unpalatable changes in their eating habits. For this reason, most gerontologists doubt that caloric restriction will ever become a widespread means of extending the human lifespan. But investigators are exploring the question of whether drugs might mimic its effects, negating the need for sweeping alterations in diet. In rodent and other animal studies, gerontologists are testing a number of synthetic substances that

produce some of the same effects as caloric restriction, such as reducing body temperature and lowering the amount of insulin in the blood. So far, the preliminary results have been promising. However, none of these substances has yet proved to extend lifespan, and some have potentially toxic side effects that may make human use impractical. Still, the search goes on. Meanwhile, it is becoming increasingly clear that lifestyle—particularly diet and exercise—can have a powerful influence on how people age.

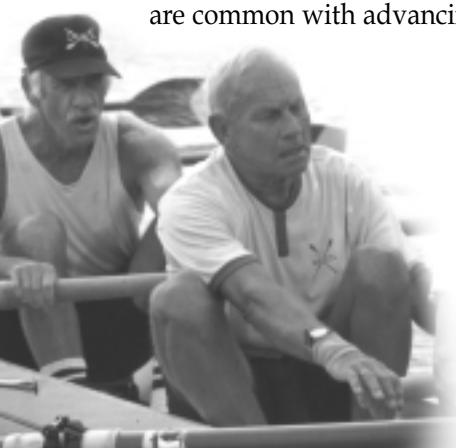
Behavioral Factors

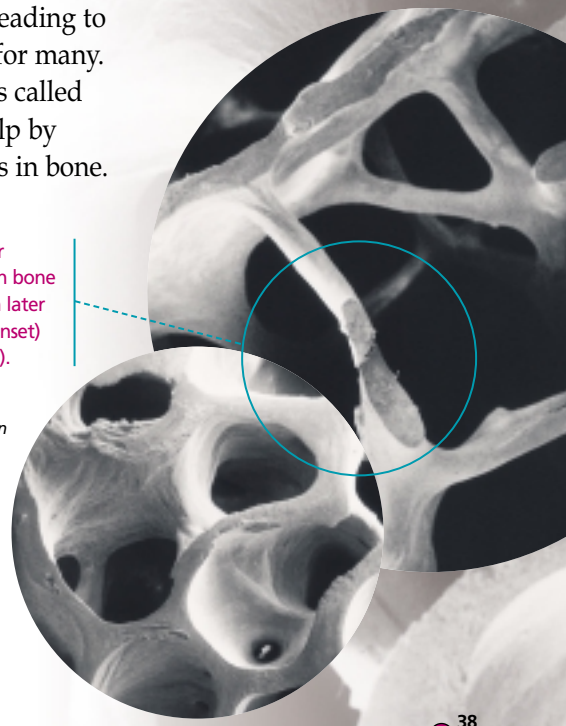
Diet and exercise are thought to have a major impact on a constellation of changes that are common with advancing age. These include higher levels of fats or lipids in the blood, changing levels of blood sugar and insulin, a tendency toward obesity, and increased central body fat that settles around the waist and abdomen. These changes are so prevalent among older people that they have been given a name, syndrome X. Many gerontologists are studying the possible relationship between this syndrome and cardiovascular diseases.

Syndrome X may be preventable through low-fat and low-cholesterol diets, but these are not the only aspects of nutrition that may influence life expectancy. Gerontologists have been scrutinizing a wide range of nutrients with an eye toward their role in aging processes. Calcium and vitamin D, for example, help reduce the thinning of bones that accompanies aging in almost everyone but particularly in older women, many of whom are at high risk for osteoporosis.

Researchers are also studying exercise as a behavioral factor that may have an impact on how long we live or at least on how healthy we are in old age. One landmark study at Tufts University in Boston has shown that exercise can strengthen muscles, improve mobility, and reduce frailty even among 90-year-olds.

Exercises that put weight on bones, such as jogging, walking, and weight-lifting, have been shown to strengthen them. Researchers, as a result, are exploring the potential of exercise to reduce the risk of osteoporosis. This condition, with its fragile, easily broken bones, is a major cause of fractures among older people, frequently resulting in disability, and eventually leading to institutionalization for many. In some cases, drugs called bisphosphonates help by slowing calcium loss in bone.





A balanced diet and regular exercise can help strengthen bone and prevent osteoporosis in later life. Normal bone (bottom inset) and osteoporotic bone (top).

Reproduced from J Bone Miner Res 1986; 1:16-21 with permision of the American Society for Bone and Mineral Research.

The Future of Aging

The aging boom is upon us. Life expectancy nearly doubled in the 20th century. Since 1900, the number of Americans age 65 and older has increased 10-fold. The oldest-old—people age 85 and older—constitute the fastest growing segment of the U.S. population. By 2050, this population— currently about 4 million people—could top 19 million. Living to 100 likely will become more commonplace. In 1950, only about 3,000 Americans were centenarians; by 2050, there could be nearly one million.

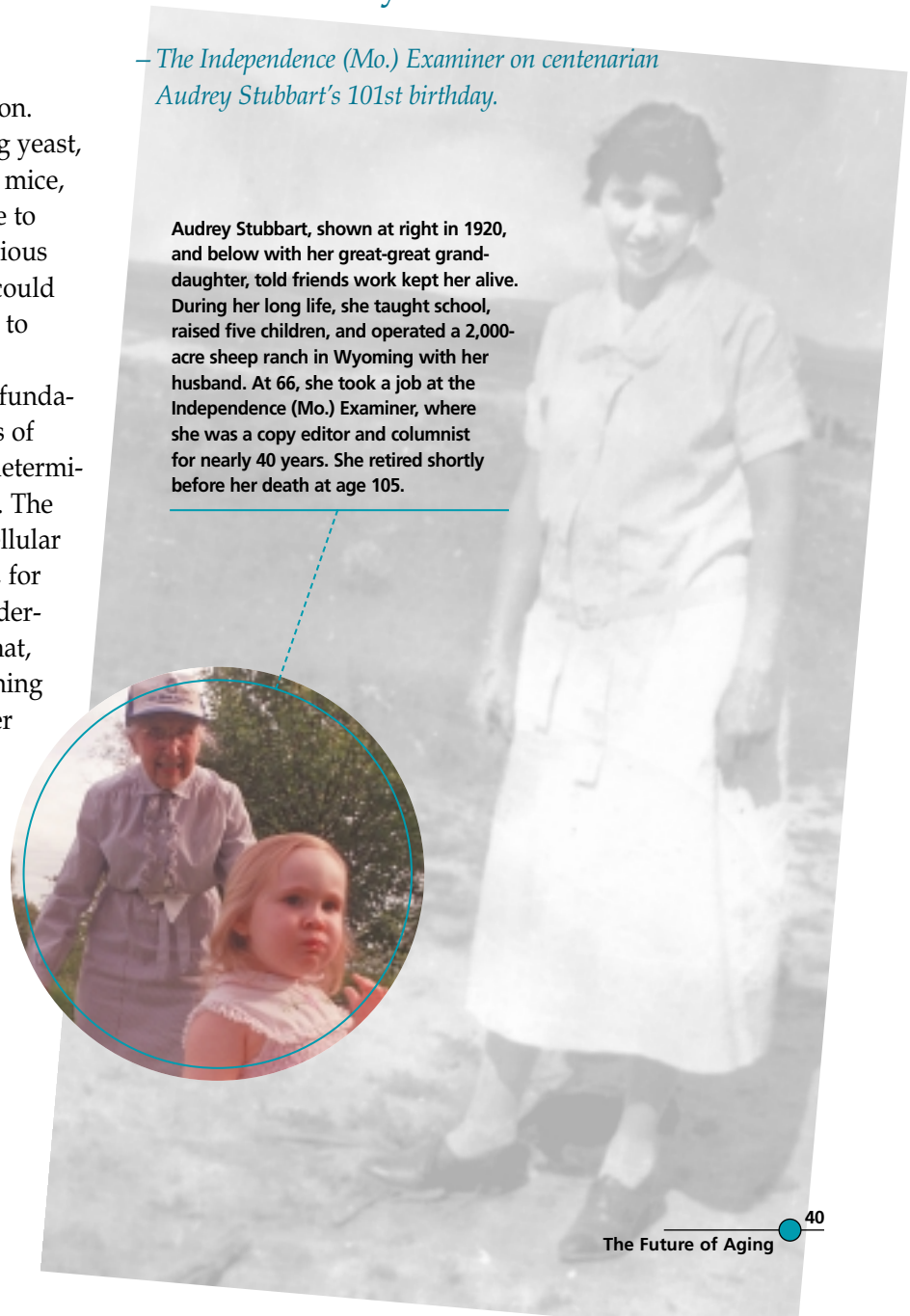
The question has been asked countless times in the 12 months since her 100th birthday…"What's the secret?"

– The Independence (Mo.) Examiner on centenarian Audrey Stubbart's 101st birthday.

This remarkable burst of longevity, unprecedented in human history, has been possible because of equally remarkable improvements in sanitation, health care, and lifestyle. These advances have led to much conjecture about how aging will evolve in the 21st century. Some gerontologists suspect an average life expectancy of 85 years or more may be possible in the not-so-distant future. Others have speculated that the first person destined to live 130 years or more is alive today. Still others predict that robust health in later life will be more common as fewer and fewer older Americans live with disabilities. Whether any of these visions become reality will greatly depend on the emerging science of aging.

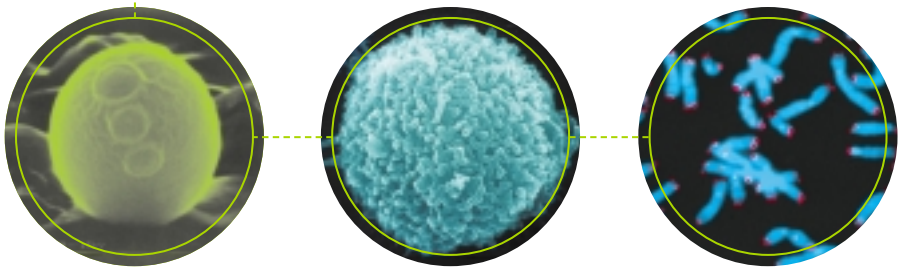
As investigators delve more deeply into how and why we age, its secrets are being deciphered at an unparalleled rate. Scientific understanding of the genetic, biochemical, and physiological aspects of this dynamic process has never been greater. Microarray technology has enabled gerontologists to characterize the expression of vast numbers of genes potentially important in human aging and longevity determination. Experiments involving yeast, fruit flies, nematodes, mice, and primates continue to yield insights into various aspects of aging that could one day be applicable to humans.

Still, many of the fundamental underpinnings of aging and longevity determination remain elusive. The role of telomeres in cellular senescence and aging, for instance, is poorly understood. It is unclear what, if any, effects diminishing hormone levels in later life have on aging, longevity, and health.



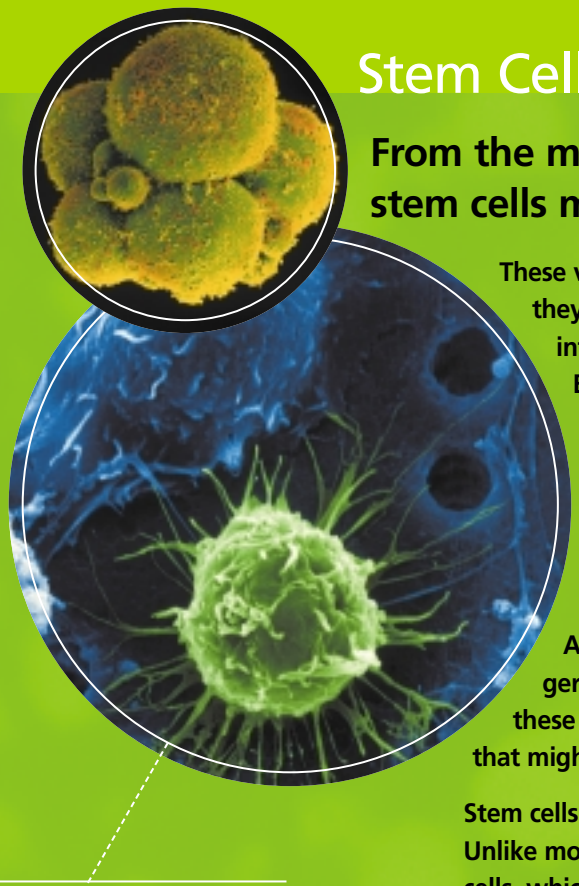
Audrey Stubbart, shown at right in 1920, and below with her great-great granddaughter, told friends work kept her alive. During her long life, she taught school, raised five children, and operated a 2,000-acre sheep ranch in Wyoming with her husband. At 66, she took a job at the Independence (Mo.) Examiner, where she was a copy editor and columnist for nearly 40 years. She retired shortly before her death at age 105.

Gerontologists have unraveled many of the secrets of aging thanks to experiments with simple organisms such as yeast (below, left). Still, much remains unknown about the processes that underlie the journey from young to old, including the roles that macrophages, a part of the immune system (center) and telomeres (right) may play.



Stem Cells: Great Expectations, but Many Barriers Remain

From the moment they were first isolated in the late 1990s, human stem cells mesmerized gerontologists. And for good reason.



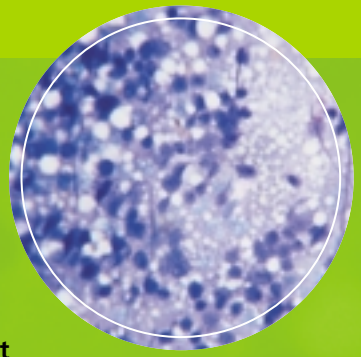
Colorized scanning electron micrograph of stem cells collected from human bone marrow. Stem cells are primitive cells that can multiply indefinitely, migrate to different parts of the body, and develop into different types of tissue. Bone marrow retains the ability to generate stem cells throughout life. Bone marrow stem cells typically give rise to bone, blood, and cartilage.

These versatile cells intrigue investigators because they are capable of transforming themselves into many different kinds of body tissue. Because of this flexibility, stem cells hold enormous potential for cell replacement or tissue repair in many age-associated degenerative disorders where loss of cells is currently irreversible, including diabetes, stroke, heart disease, and Alzheimer's and Parkinson's disease. With millions of older Americans suffering from these conditions, gerontologists are scrambling to find out if these cells will yield any practical interventions that might help promote healthy aging.

Stem cells can be derived from an embryo or an adult. Unlike most cells in the body, such as skin or heart cells, which are dedicated to perform a specific function, stem cells are not specialists. But under certain circumstances, they can differentiate into specialized cells. Another unique characteristic of stem cells is their ability to replicate for indefinite periods without becoming senescent.

Investigators suspect that embryonic stem cells can develop into almost any of the many known specialized cell types in the body, including bone, blood, and brain cells. However, these stem cells are not embryos, and cannot themselves develop into embryos. Adult stem cells apparently help repair or replace those tissues lost through natural attrition, or when they are damaged by injury or disease. Adult stem cells in bone marrow, for instance, regularly replenish the body's supply of red blood cells. Similarly, intestinal stem cells help maintain the lining of the intestines, which is frequently sloughed off in a natural process.

It is not clear, however, if adult stem cells can fully match embryonic stem cells' capacity to differentiate into vast arrays of replacement cells and tissues. In animal studies, certain adult stem cells have shown some potential to develop into multiple cell types, suggesting that both embryonic and adult stem cells could have therapeutic applications. NIA-supported investigators who injected adult mouse bone marrow cells into the circulatory systems of mice, for instance, discovered that these cells found their way into the



brains of the rodents and within 1-to-6 months became neuronal cells. A second study showed that adult mouse bone marrow cells could also develop into heart cells and vascular structures, resulting in the substantial replacement of damaged heart tissue within 2 weeks.

Despite these preliminary successes, many formidable hurdles must be overcome. Investigators still understand very little about how stem cells work, so determining how to get stem cells to do what investigators want them to do in the body remains a mystery. In adults, stem cells appear to become less spontaneously active with age, and some gerontologists suspect that inactivation of these cells may play a prominent role in the normal aging process. For investigators, finding ways to reactivate these cells and get them to where they are needed in the body are significant challenges.

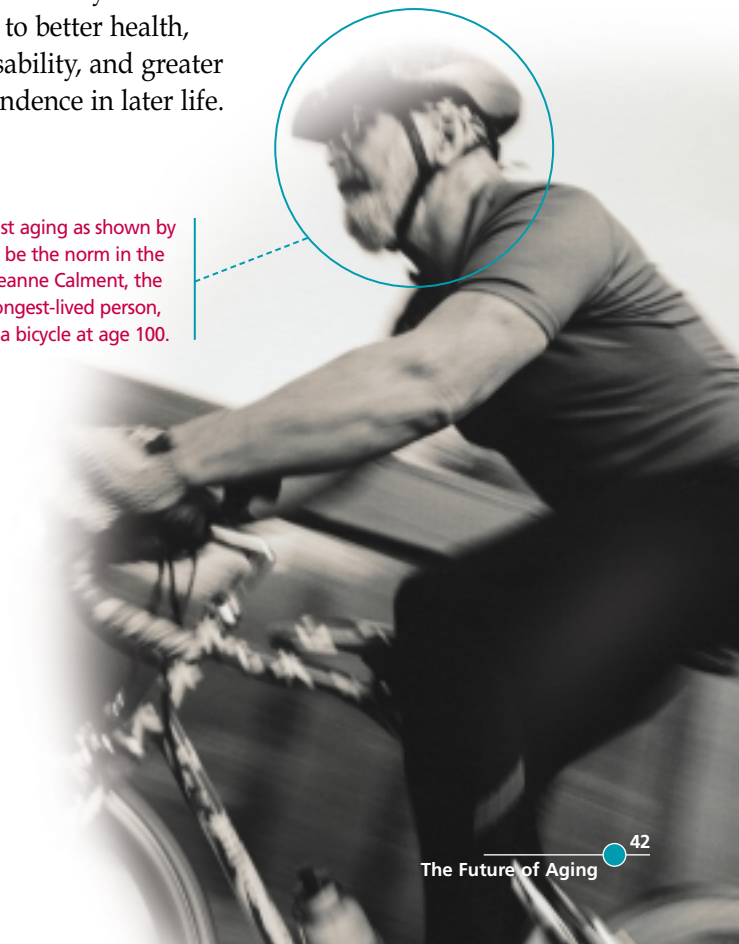
Still, the discovery of human stem cells is an important scientific breakthrough that clearly has the potential to improve the quality and length of life.

"For the first time in human history the prospect of living a long, healthy and productive life has become a reality for the majority of people... What was the privilege of the few has become the destiny of the many."

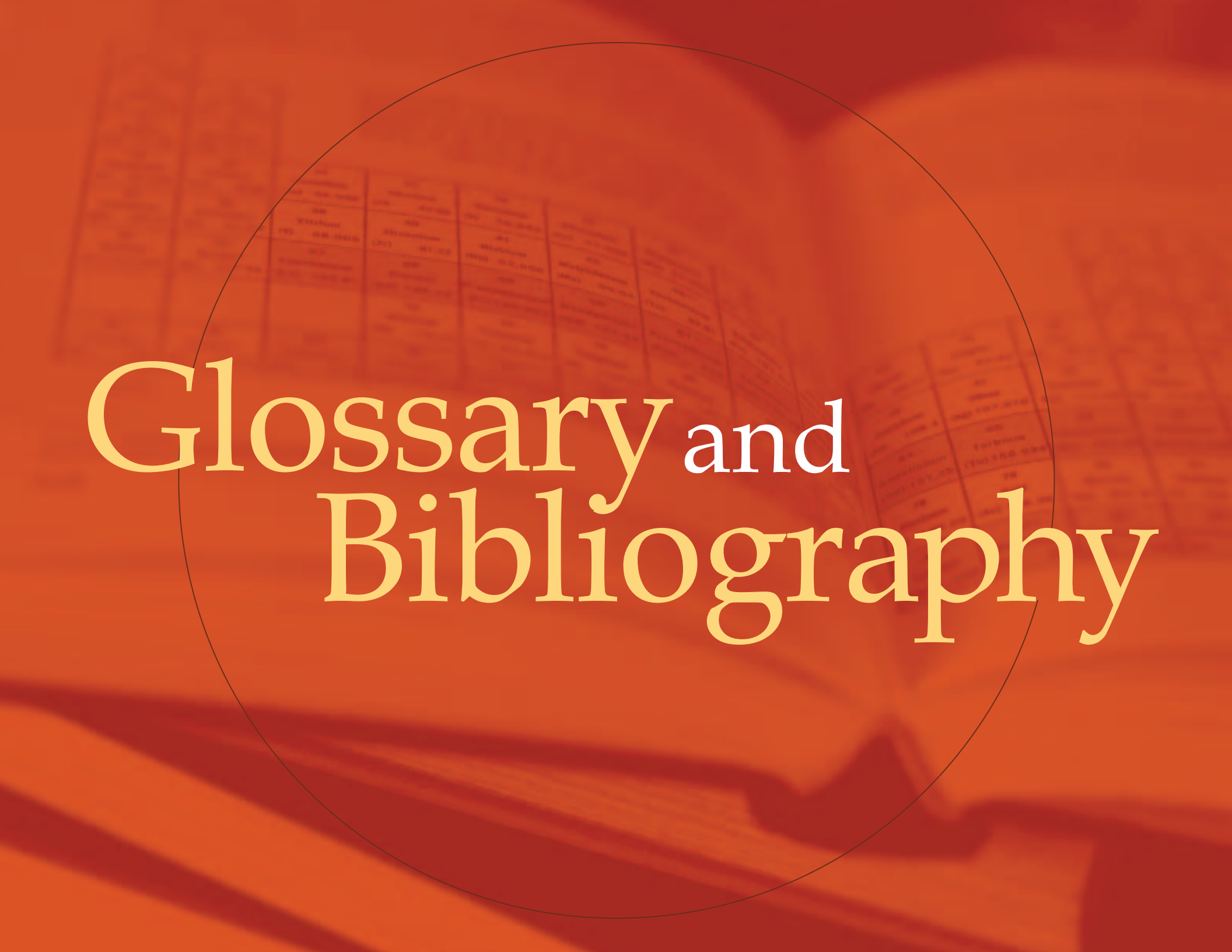
– Robert Butler, M.D., Gerontologist

Further study is needed to clarify how caloric restriction works, and to determine whether this intervention—or drugs that mimic its effects—might be effective and safe for humans.

These and other lingering research challenges underscore the enormity of the quest facing gerontologists. It is becoming increasingly clear that aging is an intricate bundle of interdependent processes, some of which are better understood than others. As gerontologists untangle these interconnecting genetic, biochemical, and physiological processes, they will likely uncover many more secrets of aging. These discoveries may lead to extended life-spans, and almost certainly will contribute to better health, less disability, and greater independence in later life.



Will robust aging as shown by this man, be the norm in the future? Jeanne Calment, the world's longest-lived person, still rode a bicycle at age 100.


Glossary and
Bibliography

Glossary

Amino acid—A chemical building block of proteins. There are 20 standard amino acids. A protein consists of a specific sequence of amino acids.

Antioxidants—Compounds that neutralize oxygen radicals. Some are enzymes like superoxide dismutase (SOD) and catalase, while others are nutrients such as vitamin C.

Anti-proliferative genes—Genes that inhibit cell division or proliferation. These genes can act as tumor suppressor genes.

Base—Part of a nucleotide. In DNA, the bases are adenine (abbreviated A), thymine (T), cytosine (C), and guanine (G). RNA contains uracil (U) instead of thymine.

Biomarkers—Biological changes that characterize the aging process. So far, no reliable biomarkers have been identified in humans.

Caloric restriction—An experimental intervention that is being studied to determine its impact on longevity. In laboratory settings, the lifespans of animals have been extended by reducing calories while maintaining the necessary levels of nutrients.

Centenarian—a person who has lived at least 100 years.

Chromosome—A cellular structure containing genes. Chromosomes are composed of DNA and proteins. Humans have 23 pairs of chromosomes in each body cell, one of each pair from the mother and the other from the father.

Cytokines—Proteins that are secreted by cells and regulate the behavior of other cells by binding to receptors on their surfaces. This binding triggers a variety of responses, depending on the nature of the cytokine and the target cell.

DNA—Abbreviation for deoxyribonucleic acid, the molecule that contains the genetic code for all life forms except for a few viruses. It consists of two long, twisted chains made up of nucleotides. Each nucleotide contains one base, one phosphate molecule, and the sugar molecule deoxyribose. The bases in DNA nucleotides are adenine, thymine, guanine, and cytosine.

Enyzme—A protein that promotes a specific biochemical reaction in the body without itself being permanently changed or destroyed. Enzymes, for instance, are involved in blood clotting and initiate the process of breaking down food.

Fibroblast— One of the major cell types found in skin. Scientists utilize human fibroblast cell cultures to study aging at the cellular level.

Free radicals—Molecules with unpaired electrons that react readily with other molecules. Oxygen-free radicals, produced during metabolism, damage cells and may be responsible for aging in tissues and organs.

Gene—A segment of DNA that contains the "code" for a specific protein.

Gene expression—The process by which the information contained in the genes is transcribed and translated into proteins. Age-related changes in gene expression may account for some of the phenomena of aging.

Glycation—A process by which glucose links with proteins and causes these proteins to bind together. In some circumstances, this can result in "stiffening" of tissues and may lead to certain complications of diabetes, and perhaps some of the physiological problems associated with aging.

Glossary

Hayflick limit—The finite number of divisions a cell is capable of when cultured in a laboratory setting (*in vitro*). A cell reaching this limit is considered to be senescent, at least when *in vitro*. However, to date there is no evidence that replicative senescence plays a physiologically significant role in normal aging or age-related disorders.

Interleukins—A type of cytokine involved in regulation of immune function. The levels of some interleukins present in the body are reported to change with age, but it is unclear whether these fluctuations are due to aging itself or are a manifestation of the many conditions and diseases associated with aging.

Lymphocytes—Small white blood cells that are important to the immune system. A decline in lymphocyte function with advancing age is being studied for insights into aging and disease.

Maximum lifespan—The greatest age reached by any member of a given species.

Mean lifespan—The average number of years that members of a species live; also known as life expectancy.

Mitochondria—Cell organelles that metabolize glucose and other sugars to produce biochemical energy. Mitochondria also contain DNA, which is damaged by the high level of free radicals produced during this process.

Mitosis—The process of replicating DNA, and dividing it into two equal parts to generate two identical "daughter" cells from one "mother" cell.

Nucleotide—A building block of DNA or RNA. It includes one base, one phosphate molecule, and one sugar molecule (deoxyribose in DNA, ribose in RNA).

Photoaging—The process initiated by sunlight through which the skin becomes drier and loses elasticity. Photoaging is being studied for clues to aging because it has the same effect as normal aging on certain skin cells.

Proliferative genes—Genes that promote cell division or proliferation. These genes can act as oncogenes (genes that promote cancer growth).

Proteins—Molecules composed of amino acids arranged in a specific order determined by the DNA sequence of the gene. Proteins are essential for all life processes. Certain ones, such as the enzymes that protect against free radicals and the lymphokines, produced in the immune system, are being studied extensively by gerontologists.

Replicative senescence—The stage at which a cell has permanently stopped dividing.

RNA—Abbreviation for ribonucleic acid, the molecule that carries out DNA's instructions for making proteins. It consists of one long chain made up of nucleotides. There are three main types of RNA: messenger RNA, transfer RNA, and ribosomal RNA.

Telomeres—Repeated short DNA sequences occurring at the end of the chromosomes; telomeres shorten each time a cell divides.

Tumor suppressor genes—Genes that inhibit cell division or proliferation.

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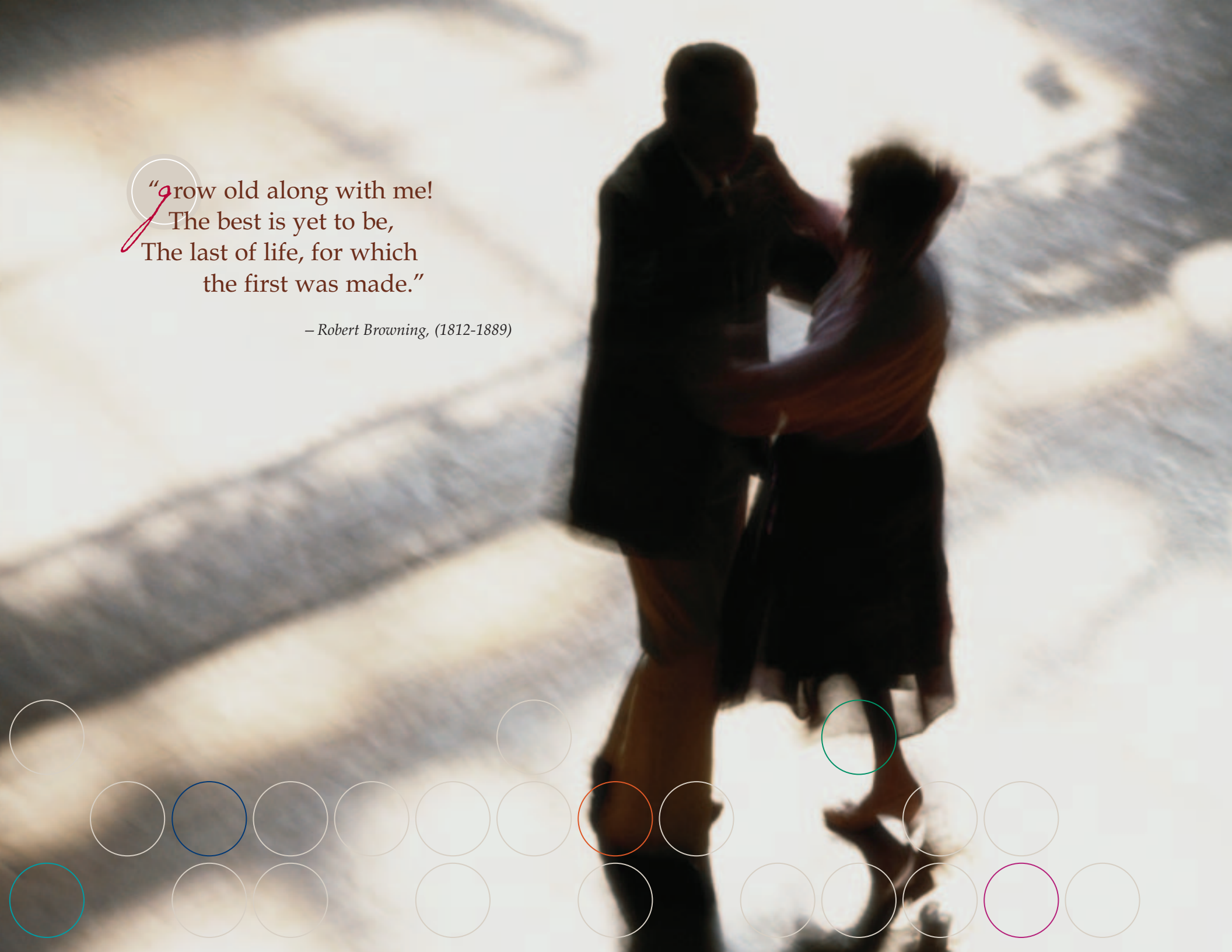
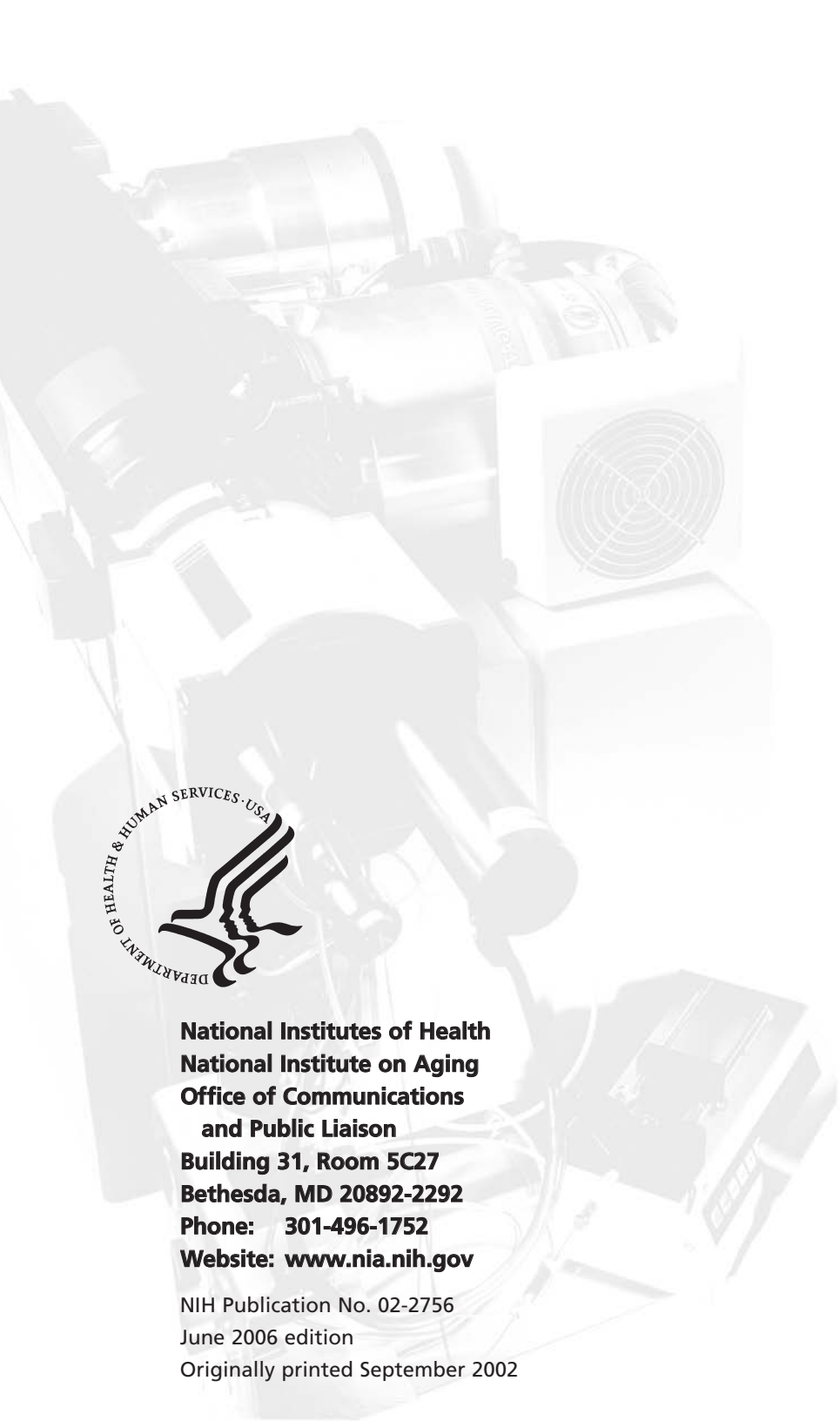

"Grow old along with me!
The best is yet to be,
The last of life, for which
the first was made."
– Robert Browning, (1812-1889)



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